# THE ELEPHANT FORMULARY

Susan K. Mikota D.V.M
Donald C. Plumb, Pharm.D.

# The Elephant Formulary

 Published by
Elephant Care International
www.elephantcare.org

## TABLE OF CONTENTS



### *Disclaimer*

The authors/publisher assume no responsibility for and make no warranty with respect to results that may be obtained from the uses, procedures, or dosages listed and do not necessarily endorse such uses, procedures, or dosages. The authors/publisher shall not be liable to any person whatsoever for any damages, or equivalencies, or by reason of any misstatement or error, negligent or otherwise obtained in this work.

While a sincere effort has been expounded to assure that the dosages and information included in this book are correct, errors may occur and it is suggested that the reader refer to the original reference or the approved labeling information of the product for additional information.

The information in the monographs is from an earlier version of Plumb's Veterinary Drug Handbook. Please consult the most current version of Plumb's Veterinary Drug Handbook for additional drugs or updated information.

To Drug Monograph Index  To Ophthalmic Product Index

# INTRODUCTION

Determining appropriate drug doses for elephants is challenging. Relatively few pharmacokinetic studies have been conducted to provide elephant-specific information. Veterinarians therefore typically determine elephant drug doses using information available from other species. The horse is the most commonly used model.

The purpose of this Formulary is to compile drug information pertinent to elephants in one place that is readily accessible globally and in a format that can be easily updated.

The Elephant Formulary was created in conjunction with Donald C. Plumb, Pharm D., author of the Veterinary Drug Handbook (Iowa State University Press). Donald's extensive work provides the basis for The Elephant Formulary. The original work has been edited to include only those drugs with known or potential application to elephants. For most drugs only the equine doses have been retained. Ruminant and selected monogastric doses have been retained in a few cases where a drug offers a potential application to elephants but lacks an equine reference. The original text has been retained as effects observed in other species may be pertinent to elephants.

*The information in the monographs is from an earlier version of Plumb's Veterinary Drug Handbook. Please consult the most current version of Plumb's Veterinary Drug Handbook for additional drugs or updated information.*

Elephant specific information, derived primarily from published literature, has been added to existing drug monographs. Drugs used in elephants but that did not appear in the original work have been added but may not have complete monograph information. Anecdotal information has been included as this remains a valuable source of information.

The elephant doses are reported in the format in which they appear in the original source. If information is missing, e.g. route of administration, it is likely absent from the original publication.

*The document is 561 pages so please do not print!*

*Please contact Susan Mikota DVM for any additions or corrections: smikota@elephantcare.org*

To Drug Monograph Index To Ophthalmic Product Index

# Drug Monograph Index

All drugs are bookmarked. The drugs in bold have elephant-specific information (may be anecdotal). Information has been added chronologically so the most current information will be at the end of the elephant section. If you find a link does not work select an adjacent drug and scroll.

* Adverse drug effect reported
pK: elephant pK study




To Drug Monograph Index  To Ophthalmic Product Index

**Enrofloxacin**
**Epinephrine**
**Erythromycin** *
**Estradiol Cypionate**
**Ethambutol** pK
**Etorphine**
Euthanasia Agents containing Pentobarbital
**Famciclovir** pK
**Famotidine**
Febantel
**Fenbendazole**
Ferrous Sulfate
**Firocoxib** pK
Florfenicol
Flumethasone
**Flunixin Meglumine** pK
Fluprostenol Sodium
Follicle Stimulating Hormone-Pituitary
Furazolidone
**Furosemide**
**Gentamicin Sulfate**
Glucocorticoid Agents, General Information
Glycopyrrolate
Griseofulvin
Guaifenesin
**Haloperidol**
**Halothane**
Heparin
**Hexachlorophene**
Hyaluronate Sodium
**Hyaluronidase**
Hydroxyzine
**Ibuprofen**
Imipenem-Cilastatin Sodium
Insulin
**Isoflurane**
**Isoniazid** * pK
Isoproterenol HCl
Isoxsuprine HCl
Itraconazole
**Ivermectin**
Kaolin/Pectin
**Ketamine HCl** *
Ketoconazole
**Ketoprofen** pk
**Levamisole** *
**Levofloxacin** pK
Levothyroxine Sodium
**Lidocaine HCl**
Magnesium Sulfate
Mannitol
Mebendazole
Meclofenamic Acid
**Medetomidine HCl**
**Meperidine**
Methocarbamol
Methylprednisolone
**Metoclopramide HCl**
**Metronidazole** pk
Midazolam HCl
Mineral Oil
**Morantel Tartrate**
**Morphine Sulfate**
**Nalmefene**
**Naloxone HCl**
**Naltrexone HCl**
Naproxen
Narcotic (Opiate) Agonist Analgesics
Neomycin Sulfate
**Neostigmine**
Nitrofurantoin
Novobiocin Sodium
Omeprazole
Opiate Antidiarrheals
Oxacillin Sodium
Oxfendazole
**Oxibendazole**
**Oxyclozanide**
Oxymorphone HCl
**Oxytetracycline** pK
**Oxytocin**
Penicillamine
Penicillins (General Info)
**Penicillin G** pK
Penicillin V Potassium
Pentazocine
Pentobarbital Sodium
Pentoxifylline
**Perphenazine**
Phenobarbital
Phenoxybenzamine HCl
**Phenylbutazone** * pK
Phenylephrine HCl
Phenytoin Sodium
Phytonadione (Vit K1)
Piperazine
Polysulfated Glycosaminoglycan
Potassium
Pralidoxime Chloride
**Praziquantel**
**Prednisolone**
Prednisone
Procainamide HCl

To Drug Monograph Index
To Ophthalmic Product Index

**Promazine HCl** *
Propantheline Bromide
Propofol
Propranolol HCl
Psyllium Hydrophilic
Mucilloid
Pyrantel
**Pyrazinamide * pK**
Pyrilamine Maleate
Pyrimethamine
Quinidine
Ranitidine HCl
**Rifampin * pK**
Saline/Hyprosmotic
Laxatives
Sodium Bicarbonate
Sodium Iodide
Sodium Sulfate
Sodium Thiosulfate
Spectinomycin HCl
Stanozolol
**Succinylcholine Chloride**
Sucralfate
**Sulfadiazine/Trimethoprim**
**Sulfamethoxazole**
**Trimethoprim pK**
Sulfadimethoxine
**Sulfadimethoxine/Ormetorpim**
Terbutaline Sulfate
Tetracycline HCl
**Thiabendazole**
Thiamine HCl
Thiamylal Sodium`
**Thiopental Sodium**
Thyrotropin
Ticarcillin Disodium
**Tiletamine HCl-**
**Zolazepam HCl**
Tilmicosin
Tobramycin Sulfate
**Tolazoline HCl**
Triamcinolone Acetonide
Tripelennamine HCl
**Tylosin**
**Vitamin E/Selenium**
Warfarin Sodium
**Xylazine HCl** *
**Yohimbine HCl**
**Zinc**
**Zuclopenthixol**

To Drug Monograph Index To Ophthalmic Product Index

## ACEPROMAZINE MALEATE * (ADVERSE EFFECT REPORTED)

**Chemistry** - Acepromazine maleate (formerly acetylpromazine) is a phenothiazine derivative which occurs as a yellow, odorless, bitter tasting powder. One gram is soluble in 27 ml of water, 13 ml of alcohol, and 3 ml of chloroform. Acepromazine is also known as “ACE” , ACP , *Plegicil*® , *Notensil*® , & *Atravet*®.

**Storage/Stability/Compatibility** - Store protected from light. Tablets should be stored in tight containers. Acepromazine injection should be kept from freezing.

Although controlled studies have not documented the compatibility of these combinations, acepromazine has been mixed with atropine, buprenorphine, chloral hydrate, ketamine, meperidine, oxymorphone, and xylazine. Both glycopyrrolate and diazepam have been reported to be physically incompatible with phenothiazines. However, glycopyrrolate has been demonstrated to be compatible with promazine HCl for injection.

**Pharmacology** - Acepromazine is a phenothiazine neuroleptic agent. While the exact mechanisms of action are not fully understood, the phenothiazines block post-synaptic dopamine receptors in the CNS and may also inhibit the release of, and increase the turnover rate of dopamine. They are thought to depress portions of the reticular activating system which assists in the control of body temperature, basal metabolic rate, emesis, vasomotor tone, hormonal balance, and alertness. Additionally, phenothiazines have varying degrees of anticholinergic, antihistaminic, antispasmodic, and alpha-adrenergic blocking effects.

The primary desired effect for the use of acepromazine in veterinary medicine is its tranquilizing action. Additional pharmacologic actions that acepromazine possess, include antiemetic, antispasmodic, and hypothermic actions. Some researchers have reported that acepromazine has anticonvulsant activity, but in veterinary medicine it is generally felt that phenothiazines should not be used in epileptic animals or those susceptible to seizures (*e.g.,* post-myelography) as it may precipitate seizures.

Acepromazine may decrease respiratory rates, but studies have demonstrated that little or no effect occurs with regard to the blood gas picture, pH or oxyhemoglobin saturation. A dose dependent decrease in hematocrit is seen within 30 minutes after dosing in the horse and the dog. In horses, hematocrit values may decrease up to 50% of pre-dose values which is probably due to increased splenic sequestration of red cells.

Besides a lowering of arterial blood pressure in the dog, acepromazine causes an increase in central venous pressure, a vagally induced bradycardic effect and transient sinoatrial arrest. The bradycardia may be negated by a reflex tachycardic effect secondary to decreases in blood pressure. Acepromazine also has antidysrhythmic effects. Acepromazine has been demonstrated to inhibit the arrhythmias induced by the ultra-short acting barbiturates, and protect against the ventricular fibrillatory actions of halothane and epinephrine. Other pharmacologic actions are discussed in the adverse effects section below.

**Uses/Indications** - Acepromazine is approved for use in dogs, cats, and horses. Approved indications for dogs and cats include: “...as an aid in controlling intractable animals.....alleviate itching as a result of skin irritation; as an antiemetic to control vomiting associated with motion sickness” and as a preanesthetic agent. In horses, “...as an aid in controlling fractious animals”, and in conjunction with local anesthesia for various procedures and treatments (Package Insert - *PromAce*®, Fort Dodge). It is also commonly used in horses as a pre-anesthetic agent, at very small doses to help control behavior.

Although not approved, it is used as a tranquilizer (see doses) in swine, cattle, rabbits, sheep and goats. Acepromazine has also been shown to reduce the incidence of halothane-induced malignant hyperthermia in susceptible pigs.

To Drug Monograph Index  To Ophthalmic Product Index

**Pharmacokinetics** - The pharmacokinetics of acepromazine has been studied in the horse (Ballard et al. 1982). The drug has a fairly high volume of distribution (6.6 L/kg), and is more than 99% protein bound. The onset of action is fairly slow, requiring up to 15 minutes following IV administration, with peak effects seen in 30-60 minutes. The elimination half-life in horses approximately 3 hours.

Acepromazine is metabolized in the liver with both conjugated and unconjugated metabolites eliminated in the urine. Metabolites may be found in equine urine for up to 96 hours after dosing. Do not administer to racing animals within 4 days of racing.

**Contraindications/Precautions** - Animals may require lower dosages of general anesthetics following acepromazine. Cautious use and smaller doses of acepromazine should be given to animals with hepatic dysfunction, cardiac disease, or general debilitation. Because of its hypotensive effects, acepromazine is relatively contraindicated in patients with hypovolemia or shock. Phenothiazines are relatively contraindicated in patients with tetanus or strychnine intoxication due to effects on the extrapyrimidal system.

Intravenous injections should be made slowly. Do not administer intra-arterially in horses; may cause severe CNS excitement/depression, seizures and death. Because of its effects on thermoregulation, use cautiously in very young or debilitated animals.

Acepromazine has no analgesic effects; treat animals with appropriate analgesics to control pain. The tranquilization effects of acepromazine can be overridden and it cannot always be counted upon when used as a restraining agent. Do not administer to racing animals within 4 days of a race.

In dogs, acepromazine's effects may be individually variable and breed dependent. In geriatric patients, very low doses have been associated with prolonged effects of the drug. Giant breeds and greyhounds may be extremely sensitive to the drug, while terrier breeds are somewhat resistant to its effects. Boxers are reported to very sensitive to the hypotensive and bradycardic effects of acepromazine and should be used cautiously and in small doses in this breed. Atropine is often suggested to be given with acepromazine to help negate its bradycardic effects.

In addition to the legal aspects (not approved) of using acepromazine in cattle, the drug may cause regurgitation of ruminal contents when inducing general anesthesia.

**Adverse Effects/Warnings** - Acepromazine's effect on blood pressure (hypotension) is well described and an important consideration in therapy. This effect is thought to be mediated by both central mechanisms and also through the alpha-adrenergic actions of the drug. Cardiovascular collapse (secondary to bradycardia and hypotension) has been described in all major species. Dogs may be more sensitive to these effects than other animals.

In male large animals, acepromazine causes protrusion of the penis and corresponds to the sedative effects of the drug. In horses, this effect may last 2 hours. Stallions should be given acepromazine with caution as injury to the penis can occur with resultant swelling and permanent paralysis of the penis retractor muscle. Other symptoms that have been reported in horses include excitement, restlessness, sweating, trembling, tachypnea, tachycardia and, rarely, seizures and recumbency.

While acepromazine is a good tranquilizer, its effects of causing penis extension in horses and prolapse of the membrana nictitans in horses and dogs, may make its use unsuitable for show animals. There are also ethical considerations regarding the use of tranquilizers prior to showing an animal or having the animal examined before sale.

To Drug Monograph Index  To Ophthalmic Product Index

Occasionally an animal may develop the contradictory symptoms of aggressiveness and generalized CNS stimulation after receiving acepromazine. IM injections may cause transient pain at the injection site.

**Overdosage** - The $LD_{50}$ in mice is 61 mg/kg after IV dosage and 257 mg/kg after oral dose. Dogs receiving 20 - 40 mg/kg over 6 weeks apparently demonstrated no adverse effects. Dogs gradually receiving up to 220 mg/kg orally exhibited signs of pulmonary edema and hyperemia of internal organs, but no fatalities were noted.

Because of the apparent relative low toxicity of acepromazine, most overdoses can be handled by monitoring the animal and treating symptoms if they occur. Massive oral overdoses should definitely be treated by emptying the gut if possible. Hypotension should not be treated with epinephrine; use either phenylephrine or norepinephrine (levarterenol). Seizures may be controlled with barbiturates or diazepam. Doxapram has been suggested as an antagonist to the CNS depressant effects of acepromazine.

**Drug Interactions** - Acepromazine should not be given within one month of worming with an **organophosphate agent** as their effects may be potentiated. **Other CNS depressant agents (barbiturates, narcotics, anesthetics**, etc.) may cause additive CNS depression if used with acepromazine. **Quinidine** when given with phenothiazines may cause additive cardiac depression. **Antidiarrheal mixtures** (*e.g.,* Kaolin/pectin, bismuth subsalicylate mixtures) and **antacids** may cause reduced GI absorption of oral phenothiazines. Increased blood levels of both drugs may result if **propranolol** is administered with phenothiazines. Phenothiazines block alpha-adrenergic receptors and if **epinephrine** is given, can lead to unopposed beta-activity causing vasodilation and increased cardiac rate. **Phenytoin** metabolism may be decreased if given concurrently with phenothiazines. **Procaine** activity may be enhanced by phenothiazines.

**Doses** - Note: The manufacturer's dose of 0.5 - 2.2 mg/kg for dogs and cats is considered by many clinicians to be 10 times greater than is necessary for most indications. Give IV doses slowly; allow at least 15 minutes for onset of action.

**Horses**:

a) 0.04 - 0.1 mg/kg IV or IM (Robinson 1987)

b) 0.044 - 0.088 mg/kg (2 - 4 mg/100 lbs. body weight) IV, IM or SQ (Package Insert, *PromAce*® - Fort Dodge)

c) 0.02 - 0.05 mg/kg IM or IV as a preanesthetic (Booth 1988a)

d) Neuroleptanalgesia:0.02 mg/kg given with buprenorphine (0.004 mg/kg IV) or xylazine (0.6 mg/kg IV) (Thurmon and Benson 1987)

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants may vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

Refer to the etorphine monograph for information on the use of acepromazine in combination with etorphine (Immobilon®).

a) Adverse effect reported: Photosensitization (appears first as a triangle on the dorsal aspect of the neck) has occurred in Asian elephants receiving acepromazine (60-80 mg) and xylazine (100 mg/metric ton) and in one 5 ton elephant that was given a total of 90 mg of acepromazine and 300 mg of xylazine and then transported in an open truck. Cheeran,J. 2002. **Adverse drug experiences in elephants**. Journal of Indian Veterinary Association Kerala 7:(3):61.

To Drug Monograph Index To Ophthalmic Product Index

b) 40-60 mg acepromazine/metric ton (0.04-0.06 mg/kg) combined with 100 mg xylazine/metric ton for Asian elephants. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Tranquilization and translocation of elephants**. Journal of Indian Veterinary Association Kerala 7:(3):42-46.

c) 0.1 mg/kg IM for Asian elephants; if combined with other drugs, dose can be reduced by up to 50%. Nayar,K.N.M., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Management of surgical affections in captive elephants**. Journal of Indian Veterinary Association Kerala 7:(3):55-59.

d) 50-60 mg/ton IM for Asian elephants; do not expose to direct sunlight for long periods. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants** . In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438.

e) For sedation of African or Asian elephants: 0.004-0.005 mg/kg (total dose 10-30 mg). Fowler,M.E., 1995. **Elephants**. In: Restraint and handling of wild and domestic animals. Iowa State University Press, Ames, Iowa, USA pp. 265-269

f) For sedation, the following are total doses by age category (no species differences are specified): Adults: 30 mg; juvenile–adult: 10-20 mg; baby-juvenile: 5-10 mg (Kock, et.al. 1993). Author's (Mikota) note: The animal category and drug dose column headings for acepromazine are misaligned in this reference and may cause confusion. The doses listed here are correctly matched to their respective age categories. Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants**. In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441.

g) Recumbent immobilization was induced in 12-15 minutes using 150 mg acepromazine combined with 350 mg xylazine IM in two Asian cows weighing 2500 and 3000 kg. Duration of effect was 60 minutes and was sufficient for resection and extraction of bullets in one case and resection and removal of glass from the foot in the other. Nayar,K.N.M., Radhakrishnan,K., Chandrasekharan,K., Cheeran,J.V., Ravindran,S., and George,P.O., 1992. **Anaesthesia for surgical manipulations in the elephant**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 156-158.

h) In elephants, the dose will depend upon the state of the animal and the level of tranquilization needed. Dosages in the range of 0.007 to 0.07 mg/kg IM will provide adequate sedation in elephants that are not excited. The lower dose dosage will calm, the higher dosage will result in heavy sedation. Schmidt,M.J., 1986. **Proboscidea (Elephants)**. In: Fowler,M.E. (Editor), Zoo and wild animal medicine. W.B. Saunders, Philadelphia,PA, USA pp. 884-923.

i) 0.03-0.07 mg/kg (Fowler, 1981). Fowler,M.E. 1981. **Problems with immobilizing and anesthetizing elephants**. Proceedings of the American Association of Zoo Veterinarians 87-91.

**Monitoring Parameters** -

1) Cardiac rate/rhythm/blood pressure if indicated and possible to measure
2) Degree of tranquilization
3) Male horses should be checked to make sure penis retracts and is not injured.
4) Body temperature (especially if ambient temperature is very hot or cold)

**Client Information/FDA Approval Status** - May discolor the urine to a pink or red-brown color; this is not abnormal.
Acepromazine is approved for use in dogs, cats, and horses not intended for food.

To Drug Monograph Index To Ophthalmic Product Index

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Acepromazine Maleate for Injection 10 mg/ml for injection in 50 ml vials;*PromAce*® (Fort Dodge); generic; (Rx). Approved for use in dogs, cats and horses not intended for food.

Acepromazine Maleate Tablets 5, 10, & 25 mg in bottles of 100 and 500 tablets; *PromAce*® (Fort Dodge); generic; (Rx). Approved for use in dogs, cats and horses not intended for food.

**Human-Approved Products**: None

## ACETAZOLAMIDE

**Chemistry** - A carbonic anhydrase inhibitor, acetazolamide occurs as a white to faintly yellowish-white, odorless, crystalline powder with $pK_a$s of 7.4 and 9.1. It is very slightly soluble in water and sparingly soluble in hot water (90-100°C), and sparingly soluble in alcohol. Acetozolamide sodium occurs as a white lyophilized solid and is freely soluble in water. The injection has a pH of 9.2 after reconstitution with Sterile Water for Injection.

**Storage/Stability/Compatibility** - Acetazolamide products should be stored at room temperature. After reconstitution, the injection is stable for one week when refrigerated, but as it contains no preservatives, it should be used within 24 hours.

Acetazolamide sodium for injection is reportedly physically compatible with all commonly used IV solutions and cimetidine HCl for injection.

**Pharmacology** - The carbonic anhydrase inhibitors act by a noncompetitive, reversible inhibition of the enzyme carbonic anhydrase. This reduces the formation of hydrogen and bicarbonate ions from carbon dioxide and reduces the availability of these ions for active transport into body secretions.

Pharmacologic effects of the carbonic anhydrase inhibitors include decreased formation of aqueous humor, thereby reducing intraocular pressure; increased renal tubular secretion of sodium and potassium and, to a greater extent, bicarbonate, leading to increased urine alkalinity and volume; anticonvulsant activity, which is independent of its diuretic effects (mechanism not fully understood, but may be due to carbonic anhydrase or a metabolic acidosis effect).

**Uses/Indications** - Acetazolamide is used principally in veterinary medicine for its effects on aqueous humor production in the treatment of glaucoma. It has also been used for its diuretic action and in the treatment of metabolic alkalosis. In humans, the drug has been used as adjunctive therapy for epilepsy and for acute high-altitude sickness.

**Pharmacokinetics** - The pharmacokinetics of this agent have apparently not been studied in domestic animals. One report (Roberts 1985) states that after a dose of 22 mg/kg, the onset of action is 30 minutes; maximal effects occur in 2-4 hours; duration of action of 4-6 hours in small animals.

In humans, the drug is well absorbed after oral administration with peak levels occurring within 1 - 3 hours. It is distributed throughout the body with highest levels found in the kidneys, plasma and erythrocytes. Acetazolamide has been detected in the milk of lactating dogs and it crosses the placenta (unknown quantities). Within 24 hours of administration, an average of 90% of the drug is excreted unchanged into the urine by tubular secretion and passive reabsorption processes.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions** - Carbonic anhydrase inhibitors are contraindicated in patients with significant hepatic disease (may precipitate hepatic coma), renal or adrenocortical insufficiency, hyponatremia, hypokalemia, hyperchloremic acidosis or electrolyte imbalance. They should not be used in patients with severe pulmonary obstruction unable to increase alveolar ventilation or those who are hypersensitive to them. Long term use of carbonic anhydrase inhibitors are contraindicated in patients with chronic, noncongestive, angle-closure glaucoma as angle closure may occur and the drug may mask the condition by lowering intraocular pressures.

Acetazolamide should be used with caution in patients with severe respiratory acidosis or who have preexisting hematologic abnormalities. Cross sensitivity between acetazolamide and antibacterial sulfonamides may occur.

**Adverse Effects/Warnings** - Potential adverse effects that may be encountered include GI disturbances, CNS effects (sedation, depression, excitement, etc.), hematologic effects (bone marrow depression), renal effects (crystalluria, dysuria, renal colic, polyuria), hypokalemia, hyperglycemia, hyponatremia, hyperuricosemia, hepatic insufficiency, dermatologic effects (rash, etc.), and hypersensitivity reactions.

**Overdosage** - Information regarding overdosage of this drug is not readily available. It is suggested to monitor serum electrolytes, blood gases, volume status, and CNS status during an acute overdose. Treat symptomatically and supportively.

**Drug Interactions** - Oral acetozolamide can inhibit **primidone** absorption. **Primidone or phenytoin,** used with acetazolamide, may cause severe osteomalacia. Because acetozolamide alkalinizes the urine, the excretion rates of many drugs (*e.g.,* **quinidine, procainamide, phenobarbital, methotrexate,** etc.) may be affected. It may also negate the effects of **methenamine** compounds in the urine. Concomitant use with **corticosteroids, amphotericin B, corticotropin, or other diuretics** may exacerbate potassium depletion; this may be especially significant in patients receiving **digitalis preparations**. Rarely, carbonic anhydrase inhibitors interfere with the hypoglycemic effects of **insulin**.

**Laboratory Interactions** - By alkalinizing the urine, carbonic anhydrase inhibitors may cause false positive results in determining **urine protein** using bromphenol blue reagent (*Albustix®, Albutest®, Labstix®*), sulfosalicylic acid (*Bumintest®, Exton's Test Reagent*), nitric acid ring test, or heat and acetic acid test methods.

Carbonic anhydrase inhibitors may **decrease iodine uptake** by the thyroid gland in hyperthyroid or euthyroid patients.

**Doses** - Directions for reconstitution of injection: Reconstitute 500 mg vial with at least 5 ml of Sterile Water for Injection; use within 24 hours after reconstitution.

**Ruminants:**

a) 6 - 8 mg/kg IV, IM, or SQ (Howard 1986)

**Monitoring Parameters** - 1) Intraocular pressure/tonometry (if used for glaucoma); blood gases if used for alkalosis; 2) Serum electrolytes; 3) Baseline CBC with differential and periodic retests if using chronically; 4) Other adverse effects

**Client Information** - If using oral preparation and GI upset occurs, give with food. Notify veterinarian if abnormal bleeding or bruising occurs or if animal develops tremors or a rash.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

To Drug Monograph Index To Ophthalmic Product Index

**Human-Approved Products**:

Acetazolamide 125 mg, 250 mg Tablets; *Diamox*® (Lederle) (Rx); .i.*Dazamide*® (Major) (Rx); generic (Rx)

Acetazolamide Extended-release Capsules 500mg; *Diamox Sequels*® (Lederle); generic (Rx)

Acetazolamide Injection: 500 mg per vial; *Diamox*®; (Lederle);

Acetazolamide Powder 500 mg for Reconstitution; *Diamox*® (Lederle); Generic; (Rx)

To prepare parenteral solution: Reconstitute with at least 5 ml of Sterile Water for Injection. If refrigerated, potency will remain for 1 week, but it should be used within 24 hours as it contains no preservatives.

## ACETIC ACID

**Chemistry** - Glacial acetic acid is $C_2H_4O_2$. Acetic acid has a distinctive odor and a sharp acid taste. It is miscible with water, alcohol or glycerin. Much confusion can occur with the percentages of $C_2H_4O_2$ contained in various acetic acid solutions. Acetic Acid USP is defined as having a concentration of 36-37% $C_2H_4O_2$. Diluted Acetic Acid NF contains 5.7 - 6.3% w/v of $C_2H_4O_2$. Solutions containing approximately 3-5% w/v of $C_2H_4O_2$ is commonly known as vinegar. Be certain of the concentration of the product you are using and your dilutions.

**Storage/Stability/Compatibility** - Acetic acid solutions should be stored in airtight containers.

**Pharmacology/Indications** - Via its acidifying qualities, acetic acid is used in ruminants to treat non-protein nitrogen-induced ammonia toxicosis. The acetic acid in the rumen lowers pH, thereby shifting ammonia to ammonium ions and reducing absorption. It is also used as a potential treatment to prevent enterolith formation in horses, supposedly by reducing colonic pH.

**Pharmacokinetics** - No information noted.

**Contraindications/Precautions** - Should not be administered to ruminants with potential lactic acidosis (grain overload, rumen acidosis) until ruled out.

**Adverse Effects/Warnings** - Because of the unpleasant taste and potential for causing mucous membrane irritation, acetic acid is generally recommended to be administered via stomach tube.

**Overdosage/Acute Toxicity** - When used for appropriate indications, there is little likelihood of serious toxicity occurring after minor overdoses. The greatest concern would occur if a concentrated form of acetic acid is mistakenly used due to its potential corrosiveness. However, one human patient who had glacial acetic acid used instead of 5% acetic acid during colposcopy (cervix), demonstrated no detectable harm.

**Drug Interactions** - There are no documented drug interactions with oral acetic acid, but because of its acidic qualities it could potentially affect the degradation of several drugs in the gut.

**Doses** -
**Horses**:

For enterolith prevention:

a) Using vinegar: 250 ml/450 kg body weight PO once daily (Robinson, 1992).

To Drug Monograph Index To Ophthalmic Product Index

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**: None

There are no systemic products commercially available. Acetic acid (in various concentrations) may be purchased from chemical supply houses.

## ACYCLOVIR

### Pharmacokinetics and analytical determination of acyclovir in Asian elephant calves (Elephas maximus)

S. Khammesri, C. Ampasavate, D. Hongwiset, R. Mektrirat, S. Sangsrijan, J. L. Brown, et al.
Vet Anim Sci 2022 Vol. 15 Pages 100227.
Accession Number: 35024493 PMCID: PMC8724961 DOI: 10.1016/j.vas.2021.100227

A therapeutic regimen that includes antiviral drugs is critical for the survival of Asian elephant (Elephas maximus) calves infected with elephant endotheliotropic herpesvirus hemorrhagic disease (EEHV-HD), with acyclovir showing considerable promise. The purpose of this study was to determine the pharmacokinetics and bioavailability of acyclovir following intravenous (IV) and oral (PO) administration in Asian elephants. A single dose of acyclovir (15 mg/kg, IV or 45 mg/kg, PO) was administered to four healthy elephant calves, with a minimum 2-week washout period between treatments. Serial plasma samples were collected after each injection for acyclovir analysis using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) technique. Maximum plasma acyclovir concentrations were 27.02 ± 6.79 μg/mL at 0.94 ± 0.31 h after IV administration, and 1.45 ± 0.20 μg/mL at 3.00 ± 0.70 h after PO administration. The half-life of the elimination phase (T(1/2)) was 5.84 ± 0.74 and 8.74 ± 2.47 h after IV and PO administration, respectively. After IV administration, acyclovir concentrations were higher than the half-maximal inhibitory concentration (IC(50)) of those found for herpes simplex virus (HSV) 1 and 2 in humans, and equid alpha herpesvirus-1 (EHV-1) for at least 12 h. By contrast, the bioavailability of oral administration was low, only 6.03 ± 0.87%, so higher doses by that route likely are needed to be effective. Due to the high concentration of plasma acyclovir after IV administration, the dose may need to be adjusted to prevent any negative side effects.

## ALBENDAZOLE

**Chemistry** - A benzimidazole anthelmintic structurally related to mebendazole, albendazole has a molecular weight of 265. It is insoluble in water and soluble in alcohol.

**Storage/Stability/Compatibility** - Albendazole suspension should be stored at room temperature(15-30°C); avoid freezing. Shake well before using.

**Uses/Indications** - Albendazole is approved for the following endoparasites of cattle: *Ostertagia ostertagi*, *Haemonchus spp.*, *Trichostrongylus spp., Nematodius spp., Cooperia spp., Bunostomum phlebotomum, Oesphagostomum spp., Dictacaulus spp., Fasciola hepatica* (adults), and *Moniezia spp*. It is also used in sheep, goats and swine for endoparasite control.

In cats, albendazole has been used to treat *Paragonimus kellicotti* infections. In dogs and cats, albendazole has been used to treat capillariasis. In dogs, albendazole has been used to treat *Filaroides* infections.

To Drug Monograph Index  To Ophthalmic Product Index

Albendazole was implicated as being an oncogen in 1984, but subsequent studies were unable to demonstrate any oncogenic or carcinogenic activity of the drug.

**Pharmacokinetics** - Pharmacokinetic data for albendazole in cattle, dogs and cats were not located. The drug is thought to be better absorbed orally than other benzimidazoles. Approximately 47% of an oral dose was recovered (as metabolites) in the urine over a 9 day period.

After oral dosing in sheep, the parent compound was either not detectable or only transiently detectable in the plasma due to a very rapid first-pass effect. The active metabolites, albendazole sulphoxide and albendazole sulfone reached peak plasma concentrations 20 hours after dosing.

**Contraindications/Precautions** - The drug is not approved for use in lactating dairy cattle. The manufacturer recommends not administering to female cattle during the first 45 days of pregnancy or for 45 days after removal of bulls. Albendazole has been associated with teratogenic and embryotoxic effects in rats, rabbits and sheep when given early in pregnancy.

In humans, albendazole is recommended to be used with caution in patients with liver or hematologic diseases.

**Adverse Effects/Warnings** - Albendazole is tolerated without significant adverse effects when dosed in cattle at recommended dosages.

Dogs treated at 50 mg/kg twice daily may develop anorexia. Cats may exhibit symptoms of mild lethargy, depression, anorexia, and resistance to taking the medication when albendazole is used to treat *Paragonimus*.

**Overdosage/Toxicity** - Doses of 300 mg/kg (30X recommended) and 200 mg/kg have caused death in cattle and sheep, respectively. Doses of 45 mg/kg (4.5X) those recommended did not cause any adverse effects in cattle tested. Cats receiving 100 mg/kg/day for 14-21 days showed signs of weight loss, neutropenia and mental dullness.

**Drug Interactions** - In humans, **dexamethasone** and **praziquantal** both have been demonstrated to increase albendazole serum levels. **Cimetidine** increased albendazole levels in bile and cystic fluid. Veterinary clinical relevance is unknown.

**Doses -**
**Cattle**:

For susceptible parasites:

a) 10 mg/kg PO (Labeled directions; *Valbazen*®—SKB)
b) 7.5 mg/kg PO; 15 mg/kg PO for adult liver flukes. (Roberson 1988b)
c) For adult liver flukes: 10 mg/kg PO; best used in fall when the majority are adults (little or no efficacy against immature forms). A second treatment in winter may be beneficial. (Herd 1986b)

**Elephants:**
a) 2.5 mg/kg orally as a single dose

Chandrasekharan,K. 2002. **Specific diseases of Asian elephants**. Journal of Indian Veterinary Association Kerala 7:(3):31-34.

Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T., 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference**

To Drug Monograph Index  To Ophthalmic Product Index

**to Kerala**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-449.

Chandrasekharan,K., 1992. **Prevalence of infectious diseases in elephants in Kerala and their treatment**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 148-155.

**Monitoring Parameters** -

1) Efficacy
2) Adverse effects if used in non-approved species or at dosages higher than recommended.

**Client Information** - Shake well before administering. Contact veterinarian if adverse effects occur.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**:

Albendazole Suspension 113.6 mg/ml (11.36%) in 500 ml, 1 liter, 5 liter

Albendazole Paste 205 g (7.2 oz); *Valbazen*® (Pfizer); (OTC) Approved for use in cattle (not female cattle of breeding age). Slaughter withdrawal=27 days.

**Human-Approved Products**:

Albendazole Tablets 200 mg *Albenza* ® (SmithKline Beecham), (Rx)

## ALBUTEROL SULFATE

**Chemistry** - A synthetic sympathomimetic amine, albuterol sulfate occurs as a white, almost tasteless crystalline powder. It is soluble in water and slightly soluble in alcohol. One mg of albuterol is equivalent to 1.2 mg of albuterol sulfate. Albuterol is also known as salbutamol.

**Storage/Stability/Compatibility** - Oral albuterol sulfate products should be stored at 2-30°C. The capsules containing powder for inhalation should be left in the original packaging until just before use.

**Pharmacology** - Like other beta-agonists, albuterol is believed to act by stimulating production of cyclic AMP through activation of adenyl cyclase. Albuterol is considered to be predominantly a $beta_2$ agonist (relaxation of bronchial, uterine, and vascular smooth muscles). At usual doses, albuterol possesses minimal $beta_1$ agonist (heart) activity. beta adrenergics can promote a shift of potassium away from the serum and into the cell, perhaps via stimulation of $Na^+$-$K^+$-ATPase. Temporary decreases in either normal or high serum potassium levels are possible.

**Uses/Indications** - Albuterol is used principally in dogs and cats for its effects on bronchial smooth muscle to alleviate bronchospasm or cough. It potentially could also be used in horses as a bronchodilator.

**Pharmacokinetics** - The specific pharmacokinetics of this agent have apparently not been thoroughly studied in domestic animals. In general, albuterol is absorbed rapidly and well after oral administration. Effects occur within 5 minutes after oral inhalation, and 30 minutes after oral administration (*e.g.*, tablets). It does not cross the blood-brain barrier, but does cross the placenta. Duration of effect generally persists for 3-6 hours after inhalation and up to 12 hours (depending on dosage form) after oral administration. The

To Drug Monograph Index  To Ophthalmic Product Index

drug is extensively metabolized in the liver, principally to the inactive metabolite, albuterol 4'-O-sulfate. After oral administration, the serum half life in humans has been reported as 2.7-5 hours.

**Contraindications/Precautions/Reproductive Safety** - Albuterol is contraindicated in patients hypersensitive to it. One veterinary school formulary (Schultz 1986) states that a related drug (**terbutaline**), is contraindicated in dogs and cats with heart disease, particularly when CHF or cardiomyopathy is present. It should be used with caution in patients with diabetes, hyperthyroidism, hypertension, seizure disorders, or cardiac disease (especially with concurrent arrhythmias).

In very large doses, albuterol is teratogenic in rodents. It should be used (particularly the oral dosage forms) during pregnancy only when the potential benefits outweigh the risks. Like some other beta agonists, it may delay pre-term labor after oral administration. It is unknown whether the drug crosses into maternal milk.

**Adverse Effects/Warnings** - Most adverse effects are dose-related and are those that would be expected with sympathomimetic agents including increased heart rate, tremors, CNS excitement (nervousness) and dizziness. These effects are generally transient and mild and usually do not require discontinuation of therapy. Decreased serum potassium values may be noted; rarely is potassium supplementation required.

**Overdosage/Acute Toxicity** - Symptoms of significant overdose after systemic administration may include arrhythmias (bradycardia, tachycardia, heart block, extrasystoles), hypertension, fever, vomiting, mydriasis, and CNS stimulation. Hypokalemia may also be noted. If recently ingested (orally), and if the animal does not have significant cardiac or CNS effects, it should be handled like other overdoses (empty gut, give activated charcoal and a cathartic). If cardiac arrhythmias require treatment, a beta-blocking agent (*e.g.,* propranolol) can be used, but may precipitate bronchoconstriction. The oral $LD_{50}$ in rats is reported to be greater than 2 g/kg. Contact a poison control center for further information.

**Drug Interactions** - Use of albuterol with **other sympathomimetic amines** may increase the risk of developing adverse cardiovascular effects. **Beta-adrenergic blocking agents** (*e.g.,* propranolol) may antagonize the actions of albuterol. **Tricyclic antidepressants or monoamine oxidase inhibitors** may potentiate the vascular effects of albuterol. Use with inhalation anesthetics (*e.g.*, **halothane, isoflurane, methoxyflurane**), may predispose the patient to ventricular arrhythmias, particularly in patients with preexisting cardiac disease—use cautiously. Use with **digitalis** glycosides may increase the risk of cardiac arrhythmias.

**Doses** -
**Horses**:

a) 8 micrograms / kg q 12 hours PO (Enos, 1993)

**Monitoring Parameters** - 1) Clinical symptom improvement; auscultation, blood gases (if indicated); 2) Cardiac rate, rhythm (if warranted); 3) Serum potassium, early in therapy if animal susceptible to hypokalemia

**Client Information** - Contact veterinarian if animal's condition deteriorates or becomes acutely ill.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** –

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Albuterol Tablets 2 mg, 4 mg tablets & 4 mg, 8 mg extended release tablets; *Proventil*® (Schering) *Proventil Repetabs* ®; *Ventolin*® (Glaxo Wellcome); *Volmax* (Muro); generic (Rx)

To Drug Monograph Index To Ophthalmic Product Index

Albuterol Oral Syrup 2 mg (as sulfate)/5 ml; *Proventil*® (Schering); *Ventolin*® (Glaxo Wellcome); Generic; (Rx)

Albuterol Aerosol: Each actualization delivers 90 mcg albuterol in 17g & 6.7g canisters; *Proventil*® (Schering); *Proventil HFA*® (Key); *Ventolin*® (Glaxo Wellcome); generic. (Rx)

Albuterol for Inhalation: Solution for Inhalation 0.083% & 0.5% (as sulfate) in 3 ml or 20 ml; 200 micrograms capsules (powder) for inhalation; Airet® (Adams); *Albuterol* (Dey, Copley); *Proventil* ® (Schering);*Ventolin Nebules*® (Glaxo Wellcome); Ventolin Rotacaps® (Glaxo Wellcome); generic. (Rx)

## ALTRENOGEST

**Chemistry** - An orally administered synthetic progestational agent, altrenogest has a chemical name of 17 alpha-Allyl-17□-hydroxyestra-4,9,11-trien-3-one. It may also be known as allyl trenbolone.

**Storage/Stability/Compatibility** - Altrenogest oral solution should be stored at room temperature.

**Pharmacology** - Progestins are primarily produced endogenously by the corpus luteum. They transform proliferative endometrium to secretory endometrium, enhance myometrium hypertrophy and inhibit spontaneous uterine contraction. Progestins have a dose-dependent inhibitory effect on the secretion of pituitary gonadotropins and also have some degree of estrogenic, anabolic and androgenic activity.

**Uses/Indications -** Altrenogest is indicated (labeled) to suppress estrus in mares to allow a more predictable occurrence of estrus following withdrawal of the drug. It is used clinically to assist mares to establish normal cycles during the transitional period from anestrus to the normal breeding season often in conjunction with an artificial photoperiod. It is more effective in assisting in pregnancy attainment later in the transition period. One group of authors (Squires et al. 1983) suggest selecting mares with considerable follicular activity (mares with one or more follicles 20 mm or greater in size) for treatment during the transitional phase. Mares that have been in estrus for 10 days or more and have active ovaries are also considered to be excellent candidates for progestin treatment.

Altrenogest is effective in normally cycling mares for minimizing the necessity for estrus detection, for the synchronization of estrus and permitting scheduled breeding. Estrus will ensue 2-5 days after treatment is completed and most mares ovulate between 8-15 days after withdrawal. Altrenogest is also effective in suppressing estrus expression in show mares or mares to be raced. Although the drug is labeled as contraindicated during pregnancy, it has been demonstrated to maintain pregnancy in oophorectomized mares and may be of benefit in mares who abort due to sub-therapeutic progestin levels.

**Pharmacokinetics** - The pharmacokinetic parameters of altrenogest were not found. Other progestin agents are rapidly metabolized by the liver.

**Contraindications/Precautions** - The manufacturer (*Regu-Mate*® — Hoechst) lists pregnancy as a contraindication to the use of altrenogest, however it has been used clinically to maintain pregnancy in certain mares (see Dosages below). Altrenogest should also not be used in horses intended for food purposes.

**Adverse Effects/Warnings** - Adverse effects of altrenogest appear to be minimal when used at labeled dosages. One study (Shideler et al. 1983) found negligible changes in hematologic and most “standard” laboratory tests after administering altrenogest to 4 groups of horses (3 dosages, 1 control) over 86 days. Occasionally, slight changes in $Ca^{++}$, $K^{+}$, alkaline phosphatase and AST were noted in the treatment group, but values were only slightly elevated and only noted sporadically. No pattern or definite changes

To Drug Monograph Index To Ophthalmic Product Index

could be attributed to altrenogest. No outward adverse effects were noted in the treatment group during the trial.

Use of progestational agents in mare's with chronic uterine infections should be avoided as the infection process may be enhanced.

The manufacturer (*Regu-Mate*® — Hoechst) lists the following people as those who should not handle the product:

1. Women who are or suspect that they are pregnant
2. Anyone with thrombophlebitis or thromboembolic disorders or with a history of these events
3. Anyone having cerebrovascular or coronary artery disease
4. Women with known or suspected carcinoma of the breast
5. People with known or suspected estrogen-dependent neoplasia
6. Women with undiagnosed vaginal bleeding
7. People with benign or malignant tumor which developed during the use of oral contraceptives or other estrogen containing products

Altrenogest can be absorbed after skin contact and absorption can be enhanced if the drug is covered by occlusive materials (*e.g.,* under latex gloves, etc.). If exposed to the skin, wash off immediately with soap and water. If the eyes are exposed, flush with water for 15 minutes and get medical attention. If the product is swallowed, do not induce vomiting and contact a physician or poison control center.

**Overdosage** - The $LD_{50}$ of altrenogest in is 175-177 mg/kg in rats. No information was located regarding the effects of an accidental acute overdose in horses.

**Drug Interactions** - **Rifampin** may decrease progestin activity if administered concomitantly. This is presumably due to microsomal enzyme induction with resultant increase in progestin metabolism. The clinical significance of this potential interaction is unknown.

**Doses** -
**Horses**:

To suppress estrus for synchronization:

a) Administer 1 ml per 110 pounds body weight (0.044 mg/kg) PO once daily for 15 consecutive days. May administer directly on tongue using a dose syringe or on the usual grain ration. (Package insert; *Regu-Mate*® — Hoechst)
b) 0.044 mg/kg PO for 8-12 days (Bristol 1987)

To maintain pregnancy in mares with deficient progesterone levels:

a) 22 - 44 mg daily PO (Squires et al. 1983)

To suppress estrus (long-term):

a) 0.044 mg/kg PO daily (Squires et al. 1983)

**Client Information** - See the Adverse Effects/Warnings section for specific recommendations on handling, etc.

**Veterinary-Approved Products**:

Altrenogest 0.22% (2.2 mg/ml) in oil solution in 150 ml & 1000 ml bottles; *Regu-Mate*® (Hoechst); (Rx)
Approved for use in horses not intended for food.

**Human-Approved Products**: None.

To Drug Monograph Index To Ophthalmic Product Index

## AMIKACIN SULFATE

**Chemistry** - A semi-synthetic aminoglycoside derived from kanamycin, amikacin occurs as a white, crystalline powder that is sparingly soluble in water. The sulfate salt is formed during the manufacturing process. 1.3 grams of amikacin sulfate is equivalent to 1 gram of amikacin. Amikacin may also be expressed in terms of units. 50,600 Units are equal to 50.9 mg of base. The commercial injection is a clear to straw-colored solution and the pH is adjusted to 3.5 - 5.5 with sulfuric acid.

**Storage/Stability/Compatibility** - Amikacin sulfate for injection should be stored at room temperature (15-30°C); freezing or temperatures above 40°C should be avoided. Solutions may become very pale yellow with time, but this does not indicate a loss of potency.

Amikacin is stable for at least 2 years at room temperature. Autoclaving commercially available solutions at 15 pounds of pressure at 120°C for 60 minutes did not result in any loss of potency.

Amikacin sulfate is reportedly **compatible** and stable in all commonly used intravenous solutions and with the following drugs: amobarbital sodium, ascorbic acid injection, bleomycin sulfate, calcium chloride/gluconate, cefoxitin sodium, chloramphenicol sodium succinate, chlorpheniramine maleate, cimetidine HCl, clindamycin phosphate, colistimethate sodium, dimenhydrinate, diphenhydramine HCl, epinephrine HCl, ergonovine maleate, hyaluronidase, hydrocortisone sodium phosphate/succinate, lincomycin HCl, metaraminol bitartrate, metronidazole (with or without sodium bicarbonate), norepinephrine bitartrate, pentobarbital sodium, phenobarbital sodium, phytonadione, polymyxin B sulfate, prochlorperazine edisylate, promethazine HCl, secobarbital sodium, sodium bicarbonate, succinylcholine chloride, vancomycin HCl and verapamil HCl.

The following drugs or solutions are reportedly **incompatible** or only compatible in specific situations with amikacin: aminophylline, amphotericin B, ampicillin sodium, carbenicillin disodium, cefazolin sodium, cephalothin sodium, cephapirin sodium, chlorothiazide sodium, dexamethasone sodium phosphate, erythromycin gluceptate, heparin sodium, methicillin sodium, nitrofurantoin sodium, oxacillin sodium, oxytetracycline HCl, penicillin G potassium, phenytoin sodium, potassium chloride (in dextran 6% in sodium chloride 0.9%; stable with potassium chloride in “standard” solutions), tetracycline HCl, thiopental sodium, vitamin B-complex with C and warfarin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

*In vitro* inactivation of aminoglycoside antibiotics by beta-lactam antibiotics is well documented. While amikacin is less susceptible to this effect, it is usually recommended to avoid mixing these compounds together in the same syringe or IV bag, unless administration occurs promptly. See also the information in the Drug Interaction and Drug/Lab Interaction sections.

**Pharmacology** - Amikacin, like the other aminoglycoside antibiotics, act on susceptible bacteria presumably by irreversibly binding to the 30S ribosomal subunit thereby inhibiting protein synthesis. It is considered to be an bactericidal antibiotic.

Amikacin’s spectrum of activity include coverage against many aerobic gram negative and some aerobic gram positive bacteria, including most species of *E. coli*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Enterobacter*, *Serratia*, and *Shigella*, *Mycoplasma*, and *Staphylococcus*. Several strains of *Pseudomonas aeruginosa*, *Proteus*, and *Serratia* that are resistant to gentamicin will still be killed by amikacin.

Antimicrobial activity of the aminoglycosides are enhanced in an alkaline environment.
The aminoglycoside antibiotics are inactive against fungi, viruses and most anaerobic bacteria.

To Drug Monograph Index  To Ophthalmic Product Index

**Uses/Indications** - While parenteral use is only approved in dogs, amikacin is used clinically to treat serious gram negative infections in most species. It is often used in settings where gentamicin-resistant bacteria are a clinical problem. The inherent toxicity of the aminoglycosides limit their systemic use to serious infections when there is either a documented lack of susceptibility to other less toxic antibiotics or when the clinical situation dictates immediate treatment of a presumed gram negative infection before culture and susceptibility results are reported. Amikacin is also approved for intrauterine infusion in mares.

**Pharmacokinetics** - Amikacin, like the other aminoglycosides is not appreciably absorbed after oral or intrauterine administration, but it is absorbed from topical administration (not skin or urinary bladder) when used in irrigations during surgical procedures. Patients receiving oral aminoglycosides with hemorrhagic or necrotic enteritises may absorb appreciable quantities of the drug. After IM administration to dogs and cats, peak levels occur from 1/2 to 1 hour later. Subcutaneous injection results in slightly delayed peak levels and with more variability than after IM injection. Bioavailability from extravascular injection (IM or SQ) is greater than 90%.

After absorption, aminoglycosides are distributed primarily in the extracellular fluid. They are found in ascitic, pleural, pericardial, peritoneal, synovial and abscess fluids, and high levels are found in sputum, bronchial secretions and bile. Aminoglycosides are minimally protein bound (<20%, streptomycin 35%) to plasma proteins. Aminoglycosides do not readily cross the bloodbrain barrier nor penetrate ocular tissue. CSF levels are unpredictable and range from 0-50% of those found in the serum. Therapeutic levels are found in bone, heart, gallbladder and lung tissues after parenteral dosing. Aminoglycosides tend to accumulate in certain tissues such as the inner ear and kidneys, that may help explain their toxicity. Volumes of distribution have been reported to be 0.15-0.3 L/kg in adult cats and dogs, and 0.26-0.58 L/kg in horses. Volumes of distribution may be significantly larger in neonates and juvenile animals due to their higher extracellular fluid fractions. Aminoglycosides cross the placenta and fetal concentrations range from 15-50% of those found in maternal serum.

Elimination of aminoglycosides after parenteral administration occurs almost entirely by glomerular filtration. The elimination half-lives for amikacin have been reported to be 1.14-2.3 hours in horses, 2.2-2.7 hours in calves, and 0.5-1.5 hours in dogs and cats. Patients with decreased renal function can have significantly prolonged half-lives. In humans with normal renal function, elimination rates can be highly variable with the aminoglycoside antibiotics.

**Contraindications/Precautions/Reproductive Safety** - Aminoglycosides are contraindicated in patients who are hypersensitive to them. Because these drugs are often the only effective agents in severe gram-negative infections there are no other absolute contraindications to their use. However, they should be used with extreme caution in patients with preexisting renal disease with concomitant monitoring and dosage interval adjustments made. Other risk factors for the development of toxicity include age (both neonatal and geriatric patients), fever, sepsis and dehydration.

Because aminoglycosides can cause irreversible ototoxicity, they should be used with caution in “working” dogs (*e.g.,* “seeing-eye”, herding, dogs for the hearing impaired, etc.).

Aminoglycosides should be used with caution in patients with neuromuscular disorders (*e.g.,* myasthenia gravis) due to their neuromuscular blocking activity.

Because aminoglycosides are eliminated primarily through renal mechanisms, they should be used cautiously, preferably with serum monitoring and dosage adjustment in neonatal or geriatric animals.

Aminoglycosides are generally considered contraindicated in rabbits/hares as they adversely affect the GI flora balance in these animals.

To Drug Monograph Index To Ophthalmic Product Index

Aminoglycosides can cross the placenta and while rare, may cause 8th cranial nerve toxicity or nephrotoxicity in fetuses. Because the drug should only be used in serious infections, the benefits of therapy may exceed the potential risks.

**Adverse Effects/Warnings** - The aminoglycosides are infamous for their nephrotoxic and ototoxic effects. The nephrotoxic (tubular necrosis) mechanisms of these drugs are not completely understood, but are probably related to interference with phospholipid metabolism in the lysosomes of proximal renal tubular cells, resulting in leakage of proteolytic enzymes into the cytoplasm. Nephrotoxicity is usually manifested by increases in BUN, creatinine, nonprotein nitrogen in the serum and decreases in urine specific gravity and creatinine clearance. Proteinuria and cells or casts may also be seen in the urine. Nephrotoxicity is usually reversible once the drug is discontinued. While gentamicin may be more nephrotoxic than the other aminoglycosides, the incidences of nephrotoxicity with all of these agents require equal caution and monitoring.

Ototoxicity (8th cranial nerve toxicity) of the aminoglycosides can be manifested by either auditory and/or vestibular symptoms and may be irreversible. Vestibular symptoms are more frequent with streptomycin, gentamicin, or tobramycin. Auditory symptoms are more frequent with amikacin, neomycin, or kanamycin, but either forms can occur with any of the drugs. Cats are apparently very sensitive to the vestibular effects of the aminoglycosides.

The aminoglycosides can also cause neuromuscular blockade, facial edema, pain/inflammation at injection site, peripheral neuropathy and hypersensitivity reactions. Rarely, GI symptoms, hematologic and hepatic effects have been reported.

**Overdosage/Acute Toxicity** - Should an inadvertant overdosage be administered, three treatments have been recommended. Hemodialysis is very effective in reducing serum levels of the drug, but is not a viable option for most veterinary patients. Peritoneal dialysis also will reduce serum levels, but is much less efficacious. Complexation of drug with either carbenicillin or ticarcillin (12-20 g/day in humans) is reportedly nearly as effective as hemodialysis. Since amikacin is less affected by this effect than either tobramycin or gentamicin, it is assumed that reduction in serum levels will also be minimized using this procedure.

**Drug Interactions** - Aminoglycosides should be used with caution with other nephrotoxic, ototoxic, and neurotoxic drugs. These include **amphotericin B**, **other aminoglycosides**, **acyclovir**, **bacitracin** (parenteral use), **cisplatin**, **methoxyflurane**, **polymyxin B**, or **vancomycin**. The concurrent use of aminoglycosides with **cephalosporins** is controversial. Potentially, cephalosporins could cause additive nephrotoxicity when used with aminoglycosides, but this interaction has only been well documented with cephaloridine (no longer marketed) and cephalothin. Concurrent use with loop (**furosemide**, **ethacrynic acid**) or osmotic diuretics (**mannitol**, **urea**) may increase the nephrotoxic or ototoxic potential of the aminoglycosides. Concomitant use with **general anesthetics** or **neuromuscular blocking agents** could potentiate neuromuscular blockade. Synergism against *Pseudomonas aeruginosa* and *enterococci* may occur with beta**-lactam antibiotics** and the aminoglycosides. This effect is apparently not predictable and its clinical usefulness is in question.

**Drug/Laboratory Interactions** - Amikacin **serum concentrations** may be falsely decreased if the patient is also receiving beta-lactam antibiotics and the serum is stored prior analysis. It is recommended that if assay is delayed, samples be frozen and if possible, drawn at times when the beta-lactam antibiotic is at a trough.

**Doses** - Note: There is significant interpatient variability with regards to aminoglycoside pharmacokinetic parameters. To insure therapeutic levels and to minimize the risks for toxicity development, it is recommended to consider monitoring serum levels for this drug.
For small animals, one pair of authors (Aronson and Aucoin 1989) make the following recommendations with regard to minimizing risks of toxicity yet maximizing efficacy:

To Drug Monograph Index To Ophthalmic Product Index

1) Dose according to animal size. The larger the animal, the smaller the dose (on a mg/kg basis).
2) The more risk factors (age, fever, sepsis, renal disease, dehydration) the smaller the dose.
3) In old patients or those suspected of renal disease, increase dosing interval from q8h to q16-24h.
4) Determine serum creatinine prior to therapy and adjust by changes in level even if it remains in "normal range".
5) Monitor urine for changes in sediment (*e.g.,* casts) or concentrating ability. Not very useful in patients with UTI.
6) Therapeutic drug monitoring is recommended when possible.

**Horses**:

For susceptible infections:

a) 6.6 mg/kg IM or IV *tid* (Robinson 1987)
b) For gram negative respiratory infections: 6.6 mg/kg IM or IV q4-6 h; IV use is recommended for bronchopneumonia. (Beech 1987a)
c) In foals: 7.5 mg/kg IV q12h; monitor serum levels if possible. (Caprile and Short 1987)
d) 4.4 - 6.6 mg/kg IV or IM *bid* - *tid*, *tid* if severe infection (serious life-threatening). (Orsini et al. 1985)
e) 4 - 8 mg/kg q8-12h IM (Baggot and Prescott 1987)

For uterine infusion:

a) 2 grams mixed with 200 ml sterile normal saline (0.9% sodium chloride for injection) and aseptically infused into uterus daily for 3 consecutive days. (Package insert; *Amiglyde-V*®—Fort Dodge)

**Elephants:**

a) 6-8 mg/kg IM q 24 h (Lodwick et.al., 1994)
Lodwick,L.J., Dubach,J.M., Phillips,L.G., Brown,C.S., and Jandreski,M.A. 1994. **Pharmacokinetics of amikacin in African elephants (*Loxodonta africana*).** Zoo Wildl.Med. 25:(3):367-375 **Abstract:** Two adult females were given single i.v. injections of 8 mg/kg. Trials using 3 mg/kg and 6 mg/kg i.m. were conducted with three adult females. Serum concentrations of amikacin were measured serially over a 24-49 h period. After i.v. administration of 8 mg/kg, the elimination half-lives (t0.5) were 4.0 and 3.7 h, the volumes of distribution at steady state were 0.21 and 0.18 litres/kg, and total body clearances were 41.8 and 40.8 ml/h/kg. At i.m. doses of 3 and 6 mg/kg, the peak concentrations observed ranged from 4.8 to 8.4 µg/ml and 14.2 to 21.8 µg/ml, respectively. The time at observed peak concentration was between 1 and 3 h, and t0.5 ranged from 3.8 to 5.9 h for the lower dose and from 3.7 to 6.3 h for the higher dose. Following the single dose trials, one elephant was treated with amikacin at a dose of 7 mg/kg i.m. at 24 h intervals for 21 days, and serum amikacin concentrations were determined 2 to 4 times on each of 11 days. Mean (SD) peak serum concentration for this elephant was 19.0±2.8 µg/ml, and mean serum concentration at 24 h (through) was 1.7±0.4 µg/ml. There was indication in this one elephant of a mild, reversible renal tubular insult based on a slight transient elevation in serum creatinine and the presence of casts in the urine. These changes resolved soon after the end of treatment. These preliminary results suggest that amikacin administered at 6-8 mg/kg i.m. once every 24 h would be appropriate for elephants with bacterial infections suspected to be susceptible to amikacin.

**Monitoring Parameters** -

1) Efficacy (cultures, clinical signs and symptoms associated with infection)
2) Renal toxicity; baseline urinalysis, serum creatinine/BUN. Casts in the urine are often the initial sign of impending nephrotoxicity. Frequency of monitoring during therapy is controversial. It can be said that monitoring daily urinalyses early in the course of treatment or daily creatinines once casts are seen or increases are noted in serum creatinine levels are not too frequent .
3) Gross monitoring of vestibular or auditory toxicity is recommended

To Drug Monograph Index To Ophthalmic Product Index

4) Serum levels if possible; see the reference by Aronson and Aucoin in Ettinger (Aronson and Aucoin 1989) for more information.

**Client Information** - With appropriate training, owners may give subcutaneous injections at home, but routine monitoring of therapy for efficacy and toxicity must still be done. Clients should also understand that the potential exists for severe toxicity (nephrotoxicity, ototoxicity) developing from this medication.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**:

Amikacin Sulfate Injection 50 mg (of amikacin base) per ml in 50 ml vials; *Amiglyde-V*® (Fort Dodge); Generic; (Rx) Approved for use in dogs.

Amikacin Sulfate Intrauterine Solution 250 mg (of amikacin base) per ml in 48 ml vials; *Amiglyde-V*® (Fort Dodge); (Rx) Approved for use in horses.

**Human-Approved Products**:

Amikacin Injection 50 mg (of amikacin base) and 250 mg (of amikacin base) per ml; *Amikin*® (Apothecon); Generic (Rx)

## AMINOPHYLLINE / THEOPHYLLINE

**Chemistry** - Xanthine derivatives, aminophylline and theophylline are considered to be respiratory smooth muscle relaxants, but also have other pharmacologic actions. Aminophylline differs from theophylline only by the addition of ethylenediamine to its structure and may have different amounts of molecules of water of hydration. 100 mg of aminophylline (hydrous) contains approximately 79 mg of theophylline (anhydrous) and 100 mg of aminophylline (anhydrous) contains approximately 86 mg theophylline (anhydrous). Conversely, 100 mg of theophylline (anhydrous) is equivalent to 116 mg of aminophylline (anhydrous) and 127 mg aminophylline (hydrous).

Aminophylline occurs as bitter-tasting, white or slightly yellow granules or powder with a slight ammoniacal odor and a $pK_a$ of 5. Aminophylline is soluble in water and insoluble in alcohol.

Theophylline occurs as bitter-tasting, odorless, white, crystalline powder with a melting point between 270-274°C. It is sparingly soluble in alcohol and only slightly soluble in water at a pH of 7, but solubility increases with increasing pH.

**Storage/Stability/Compatibility** - Aminophylline for injection should be stored in single-use containers in which carbon dioxide has been removed. It should also be stored at temperatures below 30°C and protected from freezing and light. Upon exposure to air (carbon dioxide), aminophylline will absorb carbon dioxide, lose ethylenediamine and liberate free theophylline which can precipitate out of solution. Do not inject aminophylline solutions that contain a precipitate or visible crystals.

Aminophylline for injection is reportedly **compatible** when mixed with all commonly used IV solutions, but may be **incompatible** with 10% fructose or invert sugar solutions.
Aminophylline is reportedly **compatible** when mixed with the following drugs: amobarbital sodium, bretylium tosylate, calcium gluconate, chloramphenicol sodium succinate, dexamethasone sodium phosphate, dopamine HCl, erythromycin lactobionate, heparin sodium, hydrocortisone sodium succinate, lidocaine HCl, mephentermine sulfate, methicillin sodium, methyldopate HCl, metronidazole with sodium bicarbonate,

pentobarbital sodium, phenobarbital sodium, potassium chloride, secobarbital sodium, sodium bicarbonate, sodium iodide, terbutaline sulfate, thiopental sodium, and verapamil HCl.

Aminophylline is reportedly **incompatible** (or data conflicts) with the following drugs: amikacin sulfate, ascorbic acid injection, bleomycin sulfate, cephalothin sodium, cephapirin sodium, clindamycin phosphate, codeine phosphate, corticotropin, dimenhydrinate, dobutamine HCl, doxorubicin HCl, epinephrine HCl, erythromycin gluceptate, hydralazine HCl, hydroxyzine HCl, insulin (regular), isoproterenol HCl, levorphanol bitartrate, meperidine HCl, methadone HCl, methylprednisolone sodium succinate, morphine sulfate, nafcillin sodium, norepinephrine bitartrate, oxytetracycline, penicillin G potassium, pentazocine lactate, procaine HCl, prochlorperazine edisylate or mesylate, promazine HCl, promethazine HCl, sulfisoxasole diolamine, tetracycline HCl, vancomycin HCl, and vitamin B complex w/C. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** - The theophyllines competitively inhibit phosphodiesterase, thereby increasing amounts of cyclic AMP which increases the release of endogenous epinephrine. The increased levels of cAMP may also inhibit the release of histamine and slow reacting substance of anaphylaxis (SRS-A). The myocardial and neuromuscular transmission effects that the theophyllines posses may be a result of translocating intracellular ionized calcium.

The theophyllines directly relax smooth muscles in the bronchi and pulmonary vasculature, induce diuresis, increase gastric acid secretion and inhibit uterine contractions. They also have weak chronotropic and inotropic action, stimulate the CNS and can cause respiratory stimulation (centrally-mediated).

**Uses/Indications** - The theophyllines are used primarily for their bronchodilitory effects, often in patients with myocardial failure and/or pulmonary edema.

**Pharmacokinetics** - The pharmacokinetics of theophylline have been studied in several domestic species. After oral administration, the rate of absorption of the theophyllines is limited primarily by the dissolution of the dosage form in the gut. In studies in cats, dogs, and horses, bioavailabilities after oral administration are nearly 100% when non-sustained release products are used. One study in dogs that compared various sustained-release products (Koritz, Neff-Davis, and Munsiff 1986), found bioavailabilities to range from approximately 30 - 76%, depending on the product used.

Theophylline is distributed throughout the extracellular fluids and body tissues. It crosses the placenta and is distributed into milk (70% of serum levels). In dogs, at therapeutic serum levels, only about 7-14% is bound to plasma proteins. The volume of distribution of theophylline for dogs has been reported to be 0.82 L/kg. The volume of distribution in cats is reported to be 0.46 L/kg, and in horses, 0.85 - 1.02 L/kg. Because of the low volumes of distribution and theophylline's low lipid solubility, obese patients should be dosed on a lean body weight basis.

Theophylline is metabolized primarily in the liver (in humans) to 3-methylxanthine, which has weak bronchodilitory activity. Renal clearance contributes only about 10% to the overall plasma clearance of theophylline. The reported elimination half-lives (mean values) in various species are: dogs ≈ 5.7 hours; cats ≈ 7.8 hours, pigs ≈ 11 hours; and horses ≈ 11.9 to 17 hours. In humans, there are very wide interpatient variations in serum half lives and resultant serum levels. It could be expected that similar variability exists in veterinary patients, particularly those with concurrent illnesses.

**Contraindications/Precautions** - The theophyllines are contraindicated in patients who are hypersensitive to any of the xanthines, including theobromine or caffeine. Patients who are hypersensitive to ethylenediamine should not take aminophylline.

To Drug Monograph Index To Ophthalmic Product Index

The theophyllines should be administered with caution in patients with severe cardiac disease, gastric ulcers, hyperthyroidism, renal or hepatic disease, severe hypoxia, or severe hypertension. Because it may cause or worsen preexisting arrhythmias, patients with cardiac arrhythmias should receive theophylline only with caution and enhanced monitoring. Neonatal and geriatric patients may have decreased clearances of theophylline and be more sensitive to its toxic effects. Patients with CHF may have prolonged serum half-lifes of theophylline.

**Adverse Effects/Warnings** - The theophyllines can produce CNS stimulation and gastrointestinal irritation after administration by any route. Most adverse effects are related to the serum level of the drug and may be symptomatic of toxic blood levels. Some mild CNS excitement and GI disturbances are not uncommon when starting therapy and generally resolve with chronic administration in conjunction with monitoring and dosage adjustments.

Dogs and cats can exhibit symptoms of nausea and vomiting, insomnia, increased gastric acid secretion, diarrhea, polyphagia, polydipsia, and polyuria. Side effects in horses are generally dose related and may include: nervousness, excitability (auditory, tactile, and visual), tremors, diaphoresis, tachycardia, and ataxia. Seizures or cardiac dysrhythmias may occur in severe intoxications.

**Overdosage** - Symptoms of toxicity (see above) are usually associated with levels greater than 20 micrograms/ml in humans and become more severe as the serum level exceeds that value. Tachycardias, arrhythmias, and CNS effects (seizures, hyperthermia) are considered to be the most life-threatening aspects of toxicity.

Treatment of theophylline toxicity is basically supportive. The gut should be emptied, charcoal and a cathartic administered after an oral ingestion, using the standardized methods and cautions associated with these practices. Patients suffering from seizures should have an adequate airway maintained and treated with IV diazepam. The patient should be constantly monitored for cardiac arrhythmias and tachycardia. Fluid and electrolytes should be monitored and corrected as necessary. Hyperthermia may be treated with phenothiazines and tachycardia treated with propranolol if either condition is considered life-threatening.

**Drug Interactions** - **Phenobarbital or Phenytoin** may decrease the effect of theophylline by increasing its clearance. Agents which may increase theophylline effects, include **cimetidine, erythromycin, allopurinol, thiabendazole, clindamycin, lincomycin.** Theophylline may decrease the effects of **phenytoin, lithium carbonate, or pancuronium.** Theophylline and beta**-adrenergic blockers (propranolol, etc.)** may antagonize each other's effect. Toxic synergism (arrhythmias) can occur if theophylline is used concurrently with sympathomimetics (especially **ephedrine**) or possibly **isoproterenol**. Theophylline with **halothane** may cause increased incidence of cardiac dysrhythmias. Theophylline with **ketamine** can cause an increased incidence of seizures.

**Laboratory Interactions** - Theophylline can cause falsely elevated values of serum **uric acid** if measured by the Bittner or colorimetric methods. Values are not affected if using the uricase method. Theophylline serum levels can be falsely elevated by **furosemide, phenylbutazone, probenecid, theobromine, caffeine, sulfathiazole, chocolate, or acetominophen** if using a spectrophotometric method of assay.

**Doses** - Note: Theophyllines have a low therapeutic index; determine dosage carefully. Because of aminophylline/theophylline's pharmacokinetic characteristics, it should be dosed on a lean body weight basis in obese patients. Dosage conversions between aminophylline and theophylline can be easily performed by using the information found in the Chemistry section above. Aminophylline causes intense local pain when administered IM and is rarely used or recommended via this route.

**Horses**:

Note:Intravenous aminophylline should be diluted in at least 100 ml of $D_5W$ or normal saline and administered slowly (not > than 25 mg/min).

To Drug Monograph Index To Ophthalmic Product Index

a) 4 - 7 mg/kg PO *tid* (Robinson 1987)
b) 10 - 15 mg/kg PO theophylline *bid*; or up to 15 mg/kg given slowly IV. Monitor serum levels; do not exceed 15 micrograms/ml. (Beech 1987)
c) Loading dose of 12 mg/kg PO (theophylline), followed by maintenance doses of 5 mg/kg PO *bid* (Button, Errecalde, and Mulders 1985)

**Monitoring Parameters** -

1) Therapeutic efficacy and symptoms of toxicity
2) Serum levels at steady state.The therapeutic serum levels of theophylline in humans are generally described to be between 10 - 20 micrograms/ml. Therapeutic and toxic levels have not been firmly established in veterinary species, so the human values should be used as a guide (Note: Some recommend not exceeding 15 micrograms/ml in horses).

**Client Information** - Give dosage as prescribed by veterinarian to maximize the drug's benefit.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**: The listing below is a sampling of products and sizes available; consult specialized references for a more complete listing.

Aminophylline Tablets 100 mg (78.9 mg theophylline), 200 mg (158 mg theophylline); (Rx); 225 mg (178 mg theophylline) controlled release tablets (Rx)

Aminophylline Injection 25 mg/ml (19.7 mg/ml theophylline) in 10 ml, & 20 ml vials amps and vials); (Rx)

Aminophylline oral liquid 105 mg/5 ml (90 mg theophylline); generic; (Rx)

Aminophylline suppositories 250mg (197.5 mg theophylline) & 500 mg (395 mg theophylline); (Rx)

Theophylline Time Released Capsules and Tablets; 50 mg, 60 mg, 65 mg, 75 mg, 100 mg, 125 mg, 130 mg, 200 mg, 250 mg, 260 mg, & 300 mg, 450 mg, 500 mg, 600 mg are available (Note: Different products have different claimed release rates which may or may not correspond to actual times in veterinary patients; (Rx)

Theophylline Tablets and Capsules: 100 mg, 125 mg, 200 mg, 250 mg, 300 mg (Rx)

Theophylline Syrup; 80 mg/15 ml (26.7 mg/5 ml), 150 mg/15 ml (50 mg/5 ml) (Rx)

Theophylline Elixir/Solution 80 mg/15 ml (26.7 mg/5 ml) (Rx)

## AMINOPROPAZINE FUMARATE

**Chemistry** - A phenothiazine derivative, aminopropazine fumarate occurs as a white powder with a melting point of 168°C. One gram is soluble in 11 ml of water; 200 ml of alcohol. 118 mg of the fumarate salt is equivalent to 100 mg of the base.

**Storage/Stability/Compatibility** - Protect from light and excessive heat.
The injectable solution is colorless to light amber in color. Should marked deviation occur from the above color, do not use.

**Pharmacology** - Reportedly, aminopropazine causes smooth muscle relaxation by direct action on the muscle rather than a neurotropic mechanism. It primarily reduces muscle contractions in the GI, GU, and respiratory systems. It has little CNS effect (sedation) and does not affect biliary secretion, or exhibit histaminic, sympatholytic or ganglionic blocking actions.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - Aminopropazine is indicated for: “reducing excessive smooth muscle contractions, such as occur in urethral spasms associated with urolithiasis in cats and dogs, and colic spasms in horses.” (Package insert, *Jenotone*®—Coopers)

**Pharmacokinetics** - No pharmacokinetic information was located for this agent.

**Contraindications/Precautions** - The intravenous route is not recommended in patients with history of severe cardiac, renal or hepatic disease and the oral form of the drug should be used very cautiously in these patients.

The parenteral preparation should be given IV slowly or into a large muscle mass IM (avoid IM injections near nerves). Avoid extravascular injections and do not give subcutaneously. See Drug Interactions for more information.

**Adverse Effects/Warnings** - Mild tranquilization or hyperexcitability are listed as possible side effects by the manufacturer.

**Overdosage** - No specific information was located for this agent. It is suggested that standard overdose procedures be followed, including emptying the gut after oral ingestion if possible and treating supportively. Do not give epinephrine for hypotension (use either phenylephrine or norepinephrine if sympathomimetic pressor agents are indicated).

**Drug Interactions** - Aminopropazine should not be given within one month of worming with an **organophosphate agent** as their effects may be potentiated. **Other CNS depressant agents (barbiturates, narcotics, anesthetics**, etc.) may cause additive CNS depression if used with aminopropazine. **Quinidine** when given with phenothiazines may cause additive cardiac depression. **Antidiarrheal mixtures** (*e.g.,* Kaolin/pectin, bismuth subsalicylate mixtures) and **antacids** may cause reduced GI absorption of oral phenothiazines. Increased blood levels of both drugs may occur if **propranolol** is administered with phenothiazines. Phenothiazines block alpha-adrenergic receptors, if **epinephrine** is then given, unopposed beta activity causing vasodilation and increased cardiac rate can occur. The manufacturer lists epinephrine as being contraindicated with aminopropazine. **Phenytoin** metabolism may be decreased if given concurrently with phenothiazines. **Procaine** activity may be enhanced by phenothiazines.

**Doses** - The parenteral preparation should be given slowly IV or IM into a large muscle mass.
**Horses**:

a) 0.55 mg/kg (1 ml/100 lbs body weight) IM or IV q12h (Package insert; *Jenotone*® - Coopers)

**Monitoring Parameters** - Dependent on reason for use; monitor for efficacy.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Aminopropazine Fumarate for Injection 25 mg/ml, (as base) 50 ml vials; *Jenotone*® (Schering-Plough); (Rx)

Aminopropazine Fumarate Tablets 25 mg, bottles of 100; *Jenotone*® (Schering-Plough); (Rx)

**Human-Approved Products**: None

To Drug Monograph Index To Ophthalmic Product Index

Aminopropazine Fumarate may also be known as proquamezine fumarate, tetrameprozine fumarate, or *Myspamol*® (May & Baker, U.K.).

## AMMONIUM CHLORIDE

**Chemistry** - An acid-forming salt, ammonium chloride occurs as colorless crystals or as white, fine or course, crystalline powder. It is somewhat hygroscopic, and has a cool, saline taste. When dissolved in water, the temperature of the solution is decreased. One gram is soluble in approximately 3 ml of water at room temperature; 1.4 ml at 100°C. One gram is soluble in approximately 100 ml of alcohol.

One gram of ammonium chloride contains 18.7 mEq of ammonium and chloride ions. The commercially available concentrate for injection (26.75%) contains 5 mEq of each ion per ml and contains disodium edetate as a stabilizing agent. The pH of the concentrate for injection is approximately 5. Synonyms for ammonium chloride include muriate of ammonia and sal ammoniac.

**Storage/Stability/Compatibility** - Ammonium chloride for injection should be stored at room temperature; avoid freezing. At low temperatures, crystallization may occur; it may be resolubolized by warming to room temperature in a water bath.

Ammonium chloride should not be titrated with strong oxidizing agents (*e.g.,* potassium chlorate) as explosive compounds may result.

Ammonium chloride is reported to be physically **compatible** with all commonly used IV replacement fluids and potassium chloride.

It is **incompatible** with: codeine phosphate, dimenhydrinate, methadone HCl, nitrofurantoin sodium, sulfisoxazole diolamine, and warfarin sodium. It is also reportedly incompatible with alkalis and their hydroxides.

**Pharmacology** - The acidification properties of ammonium chloride are caused by its dissociation into chloride and ammonium ions *in vivo*. The ammonium cation is converted by the liver to urea with the release of a hydrogen ion. This ion combines with bicarbonate to form water and carbon dioxide. In the extracellular fluid, chloride ions combine with fixed bases and decrease the alkaline reserves in the body. The net effects are decreased serum bicarbonate levels and a decrease in blood and urine pH.

The excess chloride ions presented to the kidney, are not completely reabsorbed by the tubules and are excreted with cations (principally sodium) and water. This diuretic effect is usually compensated for by the kidneys after a few days of therapy.

**Uses/Indications -** The veterinary indications for ammonium chloride are as a urinary acidifying agent to help prevent and dissolve certain types of uroliths (*e.g.,* struvite), to enhance renal excretion of some types of toxins (*e.g.,* strontium) or drugs (*e.g.,* quinidine), or to enhance the efficacy of certain antimicrobials (*e.g.,* chlortetracycline, methenamine mandelate, nitrofurantoin, oxytetracycline, penicillin G or tetracycline) when treating urinary tract infections. Ammonium chloride has also been used intravenously for the rapid correction of metabolic alkalosis.

**Pharmacokinetics** - No information was located on the pharmacokinetics of this agent in veterinary species. In humans, ammonium chloride is rapidly absorbed from the GI.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions** - Ammonium chloride is contraindicated in patients with severe hepatic disease as ammonia may accumulate and cause toxicity. In general, ammonium chloride should not be administered to uremic patients as it may intensify the metabolic acidosis already existing in some of these patients. Ammonium chloride should not be used alone in patients with severe renal insufficiency and metabolic alkalosis secondary to vomiting hydrochloric acid as sodium depletion can occur. In these cases, sodium chloride repletion with or without ammonium chloride administration should be performed to correct both sodium and chloride deficits. Ammonium chloride is contraindicated in patients with urate calculi or respiratory acidosis and high total $CO_2$ and buffer base. Ammonium chloride cannot alone correct hypochloremia with secondary metabolic alkalosis due to intracellular potassium chloride depletion. Potassium chloride must be administered to these patients.

Do not administer subcutaneously, rectally or intraperitoneally. Use ammonium chloride with caution in patients with pulmonary insufficiency or cardiac edema.

**Adverse Effects/Warnings** - Development of metabolic acidosis (sometimes severe) can occur unless adequate monitoring is performed. When used intravenously, pain at the injection site can develop; slow administration lessens this effect. Gastric irritation, nausea and vomiting can be associated with oral dosing of the drug.

**Overdosage** - Symptoms of overdosage may include: nausea, vomiting, excessive thirst, hyperventilation, bradycardias or other arrhythmias, and progressive CNS depression. Profound acidosis and hypokalemia may be noted on laboratory results.

Treatment should consist of correcting the acidosis by administering sodium bicarbonate or sodium acetate intravenously. Hypokalemia should be treated by using a suitable oral (if possible) potassium product. Intense acid-base and electrolyte monitoring should be performed on an ongoing basis until the patient is stable.

**Drug Interactions** - Urine acidification may increase the renal excretion of **quinidine**.
The **aminoglycosides** (*e.g.,* gentamicin) and **erythromycin** are more effective in an alkaline medium; urine acidification may diminish these drugs effectiveness in treating bacterial urinary tract infections.

**Doses** -
**Horses**:

a) 4 - 15 grams PO (Swinyard 1975)

**Monitoring Parameters** -

1) Urine pH (Urine pH's of ≤6.5 have been recommended as goals of therapy)
2) Blood pH if there are symptoms of toxicity or treating metabolic alkalosis
3) Serum electrolytes, if using chronically or if treating metabolic acidosis
4) Prior to IV use it is recommended that the carbon dioxide combining power of the patient's serum be measured to insure that serious acidosis is prevented

**Client Information** - Contact veterinarian if animal exhibits signs of nausea, vomiting, excessive thirst, hyperventilation or progressive lethargy.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None, but ammonium chloride is available in combination with methionine in the commercially available products: *MEq*® (Vet-A-Mix) and *Uroeze*® (Daniels).

**Human-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Ammonium Chloride Tablets 500 mg (enteric-coated & plain) Note: enteric-coated tablets may be excreted unchanged into the feces and are not recommended.
Generic; (OTC)

Ammonium Chloride Concentrate for Injection 26.75% (5 mEq/ml) in 20 ml (100 mEq) vials. Must be diluted before infusion.
Generically labeled (Abbott); (Rx).
Preparation of solution for IV administration: Dilute 1 or 2 vials (100 - 200 mEq) in either 500 or 1000 ml of sodium chloride 0.9% for Injection. Do not administer at a rate greater than 5 ml/min (human adult).

**Veterinary-Approved Products**:

Ammonium Chloride Tablets: 357 mg (6.7 mEq/tablet) 50 & 500 tabs/bottle *MEq-AC* ® (Vet-A-Mix); 200 mg tablets in btls of 100 and 500 *Uroeze-200*® (Daniels) Approved for use in cats and dogs. (Rx)

Ammonium Chloride Granules:*MEq-5AC*® (Vet-A-Mix) Each teasponnsful (3.35 grams) contains 535 mg (10mEq) in 4 oz and 1 lb bottles; *Uroeze*® (Daniels) each 1/4 teaspoonsful contains 200 mg of ammonium chloride. Approved for cats and dogs (Rx)

**Human-Approved Products**:

Ammonium Chloride Tablets 500 mg, 486 mg (Enteric-Coated); (OTC)

Ammonium Chloride Concentrate for Injection 26.75% (5 mEq/ml) in 20 ml (100 mEq) vials. Must be diluted before infusion. Generically labeled (Abbott); (Rx).

## AMOXICILLIN

For general information on the penicillins, including adverse effects, contraindications, overdosage, drug interactions and monitoring parameters, refer to the monograph: Penicillins, General Information.

**Chemistry** - An aminopenicillin, amoxicillin is commercially available as the trihydrate. It occurs as a practically odorless, white, crystalline powder that is sparingly soluble in water. Amoxicillin differs structurally from ampicillin only by having an additional hydroxyl group on the phenyl ring. Amoxicillin may also be known as amoxycillin, *p*-hydroxyampicillin, or BRL 2333.

**Storage/Stability/Compatibility** - Amoxicillin capsules, tablets, and powder for oral suspension should be stored at room temperature (15-30°C) in tight containers. After reconstitution, the oral suspension should preferably be refrigerated (refrigeration not absolutely necessary) and any unused product discarded after 14 days. After reconstitution, the injectable veterinary suspension is stable for 3 months at room temperature and 12 months when refrigerated.

**Pharmacology/Uses/Indications** - Although there may be some slight differences in activity against certain organisms, amoxicillin generally shares the same spectrum of activity and uses as ampicillin. Because it is better absorbed orally (in non-ruminants), higher serum levels may be attained than with ampicillin. Refer to the ampicillin monograph or the general penicillin statement for more information.

**Pharmacokinetics (specific)** - Amoxicillin trihydrate is relatively stable in the presence of gastric acid. After oral administration, it is about 74-92% absorbed in humans and animals (monogastric). Food will decrease the rate, but not the extent of oral absorption and many clinicians suggest giving the drug with food, particularly if there is concomitant associated GI distress. Amoxicillin serum levels will generally be 1.5-3 times greater than those of ampicillin after equivalent oral doses.

To Drug Monograph Index  To Ophthalmic Product Index

After absorption the volume of distribution for amoxicillin is approximately 0.3 L/kg in humans and 0.2 L/kg in dogs. The drug is widely distributed to many tissues, including liver, lungs, prostate (human), muscle, bile, and ascitic, pleural and synovial fluids. Amoxicillin will cross into the CSF when meninges are inflamed in concentrations that may range from 10-60% of those found in serum. Very low levels of the drug are found in the aqueous humor, and low levels found in tears, sweat and saliva. Amoxicillin crosses the placenta, but it is thought to be relatively safe to use during pregnancy. It is approximately 17-20% bound to human plasma proteins, primarily albumin. Protein binding in dogs is approximately 13%. Milk levels of amoxicillin are considered to be low.

Amoxicillin is eliminated primarily through renal mechanisms, principally by tubular secretion, but some of the drug is metabolized by hydrolysis to penicilloic acids (inactive) and then excreted in the urine. Elimination half-lives of amoxicillin have been reported as 45-90 minutes in dogs and cats, and 90 minutes in cattle. Clearance is reportedly 1.9 ml/kg/min in dogs.

**Doses** -

**Horses**:

For susceptible infections:

a) For respiratory infections: 20 - 30 mg/kg PO q6h (Beech 1987b)
b) Amoxicillin trihydrate: 20 mg/kg q12h IM. (Upson 1988)

**Elephants:**

a) 11 mg/kg IM q 24 h Schmidt,M.J. 1978. **Penicillin and amoxicillin in elephants: A study comparing dose regimens administered with serum levels achieved in healthy elephants**. Journal of Zoo Animal Medicine 9:(4):127-136 **Abstract:** Several dose regimens of an aqueous suspension of benzathine penicillin G combined with procaine penicillin G, and an aqueous suspension of amoxicillin were administered to five healthy adult female Asian elephants. Blood samples were drawn and serum levels of the drugs were measured after each dose was administered. Based upon serum levels, suggestions are made for therapeutic dose regimens for clinical use of both penicillin and amoxicillin in elephants, based on comparable data available for other large domestic animals.

**Client Information** - The oral suspension should preferably be refrigerated, but refrigeration is not absolutely necessary; any unused oral suspension should be discarded after 14 days. Amoxicillin may be administered orally without regard to feeding status. If the animal develops gastrointestinal symptoms (*e.g.,* vomiting, anorexia), giving with food may be of benefit.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Amoxicillin Oral Tablets 50 mg, 100 mg, 150 mg, 200 mg, , 400 mg; *Amoxi-Tabs*® (Pfizer), (Rx) Approved for use in dogs and cats. *Robamox-V*® (Fort Dodge); (Rx) Approved for use in dogs only.

Amoxicillin Powder for Oral Suspension 50 mg/ml (after reconstitution) in 15 ml or 30 ml bottles; *Amoxi-Drop*® (Pfizer); (Rx); Approved for use in dogs and cats.*Robamox-V*® (Fort Dodge) (Rx); Approved for use in dogs.

Amoxicillin Oral Bolus 400 mg; *Amoxi-Bol*® (Pfizer); (Rx) Approved for use in non-ruminating calves, including veal calves. Slaughter withdrawal = 20 days.

Amoxicillin Powder for Suspension (Injection): 3 gram vial (Dogs, Cats) and 25 g vial (non-lactating cattle); *Amoxi-Inject*® (Pfizer); (Rx) Approved for use in dogs and cats (3 g vial), Slaughter withdrawal (cattle) = 25 days. Milk withdrawal = 96 hours.

Amoxicillin Intramammary Infusion 62.5 mg/syringe in 10 ml syringes; *Amoxi-Mast*® (Pfizer); (Rx) Approved for use in lactating dairy cattle. Slaughter withdrawal = 12 days; Milk withdrawal = 60 hours.

To Drug Monograph Index To Ophthalmic Product Index

**Human-Approved Products**:

Amoxicillin Tablets (chewable) 125 mg (As trihydrate) & 250 mg (as trihydrate);*Amoxil* ®(SK Beecham); generic, (Rx)

Amoxicillin Capsules (as trihydrate) 250 mg, 500 mg; *Polymox*® (Apothecon); *Wymox*® (Wyeth-Ayerst); generic (Rx)

Amoxicillin (as the trihydrate) Powder for Oral Suspension 50 mg/ml (as trihydrate) (in 15 and 30 ml bottles), 125 mg/5 ml (as trihydrate) and 250 mg/5 ml (as trihydrate) 80 ml, 100 ml, 150 ml, and 200 ml bottles. *(Rx)*

## AMPHOTERICIN B

**Chemistry** - A polyene macrolide antifungal agent produced by *Streptomyces nodosus*, amphotericin B occurs as a yellow to orange, odorless or practically odorless powder. It is insoluble in water and anhydrous alcohol. Amphotericin B is amphoteric and can form salts in acidic or basic media. These salts are more water soluble, but possess less antifungal activity than the parent compound. Each mg of amphotericin B must contain not less than 750 micrograms of anhydrous drug. Amphotericin A may be found as a contaminant in concentrations not exceeding 5%. The commercially available powder for injection contains sodium desoxycholate as a solubolizing agent.

**Storage/Stability/Compatibility** - Vials of amphotericin B powder for injection should be stored in the refrigerator (2-8°C), protected from light and moisture. Reconstitution of the powder must be done with sterile water for injection (no preservatives—see directions for preparation in the Dosage Form section below).

After reconstitution, if protected from light, the solution is stable for 24 hours at room temperature and for 1 week if kept refrigerated. After diluting with $D_5W$ (must have pH >4.3) for IV use, the manufacturer recommends protecting the solution during administration. Additional studies however, have shown that potency remains largely unaffected if the solution is exposed to light for 8-24 hours.

Amphotericin B is reportedly **compatible** with the following solutions and drugs: $D_5W$, $D_5W$ in sodium chloride 0.2%, heparin sodium, heparin sodium with hydrocortisone sodium phosphate, hydrocortisone sodium phosphate/succinate and sodium bicarbonate.

Amphotericin B is reportedly **incompatible** with the following solutions and drugs: normal saline, lactated Ringer's, $D_5$-normal saline, $D_5$-lactated Ringer's, amino acids 4.25% - dextrose 25%, amikacin, calcium chloride/gluconate, carbenicillin disodium, chlorpromazine HCl, cimetidine HCl, diphenhydramine HCl, dopamine HCl, edetate calcium disodium (Ca EDTA), gentamicin sulfate, kanamycin sulfate, lidocaine HCl, metaraminol bitartrate, methyldopate HCl, nitrofurantoin sodium, oxytetracycline HCl, penicillin G potassium/sodium, polymyxin B sulfate, potassium chloride, prochlorperazine mesylate, streptomycin sulfate, tetracycline HCl, and verapamil HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Amphotericin B is usually fungistatic, but can be fungicidal against some organisms depending on drug concentration. It acts by binding to sterols (primarily ergosterol) in the cell membrane and alters the permeability of the membrane allowing intracellular potassium and other cellular constituents to "leak out". Because bacteria and rickettisia do not contain sterols, amphotericin B has no activity against those organisms. Mammalian cell membranes do contain sterols (primarily cholesterol) and the drug's

toxicity may be a result of a similar mechanism of action, although amphotericin binds less strongly to cholesterol than ergosterol.

Amphotericin B has *in vitro* activity against a variety of fungal organisms, including *Blastomyces*, *Aspergillus*, *Paracoccidiodes*, *Coccidiodes*, *Histoplasma*, *Cryptococcus*, *Mucor*, and *Sporothrix*. *Zygomycetes* is reportedly variable in its response to amphotericin. Aspergillosis in dogs and cats does not tend to respond satisfactorily to amphotericin therapy. Additionally, amphotericin B has *in vivo* activity against some protozoa species, including *Leishmania spp.* and *Naegleria spp.*.

It has been reported that amphotericin B has immunoadjuvant properties, but further work is necessary to confirm the clinical significance of this effect.

**Uses/Indications** - Because the potential exists for severe toxicity associated with this drug, it should only be used for progressive, potentially fatal fungal infections. Veterinary use of amphotericin has been primarily in dogs, but other species have been treated successfully. For further information on fungal diseases treated, see the Pharmacology and Dosage sections.

**Pharmacokinetics** - Pharmacokinetic data on veterinary species is apparently unavailable. In humans (and presumably animals), amphotericin B is poorly absorbed from the GI tract and must be given parenterally to achieve sufficient concentrations to treat systemic fungal infections. After intravenous injection, the drug reportedly penetrates well into most tissues, but does not penetrate well into the pancreas, muscle, bone, aqueous humor, pleural, pericardial, synovial, or peritoneal fluids. The drug does enter the pleural cavity and joints when inflamed. CSF levels are approximately 3% of those found in the serum. Approximately 90-95% of amphotericin in the vascular compartment is bound to serum proteins.

The metabolic pathways of amphotericin are not known, but it exhibits biphasic elimination. An initial serum half-life of 24-48 hours, and a longer terminal half-life of about 15 days have been described. Seven weeks after therapy has stopped, amphotericin can still be detected in the urine. Approximately 2-5% of the drug is recovered in the urine in unchanged (biologically active) form.

**Contraindications/Precautions/Reproductive Safety** - Amphotericin is contraindicated in patients who are hypersensitive to it, unless the infection is life-threatening and no other alternative therapies are available.

Because of the serious nature of the diseases treated with systemic amphotericin, it is not contraindicated in patients with renal disease, but should be used cautiously with adequate monitoring.

The safety of amphotericin B during pregnancy has not been established, but there are apparently no reports of teratogenicity associated with the drug. The risks of therapy should be weighed against the potential benefits.

**Adverse Effects/Warnings** - Amphotericin B is notorious for its nephrotoxic effects and most canine patients will show some degree of renal toxicity after receiving the drug. The proposed mechanism of nephrotoxicity is via renal vasoconstriction with a subsequent reduction in glomerular filtration rate. The drug may also directly act as a toxin to renal epithelial cells. Renal damage may be more common and severe in patients who receive higher individual doses.

The patient's renal function should be aggressively monitored during therapy. A pre-treatment serum creatinine, BUN (serum urea nitrogen/SUN), serum electrolytes (including magnesium if possible), total plasma protein (TPP), packed cell volume (PCV), body weight, and urinalysis should be done prior to starting therapy. BUN, creatinine, PCV, TPP, and body weight are rechecked before each dose is administered. Electrolytes and urinalysis should be monitored at least weekly during the course of treatment. Several different recommendations regarding stopping therapy when a certain BUN is reached

have been made. Most clinicians recommend stopping, at least temporarily, amphotericin treatment if the BUN reaches 30-40 mg/dl, serum creatinine >3 mg/dl or if other symptoms of systemic toxicity develop such as serious depression or vomiting.

At least two regimens have been used in the attempt to reduce nephrotoxicity in dogs treated with amphotericin. Mannitol (12.5 grams or 0.5 - 1 g/kg) given concurrently with amphotericin B (slow IV infusion) to dogs may reduce nephrotoxicity, but may also reduce the efficacy of the therapy, particularly in blastomycosis. Mannitol treatment also increases the total cost of therapy by approximately two times.

Sodium loading prior to treating has garnered considerable support in recent years. A tubuloglomerular feedback mechanism that induces vasoconstriction and decreased GFR has been postulated for amphotericin B toxicity; increased sodium load at the glomerulus may help prevent that feedback. One clinician (Foil 1986), uses 5 ml/kg of normal saline given in two portions, before and after amphotericin B dosing and states that is has been "... helpful in averting renal insufficiency... ".

Cats are apparently more sensitive to the nephrotoxic aspects of amphotericin B, and many clinicians recommend using reduced dosages in this species (see Dosage section).
Other adverse effects that have been reported with amphotericin B include anorexia, vomiting, hypokalemia, phlebitis and fever.

**Overdosage/Acute Toxicity** - No case reports were located regarding acute intravenous overdose of amphotericin B. Because of the toxicity of the drug, dosage calculations and solution preparation procedures should be double-checked. If an accidental overdose is administered, renal toxicity may be minimized by administering fluids and mannitol as outlined above in the Adverse effects section.

**Drug Interactions** - Since the renal effects of other nephrotoxic drugs may be additive with amphotericin B, avoid, if possible the concurrent or sequential use of **aminoglycosides (gentamicin, amikacin, kanamycin, etc), polymyxin B, colistin, cisplatin, methoxyflurane or vancomycin**. Amphotericin B therapy may cause potassium-loss or hypokalemia. This may be of particular concern in patients receiving **cardiac glycosides (***e.g.,* **digoxin), skeletal muscle relaxants, or other potassium-depleting drugs (***e.g.,* **thiazide or loop diuretics). Corticosteroids** may exacerbate the potassium-losing effects of amphotericin. Synergy between amphotericin and **flucytosine** can occur against strains of *Cryptococcus* and *Candida spp.*, but increased flucytosine toxicity may also occur. Synergism with **rifampin** (against *Candida*, *Histoplasma*, and *Aspergillus*) and **tetracycline** (*Cryptococcus* and *Candida spp.*) have also been reported against fungi susceptible to amphotericin B. Antagonism of activity has been suggested between amphotericin B and **miconazole**. Further studies need to confirm this, however. Reconstitution with **saline solutions** or with **solutions containing a preservative** may cause precipitation.

**Doses** -
Note: Some clinicians have recommended administering a 1 mg test dose (less in small dogs or cats) IV over anywhere from 20 minutes to 4 hours and monitoring pulse, respiration rates, temperature, and if possible, blood pressure. If a febrile reaction occurs some clinicians recommend adding a glucocorticoid to the IV infusion solution or using an antipyretic prior to treating, but these practices are controversial.

A recently published study (Rubin et al. 1989) demonstrated less renal impairment and systemic adverse effects in dogs who received amphotericin B IV slowly over 5 hours in 1 L of $D_5W$ than in dogs who received the drug IV in 25 ml of $D_5W$ over 3 minutes.

**Horses**:

For treatment of susceptible systemic fungal infections:

a) 0.3 mg/kg in $D_5W$ IV (Robinson 1987)

To Drug Monograph Index To Ophthalmic Product Index

b) For phycomycoses and pulmonary mycoses: After reconstitution (see below) transfer appropriate amount of drug to 1L of D5W and administer using a 16 g needle IV at a rate of 1 L/hr. Dosage schedule follows:

Day 1: 0.3 mg/kg IV
Day 2: 0.45 mg/kg IV
Day 3: 0.6 mg/kg IV; then every other day for 3 days per week (MWF or TTHSa) until clinical signs of improvement or toxicity takes place. It toxicity occurs, a dose may be skipped, dose reduced or dosage interval lengthened. Administration may extend from 10-80 days. (Brumbaugh 1987)

**Monitoring Parameters** - Also see Adverse effects section

1) BUN and serum creatinine every other day while dosage is being increased, and at least weekly thereafter during therapy
2) Serum electrolytes (sodium, potassium and magnesium) weekly
3) Liver function tests weekly
4) CBC weekly
5) Urinalysis weekly
6) TPP at least weekly
7) Animal's weight

**Client Information** - Clients should be informed of the potential seriousness of toxic effects that can occur with amphotericin B therapy, as well as the costs associated with therapy.

**Dosage Forms/Preparations/FDA Approval Status/Solution Preparation** -

**Veterinary-Approved Products**: None

Amphotericin B for Powder for Injection 50 mg/vial (as deoxycholate); *Fungizone*® *Intravenous* (Bristol-Myers Squibb); (Rx);*Amphotericin B*® (Pharma-Tek); (Rx)

Directions for reconstitution/administration: Using strict aseptic technique and a 20 gauge or larger needle, rapidly inject 10 ml of sterile water for injection (without a bacteriostatic agent) directly into the lyophylized cake; immediately shake well until solution is clear. A 5 mg/ml colloidal solution results. Further dilute (1:50) for administration to a concentration of 0.1 mg/ml with 5% dextrose in water (pH >4.2). An in-line filter may be used during administration, but must have a pore diameter >1 micron.

Amphotericin B Suspension for Injection: 100 mg/20 ml (as lipid complex) in single use vials with 5 micron filter needles:*Abelcet*® (Liposome Co.) (Rx)

Amphotericin B for Powder for Injection 50 mg/vial (as cholesteryl) in 20 ml vials with 52.8 mg sodium cholesteryl sulfate & 100 mg (as cholesteryl) in 50 ml vials with 52.8 mg sodium cholesteryl sulfate; *Amphotec*® (Sequus Pharmaceuticals) (Rx)

Amphotericin B for Powder for Injection 50 mg/vial (as liposomal) in single use vials with 5 micron filter needles:*AmBisome*® (Fujisawa) (Rx)

Amphotericin B is also available in a topical formulation.

**AMPICILLIN**
**AMPICILLIN SODIUM**
**AMPICILLIN TRIHYDRATE**

. Back to Index

To Drug Monograph Index To Ophthalmic Product Index

For general information on the penicillins, including adverse effects, contraindications, overdosage, drug interactions and monitoring parameters, refer to the monograph: Penicillins, General Information.

**Chemistry** - A semi-synthetic aminopenicillin, ampicillin anhydrous and trihydrate occur as practically odorless, white, crystalline powders that are slightly soluble in water. At usual temperatures (<42°C), ampicillin anhydrous is more soluble in water than is the trihydrate (13 mg/ml vs. 6 mg/ml at 20°C). Ampicillin anhydrous or trihydrate oral suspensions have a pH of 5-7.5 after reconstitution with water.

Ampicillin sodium occurs as an odorless or practically odorless, white to off-white, crystalline hygroscopic powder. It is very soluble in water or other aqueous solutions. After reconstitution, ampicillin sodium has a pH of 8-10 at a concentration of 10 mg/ml. Commercially available ampicillin sodium for injection has approximately 3 mEq of sodium per gram of ampicillin.

Potency of the ampicillin salts are expressed in terms of ampicillin anhydrous. Ampicillin may also be known as aminobenzylpenicillin, AY-6108, or BRL 1341.

**Storage/Stability/Compatibility** - Ampicillin anhydrous or trihydrate capsules and powder for oral suspension should be stored at room temperature (15-30°C). After reconstitution, the oral suspension is stable for 14 days if refrigerated (2-8°C) and is stable for 7 days when kept at room temperature.

Ampicillin trihydrate for injection (*Polyflex*®) is stable for 12 months if refrigerated (2-8°C) and is stable for 3 months when kept at room temperature.

Ampicillin sodium for injection is relatively unstable after reconstitution and should generally be used within 1 hour of reconstitution. As the concentration of the drug in solution increases, the stability of the drug decreases. Dextrose may also speed the destruction of the drug by acting as a catalyst in the hydrolysis of ampicillin.

While most sources recommend using solutions of ampicillin sodium immediately, studies have demonstrated that at concentrations of 30 mg/ml, ampicillin sodium solutions are stable in sterile water for injection or 0.9% sodium chloride for up to 48 hours (72 hours if concentrations are 20 mg/ml or less) if kept at 4°C. Solutions with a concentration of 30 mg/ml or less have also been shown to be stable for up to 24 hours in solutions of lactated Ringer's solution if kept at 4°C. Solutions of 20 mg/ml or less are reportedly stable for up to 4 hours in $D_5W$ if refrigerated.

Ampicillin sodium is reportedly **compatible** with the following additives (see the above paragraph for more information): heparin sodium, chloramphenicol sodium succinate, procaine HCl and verapamil HCl.

Ampicillin sodium is reportedly **incompatible** with the following additives: amikacin sulfate, chlorpromazine HCl, dopamine HCl, erythromycin lactobionate, gentamicin HCl, hydralazine HCl, hydrocortisone sodium succinate, kanamycin sulfate, lincomycin HCl, oxytetracycline HCl, polymyxin B sulfate, prochlorperazine edisylate, sodium bicarbonate and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Ampicillin and the other aminopenicillins have increased activity against many strains of gram negative aerobes not covered by either the natural penicillins or penicillinase-resistant penicillins, including some strains of *E. coli, Klebsiella* and *Haemophilus*. Like the natural penicillins they are susceptible to inactivation by beta-lactamase-producing bacteria (*e.g., Staph aureus*). Although not as active as the natural penicillins, they do have activity against many anaerobic bacteria, including *Clostridial* organisms. Organisms that are generally not susceptible include *Pseudomonas aeruginosa*, *Serratia*,

Indole-positive *Proteus* (*Proteus mirabilis* is susceptible), *Enterobacter*, *Citrobacter*, and *Acinetobacter*. The aminopenicillins also are inactive against *Rickettsia*, mycobacteria, fungi, *Mycoplasma*, and viruses.

**Uses/Indications** - In dogs and cats, ampicillin is not as well absorbed after oral administration as is amoxicillin and its oral use has largely been supplanted by amoxicillin. It is used commonly in parenteral dosage forms when an aminopenicillin is indicated in all species.

**Pharmacokinetics (specific)** - Ampicillin anhydrous and trihydrate is relatively stable in the presence of gastric acid. After oral administration, it is about 30-55% absorbed in humans (empty stomach) and animals (monogastric). Food will decrease the rate and extent of oral absorption.

When administered parenterally (IM, SQ) the trihydrate salt will achieve serum levels of approximately 1/2 of those of a comparable dose of the sodium salt. The trihydrate parenteral dosage form should not be used where higher MIC's are required for treating systemic infections.

After absorption the volume of distribution for ampicillin is approximately 0.3 L/kg in humans and dogs, and 0.167 L/kg in cats. The drug is widely distributed to many tissues, including liver, lungs, prostate (human), muscle, bile, and ascitic, pleural and synovial fluids. Ampicillin will cross into the CSF when meninges are inflamed in concentrations that may range from 10-60% of those found in serum. Very low levels of the drug are found in the aqueous humor and low levels are found in tears, sweat and saliva. Ampicillin crosses the placenta, but is thought to be relatively safe to use during pregnancy. Ampicillin is approximately 20% bound to plasma proteins, primarily albumin. Milk levels of ampicillin are considered to be low.

Ampicillin is eliminated primarily through renal mechanisms, principally by tubular secretion, but some of the drug is metabolized by hydrolysis to penicilloic acids (inactive) and then excreted in the urine. Elimination half-lives of ampicillin have been reported as 45-80 minutes in dogs and cats, and 60 minutes in swine.

**Doses** -
**Horses**:

For susceptible infections:

a) Ampicillin sodium: 10 - 50 mg/kg IV or IM *tid*

Ampicillin trihydrate: 5 - 20 mg/kg IM *bid* (Robinson 1987)

b) Ampicillin sodium: 11 - 15 mg/IM or IV *tid-qid* (Beech 1987a)

c) Foals: Ampicillin sodium 20 mg/kg IV q6-8h (dose extrapolated from adult horses; use longer dosage interval in premature foals or those less than 7 days of age) (Caprile and Short 1987)

d) Ampicillin trihydrate: 11 mg/kg IM q6h

Ampicillin sodium: 22 mg/kg IM q12h (Upson 1988)

e) Ampicillin sodium 22 mg/kg IM q6-12h or 25 - 100 mg/kg IV q6h.

Ampicillin trihydrate: 11 - 22 mg/kg IM q12h (Brumbaugh 1987)

**Elephants:**

a) 8 mg/kg PO BID-TID for susceptible staphylcoccal and streptococcal pathogens. This dose may be effective against sensitive strains of Pasteurella multocida (MIC = 0.05 µg /ml), but is not likely to be effective against Salmonella spp. (MIC = 50 µg /ml). Rosin,E., Schultz-Darken,N., Perry,B., and Teare,J.A. 1993. **Pharmacokinetics of ampicillin administered orally in Asian elephants (*Elephas maximus*)**. Journal of Zoo and Wildlife Medicine 24:(4):515-518 **Abstract:** The purpose of this study was to determine the pharmacokinetics of ampicillin in Asian elephants (*Elephas maximus*) and to relate this information to the in vitro activity of ampicillin against two pathogens isolated from one elephant. A single oral dose of ampicillin trihydrate (8 mg/kg) was given to three elephants; body weights were estimated. Capsules containing the drug were hidden in oranges that were offered to the elephants, and ingestion was complete. The ampicillin minimum inhibitory concentration (MIC) for a streptococcal and staphylococcal elephant isolate was 0.06 µg /ml. Mean peak serum ampicillin concentration (0.86 µg /ml) was reached 90 min after administration of the drug. The mean area under the concentration-time curve (AUC) was 208.6 ± 106.4 µg

To Drug Monograph Index To Ophthalmic Product Index

x min/ml. The mean terminal half-life was 53.7 ± 8.9 min. Ampicillin concentrations in serum remained above MIC for longer than 8 hr.

**Client Information** - Unless otherwise instructed by the veterinarian, this drug should be given orally on an empty stomach, at least 1 hour before feeding or 2 hours after. Keep oral suspension in the refrigerator and discard any unused suspension after 14 days. If stored at room temperature, discard unused suspension after 7 days.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Ampicillin Trihydrate Injection Powder for Suspension 10 g & 25 g (of ampicillin) vials.

*Polyflex*® (Fort Dodge); (Rx) Approved for use in dogs, cats, and cattle. Withdrawal times (cattle; do not treat for more than 7 days): Milk = 48 hours; Slaughter = 6 days.

Ampicillin Sodium for Injection 1 gram & 3 gram vials (of ampicillin)

*Amp-Equine*® (Pfizer); (Rx) Approved for use in horses not intended for food.

**Human-Approved Products**:

Ampicillin Sodium Powder for Injection Vials 125 mg, 250 mg, 500 mg, 1 g, 2 g, 10 g; 500 mg, 1 g, and 2 gram piggyback units; *Omnipen-N*® (Wyeth-Ayerst) (Rx);*Polycillin-N*® (Apothecon) (Rx);*Totacillin-N*® (SK-Beecham) (Rx); generic (Rx)

Ampicillin Capsules (as either trihydrate or anhydrous) 250 mg, 500 mg; Many tradenames and generics; (Rx)

Ampicillin (as the trihydrate) Powder for Oral Suspension 25 mg/ml, 50 mg/ ml, 100 mg/ml in 20 ml, 80 ml, 100 ml, 150 ml, and 200 ml bottles; Many tradenames; (Rx)

Also available in fixed dose combinations with:

Probenecid: Powder for Oral Suspension: 3.5 g ampicillin (as trihydrate) & 1g probenecid/probenecid (oral): *Polycillin-PRB*® (Apothecon); *Probampacin*®, generic (Rx)

Sulbactam Sodium (injection): 1.5 g (1 g ampicillin sodium/.05 g sulbactam sodium) & 3 g (2 g ampicillin sodium/1 g sulbactam sodium);*Unasyn*® (Roerig) (Rx)

Amprolium Hydrochloride.

**Chemistry** - A structural analogue of thiamine (vitamin $B_1$), amprolium hydrochloride occurs as a white or almost white, odorless or nearly odorless powder. One gram is soluble in 2 ml of water and is slightly soluble in alcohol.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, amprolium products should be stored at room temperature (15-30°C).

**Pharmacology** - By mimicking its structure, amprolium competitively inhibits thiamine utilization by the parasite. Prolonged high dosages can cause thiamine deficiency in the host and excessive thiamine in the diet can reduce or reverse the anticoccidial activity of the drug.

Amprolium reportedly acts primarily upon the first generation schizont in the cells of the intestinal wall, preventing differentiation of the metrozoites. It may also suppress the sexual stages and sporulation of the oocysts.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - Amprolium has good activity against *Eimeria tenella, E. acervulina* in poultry and can be used as a therapeutic agent for these organisms. It only has marginal activity or weak activity against *E. maxima*, *E. mivati*, *E. necatrix*, or *E. brunetti*. It is often used in combination with other agents (*e.g.,* ethopabate) to improve control against those organisms.

In cattle, amprolium has approval for the treatment and prevention of *E. bovis* and *E. zurnii* in cattle and calves. Amprolium has been used in dogs, swine, sheep, and goats for the control of coccidiosis, although there are no approved products in the U.S.A. for these species.

**Pharmacokinetics** - No information was located for this agent.

**Contraindications/Precautions/Reproductive Safety** - Not recommended to be used for over 12 days in puppies.

**Adverse Effects/Warnings** - In dogs, neural disturbances, depression, anorexia, and diarrhea have been reported but are rare and are probably dose-related. See Overdosage section below for treatment recommendations.

**Overdosage/Acute Toxicity** - Amprolium has induced polioencephalomalacia (PEM) in sheep when administered at 880 mg/kg PO for 4-6 weeks and at 1 gram/kg for 3-5 weeks. Erythrocyte production in lambs receiving these high dosages of amprolium also ceased.

It is reported that overdoses of amprolium will produce neurologic symptoms in dogs. Treatment should consist of stopping amprolium therapy and administering parenteral thiamine (1 - 10 mg/day IM or IV).

**Drug Interactions** - Exogenously administered **thiamine** in high doses may reverse or reduce the efficacy of amprolium.

**Doses** -
**Dogs**:

For coccidiosis:

a) 100 - 200 mg/kg PO in food or water for 7-10 days. (Morgan 1988), (Kirk 1989), (Greene 1984)
b) Prophylaxis: 30 ml of 9.6% solution in one gallon (3.8 L) of drinking water or (not both) 1.25 grams of 20% powder in food to feed 4 pups daily. Give as sole source of food or water for 7 days prior to shipping. Bitches may be given medicated water (as above) as the sole source of water for 10 days prior to whelping. (USPC 1989)
c) Prophylaxis: 0.075% solution as drinking water (Matz 1995)

**Cattle**:

For coccidiosis:

a) Treatment: 10 mg/kg PO for 5 days; 5 mg/kg for 21 days for prophylaxis. (Todd, Dipietro, and Guterbock 1986)

**Monitoring Parameters** -

1) Clinical efficacy

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Amprolium 1.25% Medicated Crumbles for Top Dressing in 50 lb bags.; *Corid® 1.25% Crumbles* (MSD-AgVet); (OTC) Approved for use in calves. Slaughter withdrawal = 24 hours.

To Drug Monograph Index To Ophthalmic Product Index

Amprolium 9.6% (96 mg/ml) Oral Solution; *Corid® 9.6% Oral Solution* (MSD-AgVet); (OTC) Approved for use in calves. Slaughter withdrawal = 24 hours

Amprolium 20 % Soluble Powder; *Corid® 20% Soluble Powder* (MSD-AgVet); (OTC) Approved for use in calves. Slaughter withdrawal = 24 hours

There are many combination products (medicated feeds, feed additives) containing amprolium with other therapeutic agents. These products are approved for chickens (broilers only) and/or turkeys. There are some products containing amprolium alone for use in laying hens.

**Human-Approved Products**: None

Antacids, Oral

**Pharmacology** - Oral antacids used in veterinary medicine are generally relatively non-absorbable salts of aluminum, calcium or magnesium. Up to 20% of an oral dose of magnesium can be absorbed, however. Antacids decrease HCl concentrations in the GI. One gram of these compounds generally neutralize 20-35 mEq of acid (*in vitro*). Although the pH of the gastric fluid can rarely be brought to near-neutral conditions, at a pH of 3.3, 99% of all gastric acid is neutralized, thereby reducing gastric acid back-diffusion through the gastric mucosa and reducing the amount of acid presented to the duodenum. Pepsin proteolytic activity is also reduced by raising the pH and can be minimized if the pH of the gastric contents can be increased to >4.

**Uses/Indications** - Antacids have been used in veterinary medicine for the adjunctive treatment of esophagitis, gastric hyperacidity, peptic ulcer and gastritis. Because of difficulty in administration and the frequent dosing that is often required, and with the advent of the histamine-2 blocking agents (cimetidine, ranitidine, *et al*) and/or sucralfate, antacids have largely been relegated to adjunctive roles in therapy for these indications in foals and small animals. They still remain important in reducing hyperphosphatemia in patients with renal failure.

In ruminants, magnesium hydroxide is used to increase rumen pH and as a laxative in the treatment of rumen overload syndrome (*aka* acute rumen engorgement, rumen acidosis, grain overload, engorgement toxemia, rumen impaction).

**Contraindications/Precautions** - Magnesium-containing antacids are contraindicated in patients with renal disease. Some products have significant quantities of sodium or potassium and should be used cautiously in patients who should have these electrolytes restricted in their diet. Aluminum-containing antacids may inhibit gastric emptying; use cautiously in patients with gastric outlet obstruction.

**Adverse Effects/Warnings** - In monogastric animals, the most common side effects of antacid therapy are constipation with aluminum- and calcium-containing antacids, and diarrhea or frequent loose stools with magnesium containing antacids. Many products contain both aluminum and magnesium salts in the attempt to balance the constipating and laxative actions of the other.

If the patient is receiving a low phosphate diet, hypophosphatemia can develop if the patient chronically receives aluminum antacids. Magnesium-containing antacids can cause hypermagnesemia in patients with severe renal insufficiency.

If administering calcium carbonate in high doses or chronically, significant quantities of calcium can be absorbed from the gut resulting in hypercalcemia in susceptible patients. Calcium carbonate has also been implicated in causing a gastric acid rebound phenomena. Patients with significant renal impairment or dehydration and electrolyte imbalance can develop the milk-alkali syndrome. If the patient is receiving a low

phosphate diet, hypophosphatemia can develop if the patient chronically receives calcium carbonate antacids.

In ruminants, alkalinization of the rumen may enhance the absorption ofammonia, histamine or other basic compounds.

**Overdosage** - See the Adverse Effects section above. If necessary, GI and electrolyte imbalances that can occur with chronic or acute overdose should be treated symptomatically.

**Drug Interactions** - By altering GI transit time, stomach pH, or by chelation, all orally administered non-absorbable antacids can affect the rate and potentially the extent of absorption of other drugs. The reader is referred to specific references (see bibliography) for more information on the clinical significance and the individual salt(s) that have been implicated in the listing below. As a general guideline, it is best not to give antacids within 1-2 hours of other oral medications. Orally administered **tetracycline** products can be chelated and prevented from being absorbed by antacids. Antacids should not be administered within 1-2 hours of tetracycline dosing. Antacids can decrease the amount absorbed or the pharmacologic effect of: **chlordiazepoxide, captopril, chloroquine, cimetidine, corticosteroids, digoxin, iron salts, indomethicin, isoniazid** (aluminum antacids only), **ketoconazole, nitrofurantoin, pancrelipase, penicillamine, phenothiazines, phenytoin, ranitidine, and valproic acid**.

Increased absorption or pharmacologic effect may occur when antacids are administered with the following: **dicumarol, flecainide, quinidine, and sympathomimetics**. **Aspirin** absorption and also excretion can be enhanced when concomitantly administered with antacids. Use of **sodium polystyrene sulfonate** (*Kayexalate*®) with antacids, may decrease the potassium lowering effectiveness of the drug and in patients in renal failure may cause metabolic alkalosis.

**Doses** -
**Cattle**:

For rumen overload syndrome:

a) For adult animals: Up to 1 gm/kg (MgOH) mixed in 2-3 gallons of warm water and given PO per tube. May repeat (use smaller doses) at 6-12 hour intervals. If the rumen has been evacuated, do not exceed 225 grams initially. Dehydration and systemic acidosis must be concomitantly corrected.
Calves: As above but use 1/8th-1/4th the amount. (Wass et al. 1986a)

As an antacid:

a) Aluminum hydroxide: 30 grams;
Calcium carbonate: 60 - 360 grams (Jenkins 1988)

**Horses**:

For adjunctive gastroduodenal ulcer therapy in foals:

a) Aluminum/magnesium hydroxide suspension: 15 ml 4 times a day (Clark and Becht 1987)

**Monitoring Parameters** - Monitoring parameters are dependent upon the indication for the product and the salt used. Patients receiving high dose or chronic therapy should be monitored for electrolyte imbalances outlined above.

**Client Information/FDA Approval Status** - Oral antacids are available without prescription (OTC). Most products are labeled for use in humans. There are veterinary approved products for use in food animals.

**Dosage Forms/Preparations**-

**Veterinary-Approved Products**:
Magnesium Hydroxide

To Drug Monograph Index To Ophthalmic Product Index

Oral Boluses 27 grams of magnesium hydroxide, ginger 200 mg, capsicum 100 mg, methyl salicylate 56 mg

*Magnalax*® (OTC)

Oral Powder, each pound of powder contains: 350 grams of magnesium hydroxide, ginger 2.6 grams, capsicum 1.3 grams, methyl salicylate 56 mg

*Rulax II*® (OTC)

**Human-Approved Products**: The following is a list of some antacids available, it is not meant to be all inclusive.

Aluminum Carbonate, basic

Capsules, equivalent to dried aluminum hydroxide gel 608 mg or aluminum hydroxide 500 mg

*Basalgel*® (Wyeth)

Suspension, equivalent to aluminum hydroxide 400 mg/5ml

*Basalgel*® (Wyeth)

Aluminum Hydroxide

Capsules,

475 mg; *Alu-Cap*® (Riker)

500 mg; *Dialume*® (Armour)

Suspension

320 mg/5 ml; *Amphogel*® (Wyeth-Ayerst)

400 mg/5 ml; *Aluminum Hydroxide Gel*® (Roxane)

600 mg/5 ml; *Alternagel*® (Stuart), *Aluminum Hydroxide Concentrated*® (Roxane)

Magnesium Hydroxide

Powder

Oral Suspension (Milk of Magnesia) ≈77.5 mg/gram

Aluminum Hydroxide and Magnesium Hydroxide

Suspension (Note: there are too many products and concentrations to list in this reference; a representative product is *Maalox*® Suspension (Rorer) which contains 225 mg aluminum hydroxide and 200 mg magnesium hydroxide per 5 ml.)

Other dosage forms that are available commercially include: tablets, chewable tablets, and aerosol foam suspension.

Antivenin

**NOTE: The location of antivenins for rare species and the telephone numbers for envenomation experts is available from the Arizona Poison Control Center: (602) 626-6061.**

**Chemistry** - These products are concentrated serum globulins obtained from horses immunized with the venoms of several types of snakes. They are provided as refined, lyophilized product with a suitable diluent.

**Storage/Stability/Compatibility** - Do not store above 98°F (37°C). The coral snake product should be stored in the refrigerator.

**Pharmacology** - Antivenins act by neutralizing the venoms (complex proteins) in patients via passive immunization of globulins obtained from horses immunized with the venom.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - These products are indicated for the treatment of envenomation from most venomous snakes found in North America (not Sonoran or Arizona Coral Snake) causing serious systemic toxicity or potential serious toxicity in domestic animals. There is a fair amount of controversy with regard to these products' use in domestic animals. The risks of administration (*e.g.*, anaphylaxis—see below) may outweigh their potential benefits in certain circumstances. However, these agents can be life-saving when given early in select situations. Many factors contribute to the potential for toxicity (victim's size and general health, bite site(s), number of bites, age, species and size of snake, etc.).

Antivenin can be very expensive. One 10 ml vial of Crotalidae antivenin approved for use in dogs costs approximately $100. The coral snake product (for human use) cost is >$150 per vial and to treat a coral snake bite may require 5 or more vials. Because of the high cost, not being returnable for credit, and potential adverse effects, veterinary practices need to assess all factors before stocking and using these products.

**Contraindications/Precautions** - The coral snake antivenin will not neutralize *M euryxanthus* (Sonoran or Arizona Coral Snake) venom. Because there is a risk of anaphylaxis occurring secondary to the horse serum, many recommend perform sensitivity testing before administration.

**Adverse Effects/Warnings** - The most significant adverse effect associated with the use of these products is anaphylaxis secondary to the equine serum source of this product. A 1:10 dilution of the antivenin given intracutaneously at a dose of 0.02 - 0.03 ml may be useful as a test for hypersensitivity. Wheal formation and erythema indicate a positive reaction and are generally seen within 30 minutes of administration. A negative response does not insure that anaphylaxis will not occur however.

**Drug Interactions** - Although reducing excessive movement and other supportive therapy are important parts of treating envenomation, drugs that can mask the clinical signs associated with the venom (*e.g.*, analgesics and sedatives) should be used with discretion. It has also been stated that antihistamines (Controversial: See equine dose below) and tranquilizers are contraindicated as they may potentiate the venom.

**Doses** -

**Horses**:

Crotilidae Antivenin: Use only if necessary to treat systemic effects otherwise avoid use. Administer 1-2 vials slowly IV diluted in 250-500 ml saline or lactated Ringer's. Administer antihistamines; corticosteroids are contraindicated.

Coral Snake (not Sonoran or Arizona variety): As above; same cautions. May be used with Crotilidae antivenin. (Bailey and Garland 1992b)

**Species Not Identified**:

Crotilidae Antivenin: 1 - 10 vials IV depending on severity of symptoms, time after envenomation, size of animal and snake (5-10 vials usually needed for Eastern Diamondback Rattlesnake envenomation). Best effects when given within 4 hours of envenomation.

Coral Snake: 1 - 10 vials IV given as soon as possible after envenomation. (Thompson 1992)

**Client Information** - Clients must be made aware of the potential for anaphylaxis as well as the expenses associated with treatment and associated monitoring and hospitalization.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**:

Antivenin (*Crotalidae*) Polyvalent Equine Origin single dose vial lyophilized; 10 ml diluent. *Antivenin*® (Fort Dodge); (Rx) Approved for use in dogs.

To Drug Monograph Index To Ophthalmic Product Index

**Human-Approved Products**:

Antivenin (*Crotalidae*) Polyvalent Equine Origin single dose vial lyophilized; 10 ml diluent. Includes 1 ml of normal horse serum diluted 1:10 for use for sensitivity testing; *Antivenin (Crotalidae) Polyvalent* (Wyeth-Ayerst); (Rx)

Antivenin (*Micrucus fulvius*) single dose vial lyophilized; 10 ml diluent; *Antivenin (Micrucus fulvius)* (Wyeth-Ayerst); (Rx)

## ASCORBIC ACID
## VITAMIN C

**Chemistry** - A water soluble vitamin, ascorbic acid occurs as white to slightly yellow crystal or powder. It is freely soluble in water and sparingly soluble in alcohol. The parenteral solution has a pH of 5.5-7.

**Storage/Stability/Compatibility** - Protect from air and light. Ascorbic acid will slowly darken upon light exposure. Slight discoloration does not affect potency. Because with time ascorbic acid will decompose with the production of $CO_2$, open ampules and multidose vials carefully. To reduce the potential for excessive pressure within ampules, store in refrigerator and open while still cold.

Ascorbic acid for injection is **compatible** with most commonly used IV solutions, but is **incompatible** with many drugs when mixed in syringes or IV bags. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography) for more specific information.

**Pharmacology** - Exogenously supplied ascorbic acid is a dietary requirement in some exotic species (including rainbow trout, Coho salmon), guinea pigs, and in primates. The other domestic species are able to synthesize *in vivo* enough Vitamin C to meet their nutritional needs. Vitamin C is used for tissue repair and collagen formation. It may also be involved with some oxidation-reduction reactions, and is involved with the metabolism of many substances (iron, folic acid, norepinephrine, histamine, phenylalanine, tyrosine, some drug enzyme systems). Vitamin C is believed to play a role in protein, lipid and carnitine synthesis, maintaining blood vessel integrity, and immune function.

**Uses/Indications** - Ascorbic acid may be used as a urinary acidifier, but its efficacy is in question. Sodium ascorbate does not acidify the urine. It is also used to treat copper-induced hepatopathy in dogs.

**Pharmacokinetics** - Vitamin C is generally well absorbed in the jejunum (human data) after oral administration, but absorption may be reduced with high doses as an active process is involved with absorption. Ascorbic acid is widely distributed and only about 25% is bound to plasma proteins. Vitamin C is biotransformed in the liver. When the body is saturated with vitamin C and the blood concentrations exceed the renal threshold the drug is more readily excreted unchanged into the urine.

**Contraindications/Precautions/Reproductive Safety** - Vitamin C (high doses) should be used with caution in patients with diabetes mellitus due to the laboratory interactions (see below) or in patients susceptible to urolithiasis. The reproductive safety of vitamin C has not been studied, but it is generally considered to be safe at moderate dosages.

**Adverse Effects/Warnings** - At usual doses vitamin C has minimal adverse effects. Occasionally GI disturbances have been noted in humans. At higher dosages, there is an increased potential for urate, oxalate or cystine stone formation, particularly in susceptible patients.

To Drug Monograph Index  To Ophthalmic Product Index

**Overdosage/Acute Toxicity** - Very large doses may result in diarrhea and potentially urolithiasis. Generally, treatment should consist of monitoring and keeping the patient well hydrated.

**Drug Interactions** - Large doses causing acidification of urine may increase the renal excretion of some drugs (*e.g.*, **mexiletine, quinidine)** and reduce the efficacy of some antimicrobials in the urine (*e.g.*, **aminoglycosides, erythromycin**). Vitamin C may be synergistic with **deferoxamine** in removing iron, but may in fact, lead to increased iron tissue toxicity especially in cardiac muscle. It should be used with caution, particularly in patients with preexisting cardiac disease.

**Laboratory Considerations -** Large doses may cause false-negative **urine glucose** values. False-negative results may occur if vitamin C is administered within 48-72 hours of an amine-dependent **stool occult blood** test. Vitamin C may decrease **serum bilirubin** concentrations.

**Doses** -
**Horses**:

For replacement therapy after stress (*e.g.* strenuous exercise): 20 grams PO daily (Ferrante and Kronfeld 1992)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Parenteral Injection 250 mg/ml in 100 and 250 ml vials; Generic (Rx or OTC depending on labeling)

**Human-Approved Products**:

As ascorbic acid or sodium ascorbate: Oral tablets 25 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg; chewable tablets: 60 mg, 100 mg, 250 mg, 500 mg,; (various); (OTC)

Oral extended release capsules and tablets 500 mg; 1000 mg, 1500 mg; (various); (OTC)

Crystals/Powder: 4 g/tsp (in 100 & 500g); 5 g/tsp (in 180 g); (OTC)

Liquid/Syrup: 35 mg/0.6ml, 100 mg/ml, (OTC)

Parenteral Injection 250 mg/ml in 2 ml ampules and 30 & 50 ml multidose vials; various & generic; (Rx)

## ASPIRIN

**Chemistry** - Aspirin, sometimes known as acetylsalicylic acid or ASA, is the salicylate ester of acetic acid. The compound occurs as a white, crystalline powder or tabular or needle-like crystals. It is a weak acid with a $pK_a$ of 3.5. Aspirin is slightly soluble in water and is freely soluble in alcohol. Each gram of aspirin contains approximately 760 mg of salicylate.

**Storage/Stability/Compatibility** - Aspirin tablets should be stored in tight, moisture resistant containers. Do not use products past the expiration date or if a strong vinegar-like odor is noted emitting from the bottle.

Aspirin is stable in dry air, but readily hydrolyzes to acetate and salicylate when exposed to water or moist air. It will then exude a strong vinegar-like odor. The addition of heat will speed the rate of hydrolysis. In aqueous solutions, aspirin is most stable at pH's of 2-3 and least stable at pH's below 2 or greater than 8. Should an aqueous solution be desirable as a dosage form, the commercial product *Alka-Seltzer*® will remain stable for 10 hours at room temperature in solution.

**Pharmacology** - Aspirin inhibits cyclooxygenase (prostaglandin synthetase) thereby reducing the synthesis of prostaglandins and thromboxanes. These effects are thought to be how aspirin produces analgesia,

antipyrexia, and reduces platelet aggregation and inflammation. Most cells can synthesize new cyclooxygenase, but platelets cannot. Therefore, aspirin causes an irreversible effect on platelet aggregation. Aspirin has been shown to decrease the clinical symptoms of experimentally induced anaphylaxis in calves and ponies.

**Pharmacokinetics** - Aspirin is rapidly absorbed from the stomach and proximal small intestine in monogastric animals. The rate of absorption is dependent upon factors as stomach content, gastric emptying times, tablet disintegration rates and gastric pH. Absorption is slow from the GI tract in cattle, but approximately 70% of an oral dose will be absorbed.

During absorption, aspirin is partially hydrolyzed to salicylic acid where it is distributed widely throughout the body. Highest levels may be found in the liver, heart, lungs, renal cortex, and plasma. The amount of plasma protein binding is variable, depending on species, serum salicylate and albumin concentrations. At lower salicylate concentrations, it is 90% protein bound, but only 70% protein bound at higher concentrations. Salicylate is excreted into milk, but levels appear to be very low. Salicylate will cross the placenta, and fetal levels may actually exceed those found in the mother.

Salicylate is metabolized in the liver primarily by conjugation with glycine and glucuronic acid via glucuronyl transferase. Because cats are deficient in this enzymatic pathway, they have prolonged half-lives and are susceptible to accumulating the drug. Minor metabolites formed include gentisic acid and 2,3-dihydroxybenzoic acid, and 2,3,5-trihydroxybenzoic acid. Gentisic acid appears to be the only active metabolite, but because of its small concentrations, it appears to play an insignificant role therapeutically. The rate of metabolism is determined by both first order kinetics and dose-dependent kinetics depending on which metabolic pathway is looked at. Generally, steady-state serum levels will increase to levels higher (proportionally) than expected with dosage increases. These effects have not been well studied in domestic animals, however.

Salicylate and its metabolites are rapidly excreted by the kidneys by both filtration and renal tubular secretion. Significant tubular reabsorption occurs which is highly pH dependent. Salicylate excretion can be significantly increased by raising urine pH to 5-8. Salicylate and metabolites may be removed using peritoneal dialysis or more rapidly using hemodialysis.

**Uses/Indications** - Aspirin is used in all species for its analgesic and antipyretic effects. It is the one nonsteroidal anti-inflammatory agent that is relatively safe to use in both dogs and cats. Besides its analgesic, anti-inflammatory and antipyretic effects, aspirin is used therapeutically for its effects on platelet aggregation in the treatment of DIC and pulmonary artery disease secondary to heartworm infestation in dogs. It is also used in cats with cardiomyopathy.

**Contraindications/Precautions** - Aspirin is contraindicated in patients demonstrating previous hypersensitivity reactions to it. It is also contraindicated in patients with bleeding ulcers. It is relatively contraindicated in patients with hemorrhagic disorders, asthma, or renal insufficiency.

Because aspirin is highly protein bound to plasma albumin, patients with hypoalbuminemia may require lower dosages to prevent symptoms of toxicity. Aspirin should be used cautiously, with enhanced monitoring, in patients with severe hepatic failure or diminished renal function. Because of its effects on platelets, aspirin therapy should be halted, if possible, one week prior to surgical procedures. Aspirin has been shown to delay parturition and therefore should be avoided during the last stages of pregnancy.

Aspirin must be used cautiously in cats because of their inability to rapidly metabolize and excrete salicylates. Symptoms of toxicity may occur if dosed recklessly or without stringent monitoring. Aspirin should be used cautiously in neonatal animals; adult doses may lead to toxicity.

To Drug Monograph Index To Ophthalmic Product Index

**Adverse Effects/Warnings** - The most common adverse effect of aspirin at therapeutic doses is gastric or intestinal irritation with varying degrees of occult GI blood loss occurring. The resultant irritation may result in vomiting and/or anorexia. Severe blood loss may result in a secondary anemia or hypoproteinemia. In dogs, plain uncoated aspirin may be more irritating to the gastric mucosa than either buffered aspirin or enteric coated tablets. Hypersensitivity reactions have been reported in dogs, although they are thought to occur rarely.

Salicylates are possible teratogens and their use should be avoided during pregnancy, particularly during the later stages.

**Overdosage** - Symptoms of acute overdosage in dogs and cats include: depression, vomiting (may be blood tinged), anorexia, hyperthermia, and increased respiratory rate. Initially, a respiratory alkalosis occurs with a compensatory hyperventilation response. A profound metabolic acidosis follows. If treatment is not provided, muscular weakness, pulmonary and cerebral edema, hypernatremia, hypokalemia, ataxia and seizures, may all develop with eventual coma and death.

Treatment of acute overdosage initially consists of emptying the gut if ingestion has occurred within 12 hours, giving activated charcoal and an oral cathartic, placing an intravenous line, beginning fluids and drawing appropriate lab work (*e.g.,* blood gases). Some clinicians suggest performing gastric lavage with a 3-5% solution of sodium bicarbonate to delay the absorption of aspirin. A reasonable choice for an intravenous solution to correct dehydration would be dextrose 5% in water. Acidosis treatment and forced alkaline diuresis with sodium bicarbonate should be performed for serious ingestions. Diuresis may be enhanced by the administration of mannitol (1-2 gm/kg/hr). Seizures may be controlled with IV diazepam. Treatment of hypoprothrombinemia may be attempted by using phytonadione (2.5 mg/kg divided q8-12h) and ascorbic acid (25 mg parenterally), but ascorbic acid may negate some of the urinary alkalinization effects of bicarbonate. Peritoneal dialysis or exchange transfusions may be attempted in very severe ingestions when heroic measures are desired.

**Drug Interactions** - Drugs that alkalinize the urine (*e.g.,* **acetazolamide, sodium bicarbonate**) significantly increase the renal excretion of salicylates. Because carbonic anhydrase inhibitors (*e.g.,* acetazolamide, dichlorphenamide) may cause systemic acidosis and increase CNS levels of salicylates, toxicity may occur. Urinary acidifying drugs (**methionine, ammonium chloride, ascorbic acid**) will decrease the urinary excretion of salicylates. **Furosemide** may compete with the renal excretion of aspirin and delay its excretion. This may cause symptoms of toxicity in animals receiving high aspirin doses. **Phenobarbital** may increase the rate of metabolism of aspirin by inducing hepatic enzymes. **Corticosteroids** may increase the clearance of salicylates and decrease serum levels. Increased chances of developing GI ulceration exist if administering aspirin with **corticosteroids** or **phenylbutazone or other non-steroidal agents** concurrently.
Aspirin may increase the risks of bleeding associated with **heparin** or **oral anticoagulant** therapy. At usual doses, aspirin may antagonize the uricosuric effects of **probenicid** or **sulfinpyrazone**. Aspirin may inhibit the diuretic activity of **spironolactone**. Aspirin may displace highly protein bound drugs from plasma proteins thus increasing free drug levels and pharmacologic effect. The following drugs may be affected by this mechanism (clinical significance is unknown, but increased monitoring should be performed if adding aspirin): **methotrexate, valproic acid, phenytoin, oral anticoagulants, penicillins**, and **sulfonamides**. The antacids in buffered aspirin may chelate **tetracycline** products if given simultaneously, space doses apart by at least one hour. In dogs, aspirin has been demonstrated to increase the plasma levels of **digoxin** by decreasing the clearance of the drug. Some clinicians feel that aspirin should not be given concomitantly with **aminoglycoside antibiotics** because of an increased likelihood of nephrotoxicity developing. The actual clinical significance of this interaction is not entirely clear, and the risk versus benefits should be weighed when contemplating therapy.

To Drug Monograph Index To Ophthalmic Product Index

**Laboratory Test Interference** - At high doses, aspirin may cause false-positive results for **urinary glucose** if using the cupric sulfate method (*Clinitest*® , Benedict's solution) and false-negative results if using the glucose oxidase method (*Clinistix*® or *Tes-Tape*® ).

**Urinary ketones** measured by the ferric chloride method (Gerhardt) may be affected if salicylates are in the urine (reddish-color produced). **5-HIAA** determinations by the fluorometric method may be interfered by salicylates in the urine. Falsely elevated **VMA** (vanillylmandelic acid) may be seen with most methods used if salicylates are in the urine. Falsely lowered **VMA** levels may be seen if using the Pisano method. Urinary excretion of **xylose** may be decreased if aspirin is given concurrently. Falsely elevated **serum uric acid** values may be measured if using colorimetric methods.

**Doses** -
**Horses**:

For analgesia:

a) Mature Horses: two to four 240 grain boluses PO;
Foals: one to two 240 grain boluses, allow animals to drink water after administration. (Label directions - Vedco Brand)
b) 25 mg/kg PO q12h initially, then 10 mg/kg once daily (Jenkins 1987)
c) 15 - 100 mg/kg PO once daily (Robinson 1987)

**Monitoring Parameters** -

1) Analgesic effect &/or antipyrexic effect
2) Bleeding times if indicated
3) PCV & stool guiaic tests if indicated

**Client Information** - Contact veterinarian if symptoms of GI bleeding or distress occur (black, tarry feces; anorexia or vomiting, etc).

Because aspirin is a very old drug, formal approvals from the FDA for its use in animals have not been required (so-called "grandfather" drug). There is no listed meat or milk withdrawal times listed for food-producing animals, but because there are salicylate-sensitive people, in the interest of public health this author suggests a minimum of 1 day withdrawal time for either milk or meat.

**Dosage Forms/Preparations** - Note: Many dosage forms and brand names are commercially available; the following is an abbreviated list of some products that have been used for veterinary indications:

Aspirin, Tablets, Children's; 65 mg (1 grain) and 81 mg (1.25 grains) in bottles of 36, 100, & 1000 tabs (Note: some varieties are chewable; orange flavor)

Aspirin, Tablets; plain uncoated;325 mg (5 grain), or 500 mg (7.8 grain) in bottles of 12 - 1000 tablets

Aspirin, Tablets; buffered uncoated; 325 mg (5 grain), or 500 mg (7.8 grain) with aluminum &/or magnesium salts in bottles of 12 - 1000 tablets

Aspirin Tablets (veterinary) 60 grain (3.89 grams) in 100's

Aspirin Boluses (veterinary) 240 grain (15.55 gram) in boxes/bottles of 50

Rectal suppositories, and enteric coated or sustained-release oral dosage forms are also available commercially for human use. A combination veterinary product, *Cortaba*® (Upjohn), containing 300 mg of aspirin and 0.5 mg methylprednisolone per tablet is also available commercially.

## ATIPAMEZOLE HCL

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry/Storage/Stability/Compatibility** - An alpha$_2$-adrenergic antagonist, atipamezole HCl injection should be stored at room temperature (15°-30°C) and protected from light.

**Pharmacology** - Atipamezole competitively inhibits alpha$_2$-adrenergic receptors, thereby acting as a reversal agent for alpha$_2$-adrenergic agonists (*e.g.*, medetomidine). Net pharmacologic effects are to reduce sedation, decrease blood pressure, increase heart and respiratory rates, and reduce the analgesic effects of alpha$_2$-adrenergic agonists.

**Uses/Indications** - Atipamezole is labeled for use as a reversal agent for medetomidine. It potentially could be useful for reversal of other alpha$_2$-adrenergic agonists as well (*e.g.,* amitraz, xylazine).

**Pharmacokinetics** - After IM administration in the dog, peak plasma levels occur in about 10 minutes. Atipamezole is apparently metabolized in the liver to compounds that are eliminated in the urine. The drug has an average plasma elimination half life of about 2-3 hours.

**Contraindications/Precautions/Reproductive Safety** - While the manufacturer lists no absolute contraindications to the use of atipamezole, it states that the drug is not recommended in pregnant or lactating animals due to lack of data establishing safety in these animals. Caution should be used in administration of anesthetic agents to elderly or debilitated animals.

**Adverse Effects/Warnings** - Potential adverse effects include occasional vomiting, diarrhea, hypersalivation, tremors, and brief excitation/apprehensiveness.

Because reversal can occur rapidly, care should be exercised as animals emerging from sedation and analgesia may exhibit apprehensive or aggressive behaviors. After reversal, animals should be protected from falling. Additional analgesia (*e.g.,* butorphanol) should be considered, particularly after painful procedures.

**Overdosage** - Dogs receiving up to 10X the listed dosage apparently tolerated the drug without major effects. When overdosed, dose related effects seen included panting, excitement, trembling, vomiting, soft or liquid feces, vasodilatation of sclera and some muscle injury at the IM injection site. Specific overdose therapy should generally not be necessary.

**Drug Interactions** - The manufacturer states that information on the use of atipamezole with other drugs is lacking, therefore, caution should be taken when using with other drugs (other than medetomidine).

**Doses** -

**Dogs**:

For reversal of medetomidine:

a) Give IM an equal volume of Antisedan® as Domitor® is administered (ml per ml). The actual concentration of Antisedan® will be 5X that of Domitor®, as Antisedan® is 5 mg/ml versus Domitor®'s 1 mg/ml. (Package Insert; Antisedan®—Pfizer)

b) As above, but may give IV as well as IM. If it has been at least 45 minutes since medetomidine was given, may give atipamezole at half the volume of medetomidine if administered IV. If after 10-15 minutes an IM dose of atipamezole has not seemed to reverse the effects of medetomidine, an additional dose of atipamezole at 1/2 the volume of the medetomidine dose may be given. (McGrath and Ko 1997b)

For treatment of amitraz toxicity:

a) 50 mcg/kg IM (Hugnet, Buronrosse et al. 1996)

**Elephants:**

To Drug Monograph Index To Ophthalmic Product Index

a) 1 mg atipamezole for every 8-12 mg xylazine will result in quick reversal in Asian elephants. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Tranquilization and translocation of elephants.** Journal of Indian Veterinary Association Kerala 7:(3):42-46.

b) 5-10 mg atipamezole injected IM or slow IV will reverse 100 mg xylazine Rietschel,W., Hildebrandt,T., Goritz,F., and Ratanakorn,P. 2001. **Sedation of Thai Working Elephants with Xylazine and Atipamezole as a Reversal.** A Research Update on Elephants and Rhinos; Proceedings of the International Elephant and Rhino Research Symposium, Vienna, June 7-11, 2001. Pages: 121-123.

c) 8-14 µg/kg atipamezole was given to partially reverse xylazine (33-72 µg/kg) to achieve standing sedation with responsiveness to voice commands in a 5000 kg male Asian elephant sedated on 3 occasions for treatment of a foot abscess. (Honeyman,V.L.Cooper, R.M., Black, S.R. 1998. **A protected contact approach to anesthesia and medical management of an Asian elephant (*Elephas maximus*).** Proceedings AAZV and AAWV Joint Conference. Pages: 338-341.

d) Atipamezole effectively reverses medetomidine sedation at doses of 200 mcg/kg body weight. Note that this is a general (i.e. not elephant specific dose). Lance,W.R. 1991. **New pharmaceutical tools for the 1990's.** Proceedings of the American Association of Zoo Veterinarians 354-359.

**Monitoring Parameters** - Level of sedation and analgesia; heart rate; body temperature

**Client Information -** Atipamezole should be administered by veterinary professionals only. Clients should be informed that occasionally vomiting, diarrhea, hypersalivation, excitation and tremors may be seen after atipamezole administration. Should these be severe or persist after leaving the clinic, clients should contact the veterinarian.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**:

Atipamezole HCl for Injection 5 mg/ml in 10 ml multidose vials; *Antisedan*®; (Pfizer); (Rx) Approved for use in dogs.

**Human-Approved Products**: None

## ATRACURIUM BESYLATE

**Chemistry** - A synthetic, non-depolarizing neuromuscular blocking agent, atracurium, is a bisquaternary, non-choline diester structurally similar to metocurine and tubocurarine. It occurs as white to pale yellow powder. 50 mg is soluble in 1 ml of water, 200 mg is soluble in 1 ml of alcohol, and 35 mg is soluble in 1 ml of normal saline.

The commercially available injection occurs as clear, colorless solution and is a sterile solution of the drug in sterile water for injection. The pH of this solution is 3.25 - 3.65. Atracurium besylate may also be known as: atracurium besilate.

**Storage/Stability/Compatibility** - Atracurium injection should be stored in the refrigerator and protected against freezing. At room temperature, approximately 5% potency loss occurs each month; when refrigerated, a 6% potency loss occurs over a years time.

To Drug Monograph Index To Ophthalmic Product Index

Atracurium is compatible with the standard IV solutions, but while stable in lactated Ringer's for 8 hours, degradation occurs more rapidly. It should not be mixed in the same IV bag or syringe, or given through the same needle with alkaline drugs (*e.g.,* barbiturates) or solutions (sodium bicarbonate) as precipitation may occur.

**Pharmacology** - Atracurium is a nondepolarizing neuromuscular blocking agent and acts by competitively binding at cholinergic receptor sites at the motor end-plate, thereby inhibiting the effects of acetylcholine. Atracurium is considered to be 1/4 to 1/3 as potent as pancuronium. In horses, atracurium is more potent than in other species tested and more potent than other nondepolarizing muscle relaxants studied.

At usual doses, atracurium exhibits minimal cardiovascular effects, unlike most other nondepolarizing neuromuscular blockers. While atracurium can stimulate histamine release, it is considered to cause less histamine release than either tubocurarine or metocurine. In humans, less than one percent of patients receiving atracurium exhibit clinically significant adverse reactions or histamine release.

**Uses/Indications** - Atracurium is indicated as an adjunct to general anesthesia to produce muscle relaxation during surgical procedures or mechanical ventilation and also to facilitate endotracheal intubation. Atracurium can be used in patients with significant renal or hepatic disease.

**Pharmacokinetics** - After IV injection, maximal neuromuscular blockade generally occurs within 3-5 minutes. The duration of maximal blockade increases as the dosage increases. Systemic alkalosis may diminish the degree and duration of blockade; acidosis potentiates it. In conjunction with balanced anesthesia, the duration of blockade generally persists for 20-35 minutes. Recovery times do not change after maintenance doses are given, so predictable blocking effects can be attained when the drug is administered at regular intervals.

Atracurium is metabolized by ester hydrolysis and Hofmann elimination which occurs independently of renal or hepatic function.

**Contraindications/Precautions** - Atracurium is contraindicated in patients who are hypersensitive to it. Because it may rarely cause significant release of histamine it should be used with caution in patients where this would be hazardous (severe cardiovascular disease, asthma, etc.). Atracurium has minimal cardiac effects and will not counteract the bradycardia or vagal stimulation induced by other agents. Use of neuromuscular blocking agents must be done with extreme caution, or not at all, in patients suffering from myasthenia gravis. Atracurium has no analgesic or sedative/anesthetic actions.

**Adverse Effects/Warnings** - Clinically significant adverse effects are apparently quite rare in patients (<1% in humans) receiving recommended doses of atracurium and usually are secondary to histamine release. They can include: allergic reactions, inadequate or prolonged block, hypotension vasodilatation, bradycardia, tachycardia, dyspnea, broncho-, laryngospasm, rash, urticaria, and a reaction at the injection site. Patients developing hypotension usually have preexisting severe cardiovascular disease.

**Overdosage** - Overdosage possibilities can be minimized by monitoring muscle twitch response to peripheral nerve stimulation. Increased risks of hypotension and histamine release occur with overdoses, as well as prolonged duration of muscle blockade.

Besides treating conservatively (mechanical ventilation, $O_2$, fluids, etc.), reversal of blockade may be accomplished by administering an anticholinesterase agent (edrophomium, physostigmine, or neostigmine) with an anticholinergic (atropine or glycopyrrolate). Reversal is usually attempted (in humans) approximately 20-35 minutes after the initial dose, or 10-30 minutes after the last maintenance dose. Reversal is usually complete within 8-10 minutes.

To Drug Monograph Index  To Ophthalmic Product Index

**Drug Interactions** - The following agents may enhance the neuromuscular blocking activity of atracurium: **procainamide, quinidine, verapamil, aminoglycoside antibiotics** (**gentamicin**, etc), **lincomycin, clindamycin, bacitracin, polymyxin B, lithium, magnesium sulfate, thiazide diuretics**, **enflurane, isoflurane,** and **halothane**. **Loop diuretics (***e.g.,* **furosemide)** have been reported to both decrease and increase the effects of nondepolarizing neuromuscular blockers. **Other muscle relaxant drugs** may cause a synergistic or antagonistic effect. **Succinylcholine** may speed the onset of action and enhance the neuromuscular blocking actions of atracurium. Do not give atracurium until succinylcholine effects have diminished. **Theophylline** or **phenytoin** may inhibit or reverse the neuromuscular blocking action of atracurium.

**Doses** -
**Horses**:

a) Intraoperative dose: 0.055 mg/kg IV (Mandsager 1988)

**Monitoring Parameters** -

1) Level of neuromuscular blockade; cardiac rate

**Client Information** - This drug should only be used by professionals familiar with its use.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Atracurium Besylate Injection 10 mg/ml in 5 ml amps and 10 ml vials; *Tracrium*® (Glaxo Wellcome); (Rx).

Back to Index

## ATROPINE SULFATE * (ADVERSE EFFECT REPORTED)

**Chemistry** - The prototype tertiary amine antimuscarinic agent, atropine sulfate is derived from the naturally occurring atropine. It is a racemic mixture of *d*-hyoscyamine and *l*-hyoscyamine. The *l*- form of the drug is active, while the *d*- form has practically no antimuscarinic activity. Atropine sulfate occurs as colorless and odorless crystals, or white, crystalline powder. One gram of atropine sulfate is soluble in approximately 0.5 ml of water, 5 ml of alcohol, or 2.5 ml of glycerin. Aqueous solutions are practically neutral or only slightly acidic. Commercially available injections may have the pH adjusted to 3.0 - 6.5. Atropine may also be known as *dl*-hyoscyamine.

**Storage/Stability/Compatibility** - Atropine sulfate tablets or soluble tablets should be stored in well-closed containers at room temperature (15-30°C). Atropine sulfate for injection should be stored at room temperature; avoid freezing.

Atropine sulfate for injection is reportedly **compatible** with the following agents: benzquinamide HCl, butorphanol tartrate, chlorpromazine HCl, cimetidine HCl (not with pentobarbital), dimenhydrinate, diphenhydramine HCl, dobutamine HCl, droperidol, fentanyl citrate, glycopyrrolate, hydromorphone HCl, hydroxyzine HCl (also w/meperidine), meperidine HCl, morphine sulfate, nalbuphine HCl, pentazocine lactate, pentobarbital sodium (OK for 5 minutes, not 24 hours), perphenazine, prochlorperazine edisylate, promazine HCl, promethazine HCl (also w/meperidine), and scopolamine HBr.

Atropine sulfate is reported physically **incompatible** with norepinephrine bitartrate, metaraminol bitartrate, methohexital sodium, and sodium bicarbonate. Compatibility is dependent upon factors such as pH,

concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** - Atropine, like other antimuscarinic agents, competitively inhibits acetylcholine or other cholinergic stimulants at postganglionic parasympathetic neuroeffector sites. High doses may block nicotinic receptors at the autonomic ganglia and at the neuromuscular junction. Pharmacologic effects are dose related. At low doses salivation, bronchial secretions, and sweating (not horses) are inhibited. At moderate systemic doses, atropine dilates and inhibits accommodation of the pupil, and increases heart rate. High doses will decrease GI and urinary tract motility. Very high doses will inhibit gastric secretion.

**Uses/Indications** - The principal veterinary indications for systemic atropine include:

1) Preanesthetic to prevent or reduce secretions of the respiratory tract
2) Treat sinus bradycardia, sinoatrial arrest, incomplete AV block
3) As an antidote for overdoses of cholinergic agents (*e.g.,* physostigmine, etc.)
4) As an antidote for organophosphate or muscarinic mushroom intoxication
5) Hypersialism
6) Treatment of bronchoconstrictive disease

**Pharmacokinetics** - Atropine sulfate is well absorbed after oral administration, IM injection, inhalation, or endotracheal administration. After IV administration, peak effects in heart rates occur within 3-4 minutes.

Atropine is well distributed throughout the body and crosses into the CNS, across the placenta, and can distribute into the milk in small quantities.

Atropine is metabolized in the liver and excreted into the urine. Approximately 30-50% of a dose is excreted unchanged into the urine. The plasma half-life in humans has been reported to be between 2-3 hours.

**Contraindications/Precautions** - Atropine is contraindicated in patients with narrow-angle glaucoma, synchiae (adhesions) between the iris and lens, hypersensitivity to anticholinergic drugs, tachycardias secondary to thyrotoxicosis or cardiac insufficiency, myocardial ischemia, unstable cardiac status during acute hemorrhage, GI obstructive disease, paralytic ileus, severe ulcerative colitis, obstructive uropathy, and myasthenia gravis (unless used to reverse adverse muscarinic effects secondary to therapy).

Antimuscarinic agents should be used with extreme caution in patients with known or suspected GI infections. Atropine or other antimuscarinic agents can decrease GI motility and prolong retention of the causative agent(s) or toxin(s) resulting in prolonged symptoms. Antimuscarinic agents must also be used with extreme caution in patients with autonomic neuropathy.

Antimuscarinic agents should be used with caution in patients with hepatic or renal disease, geriatric or pediatric patients, hyperthyroidism, hypertension, CHF, tachyarrhythmias, prostatic hypertrophy, or esophogeal reflux. Systemic atropine should be used cautiously in horses as it may decrease gut motility and induce colic in susceptible animals. It may also reduce the arrhythmogenic doses of epinephrine. Use of atropine in cattle may result in inappetance and rumen stasis which may persist for several days.

**Adverse Effects/Warnings** - Adverse effects are basically extensions of the drug's pharmacologic effects and are generally dose related. At usual doses effects tend to mild in relatively healthy patients. The more severe effects listed tend to occur with high or toxic doses. GI effects can include dry mouth (xerostomia), dysphagia, constipation, vomiting, and thirst. GI effects may include urinary retention or hesitancy. CNS effects may include stimulation, drowsiness, ataxia, seizures, respiratory depression, etc. Ophthalmic effects include blurred vision, pupil dilation, cycloplegia, and photophobia. Cardiovascular effects include sinus tachycardia (at higher doses), bradycardia (initially or at very low doses), hypertension, hypotension, arrhythmias (ectopic complexes), and circulatory failure.

To Drug Monograph Index  To Ophthalmic Product Index

**Overdosage** - For signs and symptoms of atropine toxicity see adverse effects above. If a recent oral ingestion, emptying of gut contents and administration of activated charcoal and saline cathartics may be warranted. Treat symptoms supportively and symptomatically. Do not use phenothiazines as they may contribute to the anticholinergic effects. Fluid therapy and standard treatments for shock may be instituted.

The use of physostigmine is controversial and should probably be reserved for cases where the patient exhibits either extreme agitation and is at risk for injuring themselves or others, or for cases where supraventricular tachycardias and sinus tachycardias are severe or life-threatening. The usual dose for physostigmine (human) is: 2 mg IV slowly (for average sized adult) If no response, may repeat every 20 minutes until reversal of toxic antimuscarinic effects or cholinergic effects takes place. The human pediatric dose is 0.02 mg/kg slow IV (repeat q10 minutes as above) and may be a reasonable choice for initial treatment of small animals. Physostigmine adverse effects (bronchoconstriction, bradycardia, seizures) may be treated with small doses of IV atropine.

**Drug Interactions** - The following drugs may enhance the activity of atropine and its derivatives: **antihistamines, procainamide, quinidine, meperidine, benzodiazepines, phenothiazines**. The following drugs may potentiate the adverse effects of atropine and its derivatives: **Primidone, disopyramide, nitrates, long-term corticosteroid use** (may increase intraocular pressure). Atropine and its derivatives may enhance the actions of **nitrofurantoin, thiazide diuretics, sympathomimetics**. Atropine and its derivatives may antagonize the actions of **metoclopramide**.

**Doses** -
**Horses**:

For treatment of bradyarrhythmias due to increased parasympathetic tone:

a) 0.02 mg/kg IV (Muir and McGuirk 1987a)
b) 0.045 mg/kg parenterally (Hilwig 1987)

As a bronchodilator:

a) 5 mg IV for a 400-500 kg animal (Beech 1987)

For organophosphate poisoning:

a) Approximately 1 mg/kg given to effect IV (use mydriasis and absence of salivation as therapy endpoints), may repeat every 1.5 - 2 hours as required subcutaneously (Oehme 1987)
b) 0.22 mg/kg, 1/4th of the dose administered IV and the remainder SQ or IM (Package Insert; Atropine Injectable, L.A. - Fort Dodge)

**Elephants:**

a) ***Adverse effect reported:** An Asian elephant became agitated following the IV administration of atropine (0.05 mg/kg) administered IV 90 minutes after azaperone was given. Gross,M.E., Clifford,C.A., and Hardy,D.A. 1994. **Excitement in an elephant after intravenous administration of atropine**. Journal of the American Veterinary Medical Association 205:(10):1437-1438 **Summary:** A 28-year-old Asian elephant (Elephas maximus) was anaesthetized for cesarean section to remove a dead calf. The elephant was sedated with azaperone (0.35 mg/kg), and atropine (.05 mg/kg) was administered i.v. 90 minutes later in preparation for induction of anaesthesia with etorphine HCl. Within a minute of the injection of atropine the elephant began swaying kicking, moving in an agitated manner around the stall and refused to obey commands. When the behavior did not abate after 30 minutes, azaperone (0.018 mg/kg) was administered IM. The elephant became calm and responsive to commands within 15 minutes. The authors suggest drug interaction with azaperone, toxicosis due to the dead calf and species differences as possible causative factors.

b) 150 mg atropine and 6 mg etorphine were administered simultaneously IM to a 3500 kg female African elephant on two occasions. Dunlop,C.I., Hodgson,D.S., Cambre,R.C., and Kenney,D. 1988. **Prolonged isoflurane anesthesia of an adult elephant on two occasions**. Veterinary Surgery 17:(3):167-168.

To Drug Monograph Index To Ophthalmic Product Index

c) Following induction with 8 mg etorphine IV, a 3050 kg female Asian elephant was given 120 mg atropine IV to decrease secretions. Mihm,F.G., Machado,C., and Snyder,R. 1988. **Pulse oximetry and end-tidal $CO_2$ monitoring of an adult Asian elephant**. Journal of Zoo Animal Medicine 19:106-109 **Abstract:** The adequacy of ventilation during etorphine anesthesia of a 20-yr-old Asian elephant (*Elephas maximus*) was monitored with a pulse oximeter to measure arterial hemoglobin oxygen saturation ($SaO_2$) and a $CO_2$ analyzer to measure end-tidal $CO_2$ concentrations ($PetCO_2$). Immediately after the first anesthetic induction, $SaO_2$ values of 45% were noted while the animal was breathing room air at a rate of 6/min. The $SaO_2$ readings increased to 93% 15 min after administration of 5 liters/min of oxygen via the trunk. Seven arterial blood gas samples obtained during two anesthetics, and once while unanesthetized, provided $PaO_2$ and $PaCO_2$ values which compared favorably with $SaO_2$ and $PetCO_2$ . In the anesthetized animal, $PaO_2$ ranged between 31 and 70 mmHg while $SaO_2$ values were 70-95%. At the same time, measurements of $PaCO_2$ ranged from 42 to 57 mmHg while values of $PetCO_2$ ranged from 35 to 57 mmHg. Pulse oximetry and end-tidal $CO_2$ monitoring are easy to apply and should increase the safety of anesthesia for these animals

d) Following induction with 7 mg etorphine IM, an African elephant (approx. 3000 kg) was given 90 mg atropine IM. Briggs,M., Schmidt,M., Black,D., Roach,R., Opdahl,J., Stark,G., Owens,D., and Driver,M. 1988. **Extraction of an infected tusk in an adult African elephant**. J Am Vet Med Assoc 192:(10):1455-1456 **Abstract:** An 18-year-old African elephant was determined to have a nonrepairable crack in its left tusk. Treatment included extraction of the tusk, using rotational and extractional forces, and administration of antibiotics, followed by 1 year of flushing the opened tusk cavity with warm tap water. Two years after surgery, the elephant was healthy, and the tusk cavity was 80% filled with normal tissue.

e) Atropine (0.04 mg/kg) administered IV corrected a second degree AV heart block in an African elephant under general anesthesia. Heard,D.J., Kollias,G.V., Webb,A.I., Jacobson,E.R., and Brock,K.A. 1988. **Use of halothane to maintain anesthesia induced with etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 193:254-256 **Excerpts:** Sixteen 3- to 5-year-old African elephants were anesthetized one or more times for a total of 27 diagnostic and surgical procedures. Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing juvenile elephants during a 45-minute transport period before administration of general anesthesia. After IM or IV administration of etorphine (1.9 ± 0.56 micrograms/kg), the mean time to lateral recumbency was 20 ± 6.6 and 3 ± 0.0 minutes, respectively. The mean heart rate, systolic blood pressure, and respiration rate during all procedures was 50 ± 12 beats/min, 106 ± 19 mm of Hg, and 10 ± 3 breaths/min, respectively.

Cardiac arrhythmias were detected during 2 procedures. In one elephant paroxysmal ventricular tachycardia was detected and the procedure terminated when the arrhythmia failed to stabilize after multiple doses of lidocaine (1 mg/kg, IV). In another elephant, second degree atrioventricular block returned to normal sinus rhythm after IV administration of atropine (0.04 mg/kg).

In one elephant, low mean blood pressure (54 mm of Hg) responded to reduction in halothane (vaporizer setting 1 to 0.75%) and slow infusion of dobutamine HCl ((250 mg/1,000 ml) given to effect. The systolic blood pressure increased to 90 mm of Hg and remained high with a continuous infusion of dobutamine (5 µg/kg/min). Immediately after induction in another elephant, profound respiratory depression (< 1breath/minute) and palpably weak arterial pulse were identified. Intravenous administration of diprenorphine at half the recommended reversal dose resulted in improvement of respiration and palpable arterial pulse, without the elephant developing signs of complete anesthetic reversal.

Alterations in systolic blood pressure, ear flapping, and trunk muscle tone were useful for monitoring depth of anesthesia. Results indicated that halothane in oxygen was effective for maintenance of surgical anesthesia in juvenile African elephants after induction with etorphine. Note: A correction appeared in a later volume 193(6): p.721.

To Drug Monograph Index To Ophthalmic Product Index

f) The administration of 4 to 5 mg/100 kg body weight is advised for elephants that lie down after xylazine has been given to prevent hypostatic congestion and counter cardiodepressant effects.Schmidt,M.J., 1986. **Proboscidea (Elephants)**. In: Fowler,M.E. (Editor), Zoo and wild animal medicine. W.B. Saunders, Philadelphia,PA, USA pp. 884-923.

g) Three adult male Asian elephants were given atropine (0.04-0.05 mg/kg) IM following induction with etorphine (1 mg/450 kg of body weight. Byron,H.T., Olsen,J., Schmidt,M.J., Copeland,J.F.Jr., and Byron,L. 1985. **Abdominal surgery in three adult male Asian elephants**. Journal of the American Veterinary Medical Association 187:(11):1236-1237.

h) An adult female Asian elephant (approx. 3500 kg) was given 450 mg atropine (0.11 mg/kg) IM/SQ 38 minutes following induction with 600 mg xylazine (Schmidt, 1983). (Author's (Mikota) note: At 0.11 mg/kg, the calculated dose of atropine for a 3500 kg elephant would be 385 mg). Schmidt,M.J. 1983. **Antagonism of xylazine sedation by yohimbine and 4-aminopyridine in an adult Asian elephant (*Elephas maximus*)**. Journal of Zoo Animal Medicine 14:94-97

**Abstract:** Heavy xylazine sedation was successfully antagonized by intravenous injection of yohimbine and 4-aminopyridine (4-AP) in an adult female Asian elephant (*Elephas maximus*) prior to euthanasia. A total xylazine dose of 1,200 mg intramuscularly plus 600 mg intravenously (approximately 0.33 mg/kg body weight) was given resulting in heavy sedation. After 50 minutes of deep recumbent sedation, 425 mg yohimbine and 1,000 mg of 4-AP were administered intravenously. Xylazine sedation was antagonized and the elephant was up and walking around within 5 minutes of antagonist administration. The elephant remained standing forother 3 hours; at which point euthanasia was performed.

**Monitoring Parameters** - Dependent on dose and indication

1) Heart rate and rhythm
2) Thirst/appetite; urination/defecation capability
3) Mouth/secretions dryness

**Client Information** - Parenteral atropine administration is best performed by professional staff and where adequate cardiac monitoring is available. If animal is receiving atropine tablets, allow animal free access to water and encourage drinking if dry mouth is a problem.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: Atropine is approved for use in dogs, cats, horses, cattle, sheep, and swine. No information is available regarding meat or milk withdrawal. Atropine products are available by prescription only.

Atropine Sulfate for Injection
- 0.5 mg/ml 30 ml, 100 ml vials
- 2 mg/ml 100 ml vial
- 15 mg/ml (Organophosphate Tx) 100 ml vial

**Human-Approved Products**:

Atropine Sulfate for Injection
- 0.05 mg/ml in 5 ml syringes
- 0.1 mg/ml in 5 and 10 ml syringes
- 0.3 mg/ml in 1 ml and 30 ml vials
- 0.4 mg/ml in 1 ml amps and 1, 20, and 30 ml vials
- 0.5mg/ml in 1 & 30 ml vials and 5 ml syringes
- 0.8 mg/ml in 0.5 & 1 ml amps and 0.5 ml syringes
- 1 mg/ml in 1 ml amps & vials and 10 ml syringes

Atropine Sulfate Tablets

To Drug Monograph Index To Ophthalmic Product Index

0.4 mg in 100's

Also see the monograph for atropine sulfate for ophthalmic use in the appendix

Aurothioglucose

**Chemistry** - A water soluble gold salt, aurothioglucose contains approximately 50% gold. It is practically insoluble in alcohol and insoluble in vegetable oils. The commercial product is a 5% (50 mg/ml) suspension in sesame oil, 2% aluminum monostearate, and propylparaben is added as a preservative.

**Storage/Stability/Compatibility** - Protect from light and store between 15-30° C; avoid freezing. A five year expiration date is assigned after manufacture. Do not mix with any other compound when injecting.

**Pharmacology** - Aurothioglucose has anti-inflammatory, antirheumatic, immunomodulating, and antimicrobial (*in vitro*) effects. The exact mechanisms for these actions are not well understood. Gold is taken up by macrophages where it inhibits phagocytosis and may inhibit lysosomal enzyme activity. Gold also inhibits the release of histamine, and the production of prostaglandins. While gold does have antimicrobial effects *in vitro*, it is not clinically useful for this purpose.

**Uses/Indications** - In human medicine, gold compounds are used primarily as a treatment for rheumatoid arthritis that has not adequately responded to less toxic treatment modalities. In veterinary medicine (primarily small animal medicine), it use has been generally used for treating immune-mediated serious skin disorders such as pemphigus complex.

**Pharmacokinetics** - After IM injection, aurothioglucose is quite rapidly absorbed and peak serum concentrations are reached in 4-6 hours. It is distributed to several tissues (liver, kidney, spleen, bone marrow, adrenals, and lymph nodes), but highest levels are found in the synovium. In the plasma, 95% is bound to plasma proteins. Gold salts may be found in the epithelial cells in the renal tubules years after dosing has ended. Plasma half-lives increase in length after multiple doses have been given. These values have ranged from 21 - 168 hours in humans. Approximately 70% of a dose is excreted by the kidneys, while the remaining 30% is excreted in the feces.

There appears to be no correlation with serum levels and efficacy. It usually takes from 6-12 weeks for a beneficial effect to be noted after beginning therapy.

**Contraindications/Precautions** - Contraindications for chrysotherapy (gold therapy) include patients with renal or hepatic disease, SLE (lupus erythematosus, diabetes mellitus (uncontrolled), severe debilitation, and preexisting hematologic disorders.

The safety of aurothioglucose has not been established during pregnancy, it should only be used when the potential benefits outweigh the risks involved. Gold salts are distributed into milk and there have been reports of human infants developing rashes after nursing from mothers taking gold.

**Adverse Effects/Warnings** - Veterinary experience with aurothioglucose is limited. Pain at the injection site is common and some animals may develop thrombocytopenia with petechia and echymoses. One author (Kummel 1995) reports that four pemphigus canine cases treated with aurothioglucose that was given immediately after cessation of azathioprine, developed a fatal toxic epidermal necrolysis.

Adverse reactions seen in people include, mucocutaneous reactions which are fairly common (15-20%) and are characterized by rashes, (with or preceded by pruritis), and mucosal lesions (usually seen as a stomatitis). Hematologic reactions (thrombocytopenia, leukopenia, aplastic anemias), although rare in

humans, can be life-threatening. Renal effects are generally mild and reversible with cessation of therapy if noted early. Proteinuria is an early sign associated with the proximal tubule damage that gold can cause. Reversible pulmonary infiltrates have been noted, but are reversible when therapy is discontinued. Enterocolitis, which may be fatal, has been reported in rare instances. Because of the serious nature of these adverse reactions, adequate patient monitoring is essential.

**Overdosage** - Overdosages resulting from a too rapid increase in dosages are exhibited by rapid development of toxic signs, primarily renal (hematuria, proteinuria) and hematologic (thrombocytopenia, granulocytopenia) effects. Other symptoms include: nausea, vomiting, diarrhea, skin lesions, and fever. Treat with dimercaprol (BAL) to chelate the gold and treat the hematologic and renal effects supportively.

**Drug Interactions** - Patients receiving aurothioglucose should generally not receive **penicillamine**, **antimalarials**, **hydroxychloroquin**, **immunosuppresive** or **cytotoxic drugs** (*e.g.,* **cyclophosphamide**, **methotrexate**, **azathioprine**) other than corticosteroids, because of similar toxicity profiles.

**Doses** -
**Horses**:

a) 1 mg/kg IM once a week decreasing to once a month (Schultz 1986)

**Monitoring Parameters** -

1) Urinalysis—baseline, then weekly
2) CBC - baseline, then every 2 weeks

After the patient is on maintenance therapy, hemograms and urinalyses may be done every month or two.

**Client Information** - Clients should be instructed to notify the veterinarian if pruritis, rash, or diarrhea develops, or if the animal becomes ill or depressed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Aurothioglucose Injection 50 mg/ml suspension (contains approximately 50% gold); in 10 ml vials; *Solganal*® (Schering); (Rx)

## Azaperone * (Adverse effect reported).

**Chemistry** - A butyrephone neuroleptic, azaperone occurs as a white to yellowish-white macrocrystalline powder with a melting point between 90 - 95°C. It is practically insoluble in water and 1 gram is soluble in 29 ml of alcohol.

**Storage/Stability/Compatibility** - Azaperone should be stored at room temperature (15-30°C) and away from light. No information was located regarding mixing azaperone with other compounds.

**Pharmacology** - The butyrephenones as a class cause tranquilization and sedation (sedation may be less so than with the phenothiazines), anti-emetic activity, reduced motor activity, and inhibition of CNS catecholamines (dopamine, norepinephrine). Azaperone appears to have minimal effects on respiration and may inhibit some of the respiratory depressant actions of general anesthetics. A slight reduction of arterial blood pressure has been measured in pigs after IM injections of azaperone, which is apparently due to slight alpha-adrenergic blockade. Azaperone has been demonstrated to prevent the development of

halothane-induced malignant hyperthermia in susceptible pigs. Preliminary studies have suggested that the effects of butyrephenones may be antagonized by 4-aminopyridine.

**Uses/Indications** - Azaperone is officially indicated for the "control of aggressiveness when mixing or regrouping weanling or feeder pigs weighing up to 36.4 kg" (Package Insert, *Stresnil*® - P/M; Mallinckrodt). It is also used clinically as a general tranquilizer for swine, in aggressive sows to allow piglets to be accepted, and as a preoperative agent prior to general anesthesia or cesarian section with local anesthesia.

Azaperone has also been used as a neuroleptic in horses, but some horses develop adverse reactions (sweating, muscle tremors, panic reaction, CNS excitement) and IV administration has resulted in significant arterial hypotension in the horse. Because of these effects, most clinicians avoid the use of this drug in equines.

**Pharmacokinetics** - Minimal information was located regarding actual pharmacokinetic parameters, but the drug is considered to have a fairly rapid onset of action following IM injections in pigs (5-10 minutes) with a peak effect at approximately 30 minutes post injection. It has a duration of action of 2-3 hours in young pigs and 3-4 hours in older swine. The drug is metabolized in the liver with 13% of it excreted in the feces. At 16 hours post-dose, practically all of the drug is eliminated from the body.

**Contraindications/Precautions** - When used as directed, the manufacturer reports no contraindications for the drug. It should not be given IV as a significant excitatory phase may be seen in pigs.

**Adverse Effects/Warnings** - Transient salivation, piling, and shivering have been reported in pigs. Pigs should be left undisturbed after injection (for approximately 20 minutes) until the drug's full effects have been expressed, as disturbances during this period may trigger excitement.

Azaperone has minimal analgesic effects and is not a substitute for appropriate anesthesia or analgesia. It is recommended that in large boars dosage not exceed 2 mg/kg IM.

**Overdosage** - No specific information was discovered regarding overdoses of azaperone, but it would be expected that symptoms would be an extension of its pharmacologic effects. It is suggested that treatment be supportive. Do not use epinephrine to treat cardiovascular symptoms. More work needs to done before 4-aminopyridine can be recommended as a reversal agent for azaperone.

**Drug Interactions** - No specific drug interactions have been reported for azaperone. The following interactions have been reported for the closely related compounds, haloperidol or droperidol: **CNS depressant agents (barbiturates, narcotics, anesthetics**, etc.) may cause additive CNS depression if used with butyrephenones.

**Doses** -
**Swine**:

a) For approved indication of mixing feeder or weanling pigs: 2.2 mg/kg deeply IM (see client information below) (Package Insert; *Stresnil*® — P/M; Mallinckrodt)
b) Preanesthetic: 2 - 4 mg/kg IM; Immobilizing agent: 5.3 - 8 mg/kg IM (Swindle 1985)
c) Sedation: 1 mg/kg IM

Reduction of aggressiveness: 2.5 mg/kg IM
Knock-down or immobilant: 5 - 10 mg/kg IM (Booth 1988a)

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other.

To Drug Monograph Index To Ophthalmic Product Index

Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised

*** Adverse effect reported.** See Schmitt et.al. 1996 below. Also see atropine monograph for adverse effect possibly related to azaperone.

a) Total dose of azaperone for adult Asian captive elephants 80-100 mg; up to 140 mg for a large elephant. Induction in 20-30 minutes; duration 45-60 minutes. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Tranquilization and translocation of elephants**. Journal of Indian Veterinary Association Kerala 7:(3):42-46

b) For capture of wild juvenile African elephants 4 mg etorphine and 60-80 mg azaperone; for capture of small calves (under 1 m shoulder height) 1 mg etorphine and 10 mg azaperone.

For transport of wild African elephants, the dose of azaperone varies with shoulder height: > 2.4 m (200 mg); 2.0-2.4 m (150 mg); all lactating females (150 mg); l .5-2.0 m (100 mg); 1.2-1.5 m (50 mg); 1.2 m (10-20 mg). du Toit,J.G., 2001. **Veterinary Care of African Elephants**. Novartis, Pretoria, Republic of South Africa, 1-59 pp

c) For standing sedation in captive African elephants, 0.056-0.107 mg/kg (median dose = 0.08 mg/kg; total dose 240-400 mg / animal; n=20). Ramsay,E. 2000. **Standing sedation and tranquilization in captive African elephants (*Loxodonta africana*)**. Proc. Am. Assoc. Zoo Vet. Pages: 111-114 **Excerpt from abstract:** Intramuscular azaperone was used to tranquilize seven animals (African) for a total of 20 immobilizations. Azaperone alone or in combination with local anesthesia (lidocaine blocks) was used 15 times. Reasons for tranquilization included treatment of tail folliculitis, treatment of abscesses, obtaining blood samples, intradermal tuberculin testing, and manual stimulation of ejaculation. Dosages for azaperone alone ranged from 0.056-0.107 mg/kg (median dosage = 0.08 mg/kg; total doses ranged from 240-400 mg/ animal). One animal, which received an initial dosage of 0.04 mg/kg required supplementation, to a total dosage of 0.056 mg/kg to be tractable enough, while in an elephant restraint device, for manual stimulation of ejaculation. All but one tranquilization were rated as good (sufficient tranquilization to accomplish the procedure) or excellent (sufficient tranquilization to perform the intended procedure and additional diagnostics). Tranquilized elephants stood, with minimal swaying, and did not make efforts to resist or pull away for the handler. Tranquilization of one female that received 0.075 mg/kg was rated as fair due to insufficient sedation for venipuncture. One tranquilization was rated good (dosage = 0.107 mg/kg) but a notation suggested that the elephant was “too deep, tried to buckle” and a lesser dosage was used more satisfactorily on that animal for subsequent immobilizations. Tranquilizations ranked as excellent were produced by dosages of 0.079- 0.0904 mg/kg (n=4). Times from initial darting to adequate sedation and to recovery (normal behavior) were infrequently recorded but the author’s impressions is that animals became sedate for handling approximately 20 minutes after the injection and recovered approximately 2 hr after initial dosing.

d) For capture of adult wild African elephants, azaperone in combination with etorphine or carfentanil as follows: adult females: 12 mg etorphine and 100 mg azaperone (or 10 mg carfentanil and 100 mg azaperone); adult males: 15 mg etorphine and 200 mg azaperone (or 13 mg carfentanil and 200 mg azaperone). For captive elephants, reduce dosage by 25 %.

For capture of wild African calves, (in combination with etorphine or carfentanil) according to shoulder height as follows:
Shoulder height 90-115 cm: etorphine 2 mg (or carfentanil 1 mg) and azaperone 20 mg
Shoulder height 116-140 cm: etorphine 5 mg (or carfentanil 3 mg) and azaperone 50 mg
Shoulder height 141-165 cm: etorphine 7 mg (or carfentanil 5 mg) and azaperone 70 mg
Shoulder height 166-200 cm: etorphine 9 mg (or carfentanil 7 mg) and azaperone 90 mg

To Drug Monograph Index To Ophthalmic Product Index

For captive elephants, reduce dosage by 25 %. Raath,J.P., 1999. **Relocation of African elephants**. In: Fowler,M.E. and Miller,R.E. (Editors), Zoo and Wild Animal Medicine: Current Therapy 4. W.B. Saunders, Philadelphia, PA, USA pp. 525-533

e) Two African elephants (estimated weights 1000 and 1200 kg) were given 120 mg azaperone for transport. Stegmann,G.F. 1999. **Etorphine-halothane anaesthesia in two five-year-old African elephants (Loxodonta africana)**. Journal of the South African Veterinary Medical Association 70:(4):164-166 **Abstract:** Anaesthesia of 2 five-year-old female African elephants (Loxodonta africana) was required for dental surgery. The animals were each premedicated with 120 mg of azaperone 60 min before transportation to the hospital. Before offloading, 1 mg etorphine was administered intramuscularly (i.m.) to each elephant to facilitate walking them to the equine induction/recovery room. For induction, 2 mg etorphine was administered i.m. to each animal. Induction was complete within 6 min. Surgical anaesthesia was induced with halothane-in-oxygen after intubation of the trunk. During surgery the mean heart rate was 61 and 45 beats/min respectively. Systolic blood pressures increased to 27.5 and 25.6 kPa respectively, and were treated with intravenous azaperone. Blood pressure decreased thereafter to a mean systolic pressure of 18.1 and 19.8 kPa, respectively. Rectal temperature was 35.6 and 33.9 degrees C at the onset of surgery, and decreased to 35.3 and 33.5 degrees C, respectively, at the end of anaesthesia. Etorphine anaesthesia was reversed with 5 mg diprenorphine at the completion of 90 min of surgery.

f) For standing sedation in captive Asian elephants: 0.024-0.038 mg/kg for minor surgical procedures. **Adverse effect noted – see info below.** Schmitt,D., Bradford,J., and Hardy,D.A. 1996. **Azaperone for standing sedation in Asian elephants (*Elephas maximus*).** Proceedings American Association of Zoo Veterinarians. Pages: 48-51 **Abstract:** Azaperone was used for standing sedation in four Asian elephants (*Elephas maximus*) in 93 trials at Dickerson Park Zoo (DPZ). Procedures including surgical artificial insemination, semen collection, and routine foot trimming were completed while utilizing azaperone as a sedative. All procedures were performed within an elephant restraint device. Azaperone has proven to be a safe and reliable drug for facilitation of routine health and reproductive-related procedures in captive Asian elephants when administered at 0.030 mg/kg. the procurement of azaperone in the United States has been difficult due to changing manufacturing and distribution procedures. The utilization of an Investigational New Animal Drug permit from the Food and Drug Administration is described, to facilitate procurement of azaperone from Canada for use in the United States. **Additional excerpt:** The sedative effects of azaperone in 93 trials were rated as good in 81 trials, fair in 12 trials, and poor in none. The calming initial effects of azaperone on the elephant could be seen in 10 to 15 min following injection. In most cases, appetite seemed to increase during this time. Maximum effect was attained in 15 to 25 min. Maximum effects were characterized by: a stuporous or somnolent mental state often accompanied by snoring, an unwillingness to move or respond to stimuli, diminished bowel movement, distended or relaxed penis or clitoris. No tendencies or desires to lie down have been noted. Maximum effects rapidly diminished after approximately 2 hr. Total duration of effects was approximately 3 hr. Repeated daily administration of azaperone during two to six day periods demonstrated no residual effects. *** Adverse effect noted:** Two abnormal responses were shown from the same cow during azaperone induction. The episodes of confused or hallucinatory behavior were responses to mild stimuli. Once maximum effect has been attained, no behavioral problems have been noted.

g) For capture of wild African elephants ≤ 600 kg: etorphine 0.35 ± 0.13 µg/(kg/min) and azaperone 3.11 ± 1.10 µg/(kg/min)

For capture of wild African elephants > 600 kg: etorphine 0.23 ± 0.09 and azaperone 2.01 ± 0.8 µg/(kg/min)

Note: Total doses of etorphine and azaperone [µg/(kg/min)] were calculated as a sum of the induction (dart) dose and any following supplements divided by the elephant's body mass and calculated anesthetic/recumbent time. Body mass of smaller elephants was determined by weighing. Body mass of larger elephants (>1000 kg) was estimated from shoulder height. See abstract below. Still,J., Raath,J.P., and Matzner,L. 1996. **Respiratory and circulatory parameters of African elephants (Loxodonta**

To Drug Monograph Index To Ophthalmic Product Index

**africana) anesthetized with etorphine and azaperone**. Journal of the South African Veterinary Medical Association 67:(3):123-127 **Abstract:** Respiratory rate, heart rate, blood-gas tensions ($PO_2$ and $PCO_2$) and pH of arterial (a) and peripheral venous (v) blood, concentration of haemoglobin in arterial blood (Hb), saturation of arterial haemoglobin with oxygen and the end-expiratory concentration of oxygen were measured in 22 juvenile African elephants anaesthetized with etorphine and azaperone during 35 to 65 min after they assumed lateral recumbency. Based on these parameters the alveolar-arterial and arterial-peripheral venous differences of $PO_2$ [$P(A\text{-}a)O_2$ and $P(a\text{-}v)O_2$, respectively], and oxygen content of arterial blood ($CaO_2$) were calculated. Elephants with body mass of ≤ 600 kg showed significant changes in the following parameters compared with elephants with a body mass of more than 600 kg (x ± SD) : $PO_2$ (64 ± 11 compared with 82 ± 8 mmHg), $P(a\text{-}v)O_2$ (9 ± 5 compared with 22 ± 9 mmHg), P(A-a)O2 (37 ± 16 compared with 15 ± 8 mmHg) and Hb (148 ± 20 compared with 130 ± 10 g/litre) ($p< 0.05$). These findings suggested a tendency towards impaired oxygen exchange in the lungs, reduced peripheral extraction of oxygen and elevated oxygen-carrying capacity of arterial blood in smaller elephants. These changes were theoretically attributed to the respiratory-depressant and sympathomimetic effects of higher dosages of etorphine used in the smaller elephants to maintain a clinically acceptable anaesthetic plane. Individual elephants spent 35 to 150 min under anaesthesia and all recovered uneventfully after reversal of etorphine with diprenorphine.

h) Following immobilization for translocation of 670 elephants in family units in 1993, haloperidol (40 to 120 mg depending on body size) was used as a tranquilizer during transport. In addition, azaperone, (50-200 mg) was often administered to avoid aggression. Trilafon [perphenazine] (100-300 mg) was administered to keep animals calm after their release into bomas. Coetsee,C. 1996. **Elephant Translocations**. Pachyderm 22:81

i) Azaperone (60-100 mg) was combined with etorphine (7-15 mg) and hyaluronidase 1500-3000 IU) in a translocation operation of 26 elephants in central Kenya. Induction time was 7-15 minutes. Five elephants died from metabolic changes unrelated to drugs doses administered. Njumbi,S.T., Waithaka,J., Gachago,S., Sakwa,J., Mwathe,K., Mungai,P., Mulama,M., Mutinda,H., Omondi,P., and Litoroh,M. 1996. **Translocation of elephants: the Kenyan experience**. Pachyderm 22: 61-65 (Author's (Mikota) note: hyalase is incorrectly described as a tranquilizer in this article.

j) In the capture of wild African elephants, azaperone in combination with etorphine or carfentanil to reduce blood pressure decreases the occurrence of pink foam syndrome. See abstract below Hattingh,J. and Knox,C.M. 1994. **Arterial blood pressure in anesthetized African elephants**. South African Journal of Wildlife Research 24:(1/2) **Abstract:** A number of elephants previously captured in the Krueger National Park developed a pink frothy discharge from the external nares. Some of these elephants subsequently died and histopathological examinations indicated severe lung oedema. In view of the current hypothesis that high blood pressure could be a causative factor, arterial blood pressure was measured in elephants immobilized with etorphine alone (n=71) and with etorphine/azaperone (n=109) and with carfentanil/azaperone (n=26) mixtures. Arterial pressure was found to be significantly lower in the groups immobilized with azaperone mixtures than in the group immobilized with etorphine alone ($p < 0.05$). In addition, no cases of lung oedema were observed in animals immobilized with etorphine/azaperone and carfentanil/azaperone mixtures. It is strongly recommended, therefore, that azaperone be added to immobilization mixtures when elephants are subjected to herding prior to darting. Additional excerpt: all elephants in this study were juveniles 200 to 1300 kg. Group 1 (n=71) was immobilized with 4-8 mg etorphine; group 2 (n=109) was immobilized with 4-8 mg etorphine and 50-90 mg azaperone; and group 3 (n=26) was immobilized with 4-8 mg carfentanil and 50-90 mg azaperone.

k) 0.1 mg/kg azaperone IM for tranquilization of wild African elephants for transportation; For emergency treatment of pink foam syndrome 0.1 mg/kg IV as a vasodilator; reverse narcotic immediately. Pink foam syndrome is caused by pulmonary edema and capillary bleeding from high mean arterial pressure. It has been associated with opioids and manifests as pink froth from the trunk. Refer to the original work for azaperone doses for wild African calves and for further information and treatment of pink foam syndrome.

To Drug Monograph Index To Ophthalmic Product Index

Raath,J.P., 1993. **Chemical capture of the African elephant**. In: The Capture and care manual : capture, care, accommodation and transportation of wild African animals. Pretoria : Wildlife Decision Support Services : South African Veterinary Foundation, Pretoria pp. 484-511

l) For sedation: 30-120 mg for babies, 120 mg for juveniles, 120-760 mg for adults. Species and route of administration not specified. Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants**. In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441Author's (Mikota) note: The animal category and drug dose column headings for azaperone are misaligned in this reference and may cause confusion. The doses listed here are correctly matched to their respective age categories.

**See also:**

Dunlop,C.I., Hodgson,D.S., Cambre,R.C., Kenny,D.E., and Martin,H.D. 1994. **Cardiopulmonary effects of three prolonged periods of isoflurane anesthesia in an adult elephant**. Journal of the American Veterinary Medical Association 205:(10):1439-1444
**Abstract:** An adult 3500-kg female African elephant (Loxodonta africana) was anaesthetized 3 times for treatment of subcutaneous fistulas over the lateral aspect of each cubitus (anaesthesia 1 and 2) and for repair of a fractured tusk (anaesthesia 3). Lateral recumbency and anaesthesia were achieved with etorphine (anaesthesia 1 and 2) or etorphine and azaperone (anaesthesia 3). Full abstract in etorphine monograph.

Still,J. 1993. **Etorphine-azaperone anaesthesia in an African elephant (Loxodonta africana)**. Journal of Veterinary Anaesthesia 20:54-55 **Summary:** Wild elephants ≤ 2000 kg were darted with a mixture of azaperone (30 to 100 mg) and etorphine (3 to 9 mg). No further drug dose detail provided. Respiratory parameters for one elephant monitored for 140 min are reported.

de Vos,V. 1978. **Immobilization of free-ranging wild animals using a new drug**. Vet Rec 103:(4):64-68
**Abstract:** Field trials were conducted with the potent morphine-like analgesic, R33799 (Janssen Pharmaceutica; Beerse, Belgium) in South African national parks on 217 free-ranging wild animals, representing 20 different species. The drug was found to be effective and safe for a wide range of ungulates and pachyderms and Burchell's zebra (Equus burchelli) did not react to expected dosage levels. A suggested dosage regime for 19 species is given. Recommended optimal dosage rates varies from about 1 microgram per kg for pachyderms to about 10 microgram per kg for most of the larger ungulates. Xylazine and azaperone were found valuable adjuncts to R33799 in dosage ratios of 10:1 and 30:1 respectively.

Silberman,M.S. 1977. **Tranquilization of the African elephant (*Loxodonta africana* Blumenbach) with neuroleptic azaperone (R-1929).** Journal of Zoo Animal Medicine 8:7-8

**Monitoring Parameters** -

1) Level of sedation

**Client Information** - Must be injected IM deeply, either behind the ear and perpendicular to the skin or in the back of the ham. All animals in groups to be mixed must be treated.

**Dosage Forms/Preparations** -

**Veterinary-Approved Products: May not be currently marketed in the USA**

Azaperone 40 mg/ml for Injection in 20 ml vials (6 vials/box); *Stresnil*®; (Schering-Plough) (Rx). Approved for use in pigs. There is no specific tolerance for residues published and there is no specified withdrawal time before slaughter.

Also known by the trade name *Suicalm*® in the United Kingdom.

To Drug Monograph Index To Ophthalmic Product Index

**Human-Approved Products: None**

Barbiturate Pharmacology

Also see the monographs for Phenobarbital, Pentobarbital, Thiamylal, & Thiopental

While barbiturates are generally considered to be CNS depressants, they can invoke all levels of CNS mood alteration from paradoxical excitement to deep coma and death. While the exact mechanisms for the CNS effects caused by barbiturates are unknown, they have been shown to inhibit the release of acetylcholine, norepinephrine, and glutamate. The barbiturates also have effects on GABA and pentobarbital has been shown to be GABA-mimetic. At high anesthetic doses, barbiturates have been demonstrated to inhibit the uptake of calcium at nerve endings.

The degree of depression produced is dependent on the dosage, route of administration, pharmacokinetics of the drug, and species treated. Additionally, effects may be altered by the age or physical condition of the patient, or the concurrent use of other drugs. The barbiturates depress the sensory cortex, lessen motor activity, and produce sedation at low dosages. Some barbiturates such as phenobarbital are useful as anticonvulsants because they tend to have sufficient motor activity depression, without causing excessive sedation. In humans, it has been shown that barbiturates reduce the rapid-eye movement (REM) stage of sleep. Barbiturates have no true intrinsic analgesic activity.

In most species, barbiturates cause a dose-dependent respiratory depression, but in some species they can cause slight respiratory stimulation. At sedative/hypnotic doses respiratory depression is similar to that during normal physiologic sleep. As doses increase, the medullary respiratory center is progressively depressed with resultant decreases in rate, depth, and volume. Respiratory arrest may occur at 4 times lower the dose that will cause cardiac arrest. These drugs must be used very cautiously in cats as they are particularly sensitive to the respiratory depressant effects of barbiturates.

Besides the cardiac arresting effects of the barbiturates at euthanatizing dosages, the barbiturates have other cardiovascular effects. In the dog, pentobarbital has been demonstrated to cause tachycardia, decreased myocardial contractility and stroke volume, and decreased mean arterial pressure and total peripheral resistance.

The barbiturates cause reduced tone and motility of the intestinal musculature, probably secondary to its central depressant action. The thiobarbiturates (thiamylal, thiopental) may,
after initial depression, cause an increase in both tone and motility of the intestinal musculature. However, these effects do not appear to have much clinical significance. Administration of barbiturates reduces the sensitivity of the motor end-plate to acetylcholine, thereby slightly relaxing skeletal muscle. Because the musculature is not completely relaxed, other skeletal muscle relaxants may be necessary for surgical procedures.

There is no direct effect on the kidney by the barbiturates, but severe renal impairment may occur secondary to hypotensive effects in overdose situations. Liver function is not directly affected when used acutely, but hepatic microsomal enzyme induction is well documented with extended barbiturate (especially phenobarbital) administration. Although barbiturates reduce oxygen consumption of all tissues, no change in metabolic rate is measurable when given at sedative dosages. Basal metabolic rates may be reduced with resultant decreases in body temperature when barbiturates are given at anesthetic doses.

To Drug Monograph Index  To Ophthalmic Product Index

## BETHANECHOL CHLORIDE

**Chemistry** - A synthetic cholinergic ester, bethanechol occurs as a slightly hygroscopic, white or colorless crystalline powder with a slight, amine-like or “fishy” odor. It exhibits polymorphism, with one form melting at 211° and the other form at 219°. One gram of the drug is soluble in approximately 1 ml of water or 10 ml of alcohol. The commercially available injection has a pH from 5.5 - 7.5.

**Storage/Stability/Compatibility** - Bethanechol tablets should be stored at room temperature in tight containers. The injectable form should be stored at room temperature; avoid freezing. It may be autoclaved at 120°C for 20 minutes without any loss of potency.

**Pharmacology** - Bethanechol directly stimulates cholinergic receptors. Its effects are principally muscarinic and at usual doses has negligible nicotinic activity. It is more resistant to hydrolysis than acetylcholine by cholinesterase and, therefore, has an increased duration of activity.

Pharmacologic effects include increased esophageal peristalsis and lower esophageal sphincter tone, increased tone and peristaltic activity of the stomach and intestines, increased gastric and pancreatic secretions, increased tone of the detrusor muscle of the bladder, and decreased bladder capacity. At high doses after parenteral administration, effects such as increased bronchial secretions and constriction, miosis, lacrimation, and salivation can be seen. When administered SQ or orally, effects are predominantly on the GI and urinary tracts.

**Uses/Indications -** In veterinary medicine, bethanechol is used primarily to stimulate bladder contractions in small animals. It also can be used as an esophageal or general GI stimulant, but metoclopramide and/or neostigmine have largely supplanted it for these uses.

**Pharmacokinetics** - No information was located on the pharmacokinetics of this agent in veterinary species. In humans, bethanechol is poorly absorbed from the GI tract, and the onset of action is usually within 30-90 minutes after oral dosing. After subcutaneous administration, effects begin within 5-15 minutes and usually peak within 30 minutes. The duration of action after oral dosing may persist for up to 6 hours after large doses and 2 hours after SQ dosing. Subcutaneous administration yields a more enhanced effect on urinary tract stimulation than does oral administration.

Bethanechol does not enter the CNS after usual doses; other distribution aspects of the drug are not known. The metabolic or excretory fate of bethanechol have not been described.

**Contraindications/Precautions** - Contraindications to bethanechol therapy include: bladder neck or other urinary outflow obstruction, when the integrity of the bladder wall is in question (*e.g.,* as after recent bladder surgery), hyperthyroidism, peptic ulcer disease or when other inflammatory GI lesions are present, recent GI surgery with resections/anastomoses, GI obstruction or peritonitis, hypersensitivity to the drug, epilepsy, asthma, coronary artery disease or occlusion, hypotension, severe bradycardia or vagotonia or vasomotor instability. If urinary outflow resistance is increased due to enhanced urethral tone (not mechanical obstruction!), bethanechol should only be used in conjunction with another agent that will sufficiently reduce outflow resistance (*e.g.,* diazepam, dantrolene (striated muscle) or phenoxybenzamine (smooth muscle)).

**Adverse Effects/Warnings** - When administered orally to small animals, adverse effects are usually mild, with vomiting, diarrhea, salivation, and anorexia being the most likely to occur. Cardiovascular (arrhythmias, hypotension) and respiratory effects (asthma) are most likely only seen after overdosage situations or with high dose SQ therapy.

IM or IV use is not recommended, except in emergency situations when the IV route may be used. Severe cholinergic reactions are likely if given IV. If injecting the drug (SQ or IV), it is recommended that atropine be immediately available.

To Drug Monograph Index  To Ophthalmic Product Index

**Overdosage** - Symptoms of overdosage are basically cholinergic in nature. Muscarinic effects (salivation, urination, defecation, etc.) are usually seen with oral or SQ administration. If given IM or IV, a full-blown cholinergic crisis can occur with circulatory collapse, bloody diarrhea, shock and cardiac arrest possible.

Treatment for bethanechol toxicity is atropine. Refer to the atropine monograph for more information on its use. Epinephrine may also be employed to treat symptoms of bronchospasm.

**Drug Interactions** - Bethanechol should not be used concomitantly with other **cholinergic (***e.g.,* **carbachol) or anticholinesterase (***e.g.,* **neostigmine) agents** because of additive effects and increased likelihood of toxicity developing. **Quinidine, procainamide, epinephrine (or sympathomimetic amines) or atropine** can antagonize the effects of bethanechol.
Bethanechol used in combination with **ganglionic blocking drugs** (*e.g.,* mecamylamine) can produce severe GI and hypotensive effects.

**Doses** -
**Horses**:

a) 0.05 mg/kg SQ; 0.11 - 0.22 mg/kg IV; Start at lower dose first and use cautiously (McConnell and Hughey 1987)

**Monitoring Parameters** - Clinical efficacy; urination frequency, amount voided, bladder palpation; Adverse effects (see above section)

**Client Information** - Give medication on an empty stomach unless otherwise instructed by veterinarian. Contact veterinarian if salivation or GI (vomiting, diarrhea, or anorexia) effects are pronounced or persist.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Bethanechol Chloride Tablets 5 mg, 10 mg, 25 mg, 50 mg; *Urecholine*® (Merck, Frosst); *Duvoid*® (Roberts); *Myotonachol*® (Glenwood); *PMS-Bethanechol Chloride*® (Glenwood); Generic; (Rx)

Bethanechol Chloride for Injection 5 mg/ml in 1 ml vials and amps; *Urecholine*® (Frosst); (Rx)

**Bicarbonate — see Sodium Bicarbonate**

## BISMUTH SUBSALICYLATE

**Chemistry** - Bismuth subsalicylate occurs as white or nearly white, tasteless, odorless powder and contains about 58% bismuth. It is insoluble in water, glycerin and alcohol. It may also be known as bismuth salicylate, or bismuth oxysalicylate.

**Storage/Stability/Compatibility** - Bismuth subsalicylate should be stored protected from light. It is incompatible with mineral acids and iron salts. When exposed to alkali bicarbonates, bismuth subsalicylate decomposes with effervescence.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Bismuth subsalicylate is thought to posses protectant, anti-endotoxic and weak antibacterial properties. It is believed that the parent compound is cleaved in the small intestine into bismuth carbonate and salicylate. The protectant, anti-endotoxic and weak antibacterial properties are thought to be as a result of the bismuth. The salicylate component has antiprostaglandin activity which may contribute to its effectiveness and reduce symptoms associated with secretory diarrheas.

**Uses/Indications -** In veterinary medicine, bismuth subsalicylate products are used to treat diarrhea. The drug is also used in humans for other GI symptoms (indigestion, cramps, gas pains) and in the treatment and prophylaxis of traveler's diarrhea.

**Pharmacokinetics** - No specific veterinary information was located. In humans, the amount of bismuth absorbed is negligible while the salicylate component is rapidly and completely absorbed. Salicylates are highly bound to plasma proteins and are metabolized in the liver to salicylic acid. Salicylic acid, conjugated salicylate metabolites and any absorbed bismuth are all excreted renally.

**Contraindications/Precautions** - Salicylate absorption may occur; use with caution in patients with preexisting bleeding disorders. Because of the potential for adverse effects caused by the salicylate component, this drug should be used cautiously, if at all, in cats.

**Adverse Effects/Warnings** - Antidiarrheal products are not a substitute for adequate fluid and electrolyte therapy when required. May change stool color to a gray-black or greenish-black; do not confuse with melena. In human infants and debilitated individuals, use of this product may cause impactions to occur. As bismuth is radiopaque, it may interfere with GI tract radiologic examinations.

**Overdosage** - No specific information located, but theoretically may cause salicylism. See the Aspirin monograph for more information.

**Drug Interactions** - Bismuth containing products can decrease the absorption or orally administered **tetracycline** products. If both agents are to be used, separate drugs by at least 2 hours and administer tetracycline first. Because bismuth subsalicylate contains salicylate, concomitant administration with **aspirin** may increase salicylate serum levels; monitor appropriately.

**Laboratory Test Interference** - At high doses, salicylates may cause false-positive results for **urinary glucose** if using the cupric sulfate method (Clinitest®, Benedict's solution) and false-negative results if using the glucose oxidase method (Clinistix® or Tes-Tape®). **Urinary ketones** measured by the ferric chloride method (Gerhardt) may be affected if salicylates are in the urine (reddish-color produced). **5-HIAA** determinations by the fluoremetric method may be interfered by salicylates in the urine. Falsely elevated **VMA** (vanillylmandelic acid) may be seen with most methods used if salicylates are in the urine. Falsely lowered **VMA** levels may be seen if using the Pisano method. Urinary excretion of **xylose** may be decreased if salicylates are given concurrently. Falsely elevated **serum uric acid** values may be measured if using colorimetric methods.

**Doses** -
**Horses**:

For diarrhea:

a) For foals: 0.5 ml per kg PO q4-6h, response usually within 48 hours. After diarrhea resolves, taper off drug. (Wilson 1987)
b) For foals or adults: 1 ounce per 8 kg of body weight PO *tid-qid* (Clark and Becht 1987)
c) For foals: 3 - 4 oz. PO q6-8h (Martens and Scrutchfield 1982)
d) For foals: 60 ml *bid-qid* for two days (Label Directions - *Corrective Mixture*® (Beecham))

**Monitoring Parameters** -

To Drug Monograph Index To Ophthalmic Product Index

1) Clinical efficacy
2) Fluid & electrolyte status in severe diarrhea

**Client Information** - Shake well before using. If diarrhea persists, contact veterinarian. May change stool color to a gray-black or greenish-black; contact veterinarian if stool becomes “tarry” black. Refrigeration of the suspension may improve palatability. Do not mix with milk before administering.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

*Corrective Suspension*® (Phoenix): Bismuth subsalicylate 17.5 mg/ml. Available in gallons.; (OTC) Labeled for use in cattle, horses, calves, folas, dogs and cats.

**Human-Approved Products**:

Bismuth Subsalicylate Suspension 262 mg/15 ml & 524 mg/15 ml in 120 ml, 240 ml, 360 ml bottles.; *Pepto-Bismol*® (Procter & Gamble); *Bismatrol Extra Strength*® (Major); *Pepto-Bismol Extra Strength*® (Procter & Gamble); Generic (OTC)

Bismuth Subsalicylate Tablets & Caplets (Chewable) 262 mg;*Pepto-Bismol*® (Procter & Gamble); (OTC);*Bismatrol*® (Major); (OTC)

## BOLDENONE UNDECYLENATE

**Chemistry** - An injectable anabolic steroid derived from testosterone, boldenone undecylenate has a chemical name of 17 beta-hydroxyandrosta-1,4-dien-3-one. The commercially available product is in a sesame oil vehicle. It may also be known by the name boldenone undecenoate or in the U.K. by the trade name, *Vebonol*® (Ciba-Geigy).

**Storage/Stability/Compatibility** - Boldenone injection should be stored at room temperature; avoid freezing. Because it is in an oil vehicle, it should not be physically mixed with any other medications.

**Pharmacology** - In the presence of adequate protein and calories, anabolic steroids promote body tissue building processes and can reverse catabolism. As these agents are either derived from or are closely related to testosterone, the anabolics have varying degrees of androgenic effects. Endogenous testosterone release may be suppressed by inhibiting lutenizing hormone (LH). Large doses can impede spermatogenesis by negative feedback inhibition of FSH.

Anabolic steroids can also stimulate erythropoiesis. The mechanism for this effect may occur by stimulating erythropoeitic stimulating factor. Anabolics can cause nitrogen, sodium, potassium and phosphorus retention and decrease the urinary excretion of calcium.

**Uses/Indications -** Boldenone is labeled for use as adjunctive therapy “... as an aid for treating debilitated horses when an improvement in weight, haircoat, or general physical condition is desired” (*Equipoise*® package insert—Solvay).

**Pharmacokinetics** - No specific information was located for this agent. It is considered to be a long-acting anabolic, with effects persisting for up to 8 weeks. It is unknown if the anabolic agents cross into milk.

**Contraindications/Precautions** - The manufacturer (Solvay) recommends not using the drug on stallions or pregnant mares. Other clinicians state the that anabolic steroids should not be used in either stallions or

non-pregnant mares intended for reproduction. Boldenone should not be administered to horses intended for food purposes.

In humans, anabolic agents are also contraindicated in patients with hepatic dysfunction, hypercalcemia, patients with a history of myocardial infarction (can cause hypercholesterolemia), pituitary insufficiency, prostate carcinoma, in selected patients with breast carcinoma, benign prostatic hypertrophy and during the nephrotic stage of nephritis.

The anabolic agents are category X (risk of use outweighs any possible benefit) agents for use in pregnancy and are contraindicated because of possible fetal masculinization.

**Adverse Effects/Warnings** - In the manufacturer's (*Equipoise*®—Solvay) package insert, only androgenic (overaggressiveness) effects are listed. However, in work reported in both stallions and mares (Squires and McKinnon 1987), boldenone caused a detrimental effect in testis size, sperm production and quality in stallions. In mares, the drug caused fewer total and large follicles, smaller ovaries, increased clitoral size, shortened estrus duration, reduced pregnancy rates and severely altered sexual behavior. Although not reported in horses, anabolic steroids have the potential to cause hepatic toxicity.

**Overdosage** - No information was located for this specific agent. In humans, sodium and water retention can occur after overdosage of anabolic steroids. It is suggested to treat supportively and monitor liver function should an inadvertent overdose be administered.

**Drug Interactions** - No drug interactions were located for boldenone specifically. Anabolic agents as a class may potentiate the effects of **anticoagulants**. Monitoring of PT's and dosage adjustment, if necessary, of the anticoagulant are recommended.

Diabetic patients receiving **insulin**, may need dosage adjustments if anabolic therapy is added or discontinued. Anabolics may decrease blood glucose and decrease insulin requirements.
Anabolics may enhance the edema that can be associated with **ACTH** or **adrenal steroid** theapy.

**Drug/Laboratory Interactions -** Concentrations of **protein bound iodine (PBI)** can be decreased in patients receiving androgen/anabolic therapy, but the clinical significance of this is probably not important. Androgen/anabolic agents can decrease amounts of **thyroxine-binding globulin** and decrease **total $T_4$** concentrations and increase **resin uptake of $T_3$ and $T_4$**. Free thyroid hormones are unaltered and clinically, there is no evidence of dysfunction. Both **creatinine** and **creatine excretion** can be decreased by anabolic steroids. Anabolic steroids can increase the urinary excretion of **17-ketosteroids**. Androgenic/anabolic steroids may alter **blood glucose** levels. Androgenic/anabolic steroids may suppress **clotting factors II, V, VII, and X**. Anabolic agents can affect **liver function tests** (BSP retention, SGOT, SGPT, bilirubin, and alkaline phosphatase).

**Doses** -
**Horses**:

a) 1.1 mg/kg IM; may repeat in 3 week intervals (most horses will respond with one or two treatments) (Package Insert; *Equipoise*®—Solvay)
b) 1 mg/kg IM; repeated at 3 week intervals (Robinson 1987)

**Monitoring Parameters** -

1) Androgenic side effects
2) Fluid and electrolyte status, if indicated
3) Liver function tests if indicated
4) Red blood cell count, indices, if indicated
5) Weight, appetite

To Drug Monograph Index To Ophthalmic Product Index

**Client Information** - Because of the potential for abuse of anabolic steroids by humans, many states have included, or are considering including this agent as a controlled drug. It should be kept in a secure area and out of the reach of children.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Boldenone Undecylenate for Injection 25 mg/ml in 10 ml vials; 50 mg/ml in 10 ml & 50 ml vials;
*Equipoise*® (Fort Dodge); (Rx) Approved for use in horses not to be used for food.

**Human-Approved Products**: None

## BROMOCRIPTINE MESYLATE

**Chemistry** - A dopamine agonist and prolactin inhibitor, bromocriptine mesylate is a semisynthetic ergot alkaloid derivative. It occurs as a yellowish-white powder and is slightly soluble in water and sparingly soluble in alcohol. Bromocriptine mesylate may also be known as bromocryptine, Brom-ergocryptine, or 2-Bromergocryptine.

**Storage/Stability/Compatibility** - Tablets and capsules should be protected from light and stored in tight containers at temperatures less than 25°C.

**Pharmacology** - Bromocriptine exhibits multiple pharmacologic actions. It inhibits prolactin release from the anterior pituitary thereby reducing serum prolactin. The mechanism for this action is by a direct effect on the pituitary and/or stimulating postsynaptic dopamine receptors in the hypothalamus to cause release of prolactin-inhibitory factor. Bromocriptine also activates dopaminergic receptors in the neostriatum of the brain.

**Uses/Indications** - Bromocriptine may potentially be of benefit in treating acromegaly/pituitary adenomas or pseudopregnancy in a variety of species. However, because of adverse effects, its potential value for treating hyperadrenocorticism in dogs is low.

**Pharmacokinetics** - In humans, only about 28% of a bromocriptine dose is absorbed from the gut and due to a high first-pass effect only about 6% reaches the systemic circulation. Distribution characteristics are not well described, but in humans it is highly protein bound (90-96%) to serum albumin. Bromocriptine is metabolized by the liver to inactive and non-toxic metabolites. It has a biphasic half life; the alpha phase is about 4 hours and the terminal phase is about 15 hours (Note: one source says 45-50 hours).

**Contraindications/Precautions/Reproductive Safety** - Bromocriptine is generally contraindicated in patients with hypertension. It should be used with caution in patients with hepatic disease as metabolism of the drug may be reduced. Usage during pregnancy is contraindicated, although documented teratogenicity has not been established. Because bromocriptine interferes with lactation, it should not be used in animals who are nursing.

**Adverse Effects/Warnings** - Bromocriptine may cause a plethora of adverse effects which are usually dose related and minimized with dosage reduction. Some more likely possibilities include: gastrointestinal effects (nausea, vomiting), nervous system effects (sedation, fatigue, etc.), and hypotension (particularly with the first dose, but it may persist).

To Drug Monograph Index To Ophthalmic Product Index

**Overdosage/Acute Toxicity** - Overdosage may cause vomiting, severe nausea, and profound hypotension. Standardized gut removal techniques should be employed when applicable and cardiovascular support instituted as needed.

**Drug Interactions** - If using bromocriptine for serum prolactin reduction: **butyrophenones** (*e.g.*, haloperidol, azaperone), **amitriptyline, phenothiazines, & reserpine** may increase prolactin concentrations and bromocriptine doses may need to be increased. **Estrogens** or **progestins** may interfere with the effects of bromocriptine. When used with other **antihypertensive drugs**, hypotensive effects may be additive. Although no conclusive evidence exists, use of bromocriptine and **ergot alkaloids** is not recommended. Some human patients receiving both have developed severe hypertension and myocardial infarction. Use with **alcohol** may cause a disulfiram-type reaction.

**Doses** -
**Horses**:

For treatment of pituitary adenoma:

a) 5 mg IM q12h. To prepare an injectable formulation for IM use from oral dosage forms: Bromocriptine mesylate 70 mg is added to 7 ml of a solution of 80% normal saline and 20% absolute alcohol (v/v). Final concentration is 1% (10 mg/ml). (Beck 1992)

**Monitoring Parameters** - Monitoring is dependent upon the reason for use to evaluate efficacy. However, blood pressures should be evaluated if patients have symptoms associated with hypotension.

**Client Information** - Have client administer drug with food to reduce GI adverse effects.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Bromocriptine mesylate 5 mg (of bromocriptine) Capsules; *Parlodel*® (Sandoz); Rx

Bromocriptine mesylate 2.5 mg (of bromocriptine) Tablets; *Parlodel*® *Snaptabs* (Sandoz); Rx

## BUPRENORPHINE HCL

**Chemistry** - A thebaine derivative, buprenorphine is a synthetic partial opiate agonist. It occurs as a white, crystalline powder with a solubility of 17 mg/ml in water and 42 mg/ml in alcohol. The commercially available injectable product (*Buprenex*® - Norwich Eaton) has a pH of 3.5-5 and is a sterile solution of the drug dissolved in $D_5W$. Terms of potency are expressed in terms of buprenorphine. The commercial product contains 0.324 mg/ml of buprenorphine HCl, which is equivalent to 0.3 mg/ml of buprenorphine.

**Storage/Stability/Compatibility** - Buprenorphine should be stored at room temperature (15-30° C). Temperatures above 40° C or below freezing should be avoided. Buprenorphine products should be stored away from bright light. Autoclaving may decrease drug potency considerably. The drug is stable between a pH of 3.5-5.

Buprenorphine is reported to be **compatible** with the following IV solutions and drugs: acepromazine, atropine, diphenhydramine, $D_5W$, $D_5W$ & normal saline, droperidol, glycopyrrolate, hydroxyzine, lactated Ringer's, normal saline, scopolamine, and xylazine. Buprenorphine is reportedly **incompatible** with diazepam and lorazepam.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Buprenorphine has partial agonist activity at the *mu* receptor. This is in contrast to pentazocine which acts as an antagonist at the *mu* receptor. Buprenorphine is considered to be 30 times as potent as morphine and exhibits many of the same actions as the opiate agonists; it produces a dose-related analgesia. It appears to have a high affinity for *mu* receptors in the CNS, which may explain its relatively long duration of action.

The cardiovascular effects of buprenorphine may cause a decrease in both blood pressure and cardiac rate. Rarely, human patients may exhibit increases in blood pressure and cardiac rate. Respiratory depression is a possibility, and decreased respiratory rates have been noted in horses treated with buprenorphine. Gastrointestinal effects appear to be minimal with buprenorphine, but further studies are needed to clarify this.

**Pharmacokinetics** - Buprenorphine is rapidly absorbed following IM injection, with 40-90% absorbed systemically when tested in humans. The drug is also absorbed sublingually (bioavailability≈55%) in people. Oral doses appear to undergo a high first-pass effect with metabolism occurring in the GI mucosa and liver.

The distribution of the drug has not been well studied. Data from work done in rats reflects that buprenorphine concentrates in the liver, but is also found in the brain, GI tract, and placenta. It is highly bound (96%) to plasma proteins (not albumin), crosses the placenta, and it (and metabolites) are found in maternal milk at concentrations equal to or greater than those found in plasma.

Buprenorphine is metabolized in the liver by N-dealkylation and glucuronidation. These metabolites are then eliminated by biliary excretion into the feces (≈70%) and urinary excretion (≈27%).

In the horse, onset of action is approximately 15 minutes after IV dosing. The peak effect occurs in 30-45 minutes and the duration of action may last up to 8 hours. Because acepromazine exhibits a similar onset and duration of action, many clinicians favor using this drug in combination with buprenorphine in the horse.

**Uses/Indications** - Because buprenorphine is a relatively new addition to the pharmacologic armamentarium, present indications appear to be limited to its use in horses as a neuroleptanalgesic (when used in combination with either acepromazine or xylazine) and as an analgesic in dogs and cats.

**Contraindications/Precautions** - All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's), and in geriatric or severely debilitated patients.

Rarely, patients may develop respiratory depression from buprenorphine, it therefore should be used cautiously in patients with compromised cardiopulmonary function. Like other opiates, buprenorphine must be used with extereme caution in patients with head trauma, increased CSF pressure or other CNS dysfunction (*e.g.,* coma).

Patients with severe hepatic dysfunction may eliminate the drug more slowly than normal patients. Buprenorphine may increase bile duct pressure and should be used cautiously in patients with biliary tract disease.

Although no controlled studies have been performed in domestic animals or humans, the drug has exhibited no evidence of teratogenicity or of causing impaired fertility in laboratory animals.
The drug is contraindicated in patients having known hypersensitivity to it.

**Adverse Effects/Warnings** - Although rare, respiratory depression appears to be the major adverse effect to monitor with this agent, but because it has only recently been used in veterinary medicine, other adverse

To Drug Monograph Index To Ophthalmic Product Index

effects may be noted. The primary side effect seen in humans is sedation with an incidence of approximately 66%.

**Overdosage** - The intraperitoneal $LD_{50}$ of buprenorphine has been reported to be 243 mg/kg in rats. The ratio of lethal dose to effective dose is at least 1000:1 in rodents. Because of the apparent high index of safety, acute overdoses should be a rare event in veterinary medicine. In such a case however, treatment with naloxone and doxapram has been suggested in cases with respiratory or cardiac effects. High doses of nalaxone may be required to treat respiratory depression should it occur.

**Drug Interactions** - Other **CNS depressants** (*e.g.,* anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with buprenorphine. Buprenorphine may decrease the analgesic effects of the **opiate agonists** (morphine, etc.). **Pancuronium** if used with buprenorphine may cause increased conjunctival changes. Buprenorphine is contraindicated in human patients receiving **monamine oxidase (MOA) inhibitors** (rarely used in veterinary medicine) for at least 14 days after receiving MOA inhibitors in humans. One study done in rabbits did not demonstrate any appreciable interaction, however. **Local anesthetics** (mepivicaine, bupivicaine) may be potentiated by concomitant use of buprenorphine.

**Doses** -
**Horses**:

For neuroleptanalgesia:

a) 0.004 mg/kg IV (given with acepromazine 0.02 mg/kg) (Thurmon and Benson 1987)
b) 0.006 mg/kg IV (given with xylazine 0.07 mg/kg) (Thurmon and Benson 1987)

**Monitoring Parameters** -

1) Analgesic efficacy
2) Respiratory status
3) Cardiac status

**Client Information** - This agent should be used in an inpatient setting or with direct professional supervision.

## BUTORPHANOL TARTRATE pK

**Chemistry** - A synthetic opiate partial agonist, butorphanol tartrate is related structurally to morphine but exhibits pharmacologic actions similar to other partial agonists such as pentazocine or nalbuphine. The compound occurs as a white, crystalline powder that is sparingly soluble in water and insoluble in alcohol. It has a bitter taste and a $pK_a$ of 8.6. The commercial injection has a pH of 3-5.5. One mg of the tartrate is equivalent to 0.68 mg of butorphanol base.

**Storage/Stability/Compatibility** - The injectable product should be stored out of bright light and at room temperature; avoid freezing.

The injectable product is reported to be **compatible** with the following IV fluids and drugs: acepromazine, atropine sulfate, chlorpromazine, diphenhydramine HCl, droperidol, fentanyl citrate, hydroxyzine HCl, meperidine, morphine sulfate, pentazocine lactate, perphenazine, prochlorperazine, promethazine HCl, scopolamine HBr, and xylazine.

The drug is reportedly **incompatible** with the following agents: dimenhydrinate, and pentobarbital sodium.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Butorphanol is considered to be, on a weight basis, 4-7 times as potent an analgesic as morphine, 15-30 times as pentazocine, and 30-50 times as meperidine. Its agonist activity is thought to be exerted primarily at the *kappa* and *sigma* receptors and the analgesic actions at sites in the limbic system (sub-cortical level and spinal levels).

The antagonist potency of butorphanol is considered to be approximately 30 times that of pentazocine and 1/40$^{th}$ that of naloxone and will antagonize the effect of true agonists (*e.g.,* morphine, meperidine, oxymorphone).

Besides the analgesic qualities of butorphanol, it possesses significant antitussive activity. In dogs, butorphanol has been shown to elevate CNS respiratory center threshold to $CO_2$, but unlike opiate agonists, not depress respiratory center sensitivity. Butorphanol, unlike morphine, apparently does not cause histamine release in dogs. CNS depression may occur in dogs, while CNS excitation has been noted (usually at high doses) in horses and dogs.

Although possessing less cardiovascular effects than the classical opiate agonists, butorphanol can cause a decrease in cardiac rate secondary to increased parasympathetic tone and mild decreases in arterial blood pressures.

The risk of causing physical dependence seems to be minimal when butorphanol is used in veterinary patients.

**Pharmacokinetics** - Butorphanol is absorbed completely in the gut when administered orally, but because of a high first-pass effect only about 1/6$^{th}$ of the administered dose reaches the systemic circulation. The drug has also been shown to be completely absorbed following IM administration.

Butorphanol is well distributed, with highest levels (of the parent compound and metabolites) found in the liver, kidneys, and intestine. Concentrations in the lungs, endocrine tissues, spleen, heart, fat tissue and blood cells are also higher than those found in the plasma. Approximately 80% of the drug is bound to plasma proteins (human data). Butorphanol will cross the placenta and neonatal plasma levels have been roughly equivalent to maternal levels. The drug is also distributed into maternal milk.

Butorphanol is metabolized in the liver, primarily by hydroxylation. Other methods of metabolism include N-dealkylation and conjugation. The metabolites of butorphanol do not exhibit any analgesic activity. These metabolites and the parent compound are mainly excreted into the urine (only 5% is excreted unchanged), but 11-14% of a dose is excreted into the bile and eliminated with the feces.

Following IV doses in horses, the onset of action is approximately 3 minutes with a peak analgesic effect at 15-30 minutes. The duration of action in horses may be up to 4 hours after a single dose.

**Uses/Indications** - Approved indication for dogs is “for the relief of chronic non-productive cough associated with tracheobronchitis, tracheitis, tonsillitis, laryngitis and pharyngitis originating from inflammatory conditions of the upper respiratory tract” (Package Insert; *Torbutrol*® — Fort Dodge). It is also used in practice in both dogs and cats as a preanesthetic medication, analgesic, and as an antiemetic prior to cisplatin treatment.

The approved indication for horses is “for the relief of pain associated with colic in adult horses and yearlings” (Package Insert; *Torbugesic*® — Fort Dodge). It has also been used clinically as an analgesic in cattle, although published data is apparently lacking.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions** - All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's), and in geriatric or severely debilitated patients.

Like other opiates, butorphanol must be used with extreme caution in patients with head trauma, increased CSF pressure or other CNS dysfunction (*e.g.,* coma).

The manufacturer states that butorphanol "should not be used in dogs with a history of liver disease", and because of its effects on suppressing cough, "it should not be used in conditions of the lower respiratory tract associated with copious mucous production." The drug should be used cautiously in dogs with heartworm disease as safety for butorphanol has not been established in these cases.

Although no controlled studies have been performed in domestic animals or humans, the drug has exhibited no evidence of teratogenicity or of causing impaired fertility in laboratory animals. The manufacturer, however, does not recommend its use in pregnant bitches, foals, weanlings (equine), and breeding horses.

The drug is contraindicated in patients having known hypersensitivity to it.

**Adverse Effects/Warnings** - Adverse effects reported in dogs include, sedation (occasionally), anorexia or diarrhea (rarely).

Adverse effects seen in horses (at usual doses) may include a transient ataxia and sedation. Although reported to have minimal effects, butorphanol has the potential to decrease intestinal motility. Horses may exhibit CNS excitement (tossing and jerking of head, increased ambulation, augmented avoidance response to auditory stimuli) if given high doses (0.2 mg/kg) IV rapidly. Very high doses IV (1 - 2 mg/kg) may lead to the development of nystagmus, salivation, seizures, hyperthermia and decreased GI motility. These effects are considered to be transitory in nature.

**Overdosage** - Acute life-threatening overdoses with butorphanol should be unlikely. The $LD_{50}$ in dogs is reportedly 50 mg/kg. However, because butorphanol injection is available in two dosage strengths (0.5 mg/ml and 10 mg/ml) for veterinary use, the possibility exists that inadvertent overdoses may occur in small animals. It has been suggested that animals exhibiting symptoms of overdose (CNS effects, cardiovascular changes, and respiratory depression) be treated immediately with intravenous naloxone. Additional supportive measures (*e.g.,* fluids, $O_2$, vasopressor agents, & mechanical ventilation) may be required. Should seizures occur and persist, diazepam may used for control.

**Drug Interactions** - Other **CNS depressants** (*e.g.,* anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with butorphanol, dosage may need to be decreased.
**Pancuronium** if used with butorphanol may cause increased conjunctival changes.

**Doses** - Note: All doses are expressed in mg/kg of the base activity. If using the human product (*Stadol*®), 1 mg of tartrate salt = 0.68 mg base.
**Horses**:

As an analgesic:

a) 0.1 mg/kg IV q3-4h; not to exceed 48 hours (Package Insert; *Torbugesic*®; - Fort Dodge)
b) 0.02 - 0.05 mg/kg IV (Muir 1987)
c) 0.01 - 0.1 mg/kg IV (Thurmon and Benson 1987)
d) 0.02 - 0.1 mg/kg IV; or 0.04 - 0.2 mg/kg IM q3-4h (combined with acepromazine or xylazine) (Orsini 1988)

As a preanesthetic, outpatient surgery, or chemical restraint:

To Drug Monograph Index To Ophthalmic Product Index

a) 0.01 - 0.04 mg/kg IV (with xylazine 0.1 - 0.5 mg/kg IV) (Orsini 1988)

As an antitussive:

a) 0.02 mg/kg IM *bid-tid* (Orsini 1988)

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

a) Ramsay,E. 2000. **Standing sedation and tranquilization in captive African elephants (*Loxodonta africana*)**. Proc. Am. Assoc. Zoo Vet. Pages: 111-114
**Excerpt from abstract:** Intramuscular azaperone in combination with butorphanol was used on one female elephant for aggressive debridement of a facial abscess and on another aggressive cow. The azaperone doses ranged from 0.068 – 0.12 mg/kg. In one immobilization, 10 mg butorphanol was mixed with azaperone (0.12 mg/kg) in the initial dart (tranquilization was rated good). In the other procedures, butorphanol, 0.006 – 0.014 mg/kg (total doses = 20 – 50 mg), was given IV 24 – 73 minutes post-azaperone administration, to attain (0.006 mg/kg given at 24 and 25 minutes) or maintain (0.013 and 0.014 mg/kg given at 40 and 73 min, respectively) control. The azaperone and butorphanol combination sedation events were ranked as good (n=3) or excellent (n=2). Naloxone (0.004 mg/kg IV; total dose =12.8 mg) was used to reverse the effects of butorphanol in the animal receiving the highest butorphanol dosage.

**Excerpt from abstract:** Xylazine in combination with butorphanol was used to sedate 2 African elephants, twice each. The adult male elephant (estimated weight = 5000 kg) received a total dose of 800 mg (0.16 mg/kg) xylazine IM, and 26 minutes later received 180 mg (0.036 mg/kg) butorphanol IV for radiology, performed outside of the elephant restraint device. This immobilization was rated excellent but when the same dosages were used 2 years later, the immobilization was initially rated only as good. Supplemental butorphanol (20 mg) was given during the second immobilization 77 min after xylazine injection and the subsequent phase of the immobilization was rated as fair. One female elephant (estimated weight = 3500 kg) received 100 mg (0.035 mg/kg) xylazine IV mixed with 15 mg (0.005 mg/kg) butorphanol IV. Fourteen minutes later an additional 50 mg xylazine and 10 mg butorphanol were given IV. A local block was subsequently used to lance a subcutaneous abscess on the abdomen and this immobilization was rated as good. On a subsequent immobilization for physical examination and blood collection, this animal received 500 mg (0.14 mg/kg) xylazine IM, followed 44 min later by 50 mg (0.014 mg/kg) butorphanol IV. This immobilization was rated only as fair.

c) For sedation of adult captive African elephants: 0.01 ± 0.003 mg/kg. Fowler,M.E., 1995. **Elephants**. In: Restraint and handling of wild and domestic animals. Iowa State University Press, Ames, Iowa, USA p. 265.

d) 8-10 mg total dose was given IV to 1500 kg African elephants following administration of a xylazine-ketamine combination to improve upon the sedative response to this drug combination. Jacobson,E.R. 1988. **Chemical restraint and anesthesia of elephants**. Proc.Ann.Elephant Workshop 9. pp. 112-119.

e) Ingram, L.M., Isaza, R., Koch, D.E., and Hunter, R.P. 2005. Pharmacokinetics of intravenous and intramuscular butorphanol in Asian elephants (*Elephas maximus*). 2005 Proceedings AAZV, AAWV, AZA Nutrition Advisory Group, pp. 70-71.

To Drug Monograph Index To Ophthalmic Product Index

Captive Asian elephants (*Elephas maximus*) are susceptible to lameness resulting from foot and joint pain.1 In the past, opioid analgesics, such as the agonist-antagonist butorphanol, have been used clinically for pain management. However, dosages used in treating elephants were often extrapolated from data in horses, with the risk of administering either a sub-efficacious dose or an overdose, both of which are undesirable. In this study, six adult captive Asian elephants (five female, one male) were administered butorphanol intravenously (i.v.) and intramuscularly (i.m.) in a cross over design. The dose was 0.015 mg/kg for both routes with at least 21 days between administrations. Serial blood samples were collected immediately prior to butorphanol administration and at 5, 10, 20, 40 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 24 hr after injection. The samples were collected into Li heparin vacutainer tubes and centrifuged to obtain plasma. The plasma was separated into cryovials and frozen at -70°C until analyzed using a validated LC/MS assay with a LOQ of 0.025 ng/ml. The dosage selected for this pharmacologic study in elephants is within the recommended analgesic butorphanol dose range for horses.2 Following i.v. administration the median pharmacokinetic values that were calculated include: Vdarea, Vdss, Clp, MRT, and half life (t½). After i.m. injection the median Cmax, Tmax, and bioavailability (F) were calculated. The Vd data used for extrapolation from published literature on five domestic mammalian species correlated with the values found for elephants. Thus, Vd may be useful to extrapolate an efficacious dose in Asian elephants. Our preliminary results suggest a dosage of 0.015 mg/kg may provide analgesia without evidence of severe sedation. Further studies are necessary to determine the quality and duration of analgesia from the administration of butorphanol in elephants at this recommended dose.

f) Tana, L.M., Isaza, R., Koch, D.E., and Hunter, R.P. 2010. Pharmacokinetics and intramuscular bioavailability of a single dose of butorphanol in Asian Elephants (Elephas maximus). Journal of Zoo and Wildlife Medicine 41 (3): 418-425.

Abstract: Captive Asian elephants (Elephas maximus) are susceptible to lameness resulting from foot and joint pain, including chronic arthritis. In the past, opioid analgesics, such as butorphanol, have been used clinically for pain management. However, dosages used in treating elephants were often extrapolated from data in horses, with no pharmacokinetic information on the specific agents used in elephant species. In this pharmacokinetic study, six adult captive Asian elephants (5 female, 1 male castrate) were administered a 0.015 mg/kg dose of butorphanol by both i.v. and i.m. routes. A complete crossover design was used with a 3-wk washout period between treatments. Serial blood samples were collected immediately prior to butorphanol administration and at 5, 10, 20, and 40 min and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 24 h after administration. The butorphanol analysis was performed using a validated liquid chromatography–mass spectrophotometric assay with a limit of quantitation of 0.025 ng/ml. The mean Cmax after i.m. administration was 7.9 ng/ml, with a corresponding Tmax of 40 min and tK of 7.1 h. After i.v. administration, the mean Vdss was 1.4 L/kg and the mean Clp was 0.26 L/kg/h. Mean i.m. bioavailability was 37%. The results indicate that butorphanol used at 0.015 mg/kg i.m. or i.v. could be useful in elephants when given for pain control.

**Monitoring Parameters** -

1) Analgesic &/or antitussive efficacy
2) Respiratory rate/depth
3) Appetite/bowel function
4) CNS effects

**Client Information** - Clients should report any significant changes in behavior, appetite, bowel or urinary function in their animals.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** - Note: Butorphanol is a class IV controlled substance. The veterinary products (*Torbutrol*®, *Torbugesic*®) strengths are listed as base activity. The human product (*Stadol*®) strength is labeled as the tartrate salt.

**Veterinary-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Butorphanol Tartrate Injection; 0.5 mg/ml (activity as base) 10 ml vials; *Torbutrol*® (Fort-Dodge); (Rx) Approved for use in dogs.

Butorphanol Tartrate Injection; 10 mg/ml (activity as base) 50 ml vials; *Torbugesic*® (Fort-Dodge); (Rx) Approved for use in horses not intended for food.

Butorphanol Tartrate Tablets (Veterinary); 1 mg, 5 mg, & 10 mg (activity as base) tablets; bottles of 100; *Torbutrol*® (Fort-Dodge); (Rx) Approved for use in dogs.

**Human-Approved Products**:

Butorphanol Tartrate Injection; 1 mg/ml (as tartrate salt; equivalent to 0.68 mg base) in 1 ml vials and 2 mg/ml (as tartrate salt) in 1, 2, & 10 ml vials; *Stadol*® (Mead Johnson); (Rx)

Butorphanol Nasal Spray: 10 mg/ml (2.5 ml metered dose) *Stadol NS*® (Mead Johnson) (Rx)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

Buprenorphine HCl for Injection: 0.324 mg/ml (equivalent to 0.3 mg/ml buprenorphine); 1 ml ampules; *Buprenex*® (Reckitt & Colman); (Rx)

**Calcium EDTA — see Edetate Calcium Disodium**

**CALCIUM SALTS**
**CALCIUM GLUCONATE**
**CALCIUM GLUCEPTATE**
**CALCIUM CHLORIDE**
**CALCIUM LACTATE**

**Chemistry** - Several different salts of calcium are available in various formulations. Calcium gluceptate and calcium chloride are freely soluble in water; calcium lactate is soluble in water; calcium gluconate and calcium glycerophosphate are sparingly soluble in water, and calcium phosphate and carbonate are insoluble in water. Calcium gluconate for injection has a pH of 6-8.2; calcium chloride for injection has a pH of 5.5-7.5; and calcium gluceptate for injection has a pH of 5.6-7.

**Storage/Stability/Compatibility** - Calcium gluconate tablets should be stored in well-closed containers at room temperature. Calcium lactate tablets should be stored in tight containers at room temperature. Calcium gluconate injection, calcium gluceptate injection, and calcium chloride injection should be stored at room temperature and protected from freezing.

**Calcium chloride** for injection is reportedly **compatible** with the following intravenous solutions and drugs: amikacin sulfate, ascorbic acid, bretylium tosylate, cephapirin sodium, chloramphenicol sodium succinate, dopamine HCl, hydrocortisone sodium succinate, isoproterenol HCl, lidocaine HCl, methicillin sodium, norepinephrine bitartrate, penicillin G potassium/sodium, pentobarbital sodium, phenobarbital sodium, sodium bicarbonate, verapamil HCl, and vitamin B-complex with C.

Calcium chloride for injection **compatibility information conflicts** or is dependent on diluent or concentration factors with the following drugs or solutions: fat emulsion 10%, dobutamine HCl, oxytetracycline HCl, and tetracycline HCl. Compatibility is dependent upon factors such as pH,

concentration, temperature and diluents used. It is suggested to consult specialized references (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography) for more specific information.
Calcium chloride for injection is reportedly **incompatible** with the following solutions or drugs: amphotericin B, cephalothin sodium, and chlorpheniramine maleate.

**Calcium gluceptate** for injection is reportedly **compatible** with the following intravenous solutions and drugs: sodium chloride for injection 0.45% and 0.9%, Ringer's injection, lactated Ringer's injection, dextrose 2.5%-10%, dextrose-Ringer's injection, dextrose-lactated Ringer's injection, dextrose-saline combinations, ascorbic acid injection, isoproterenol HCl, lidocaine HCl, norepinephrine bitartrate, phytonadione, and sodium bicarbonate.

Calcium gluceptate for injection is reportedly **incompatible** with the following solutions or drugs: cefamandole naftate, cephalothin sodium, magnesium sulfate, prednisolone sodium succinate, and prochlorperazine edisylate. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography) for more specific information.

**Calcium gluconate** for injection is reportedly **compatible** with the following intravenous solutions and drugs: sodium chloride for injection 0.9%, lactated Ringer's injection, dextrose 5%-20%, dextrose-lactated Ringer's injection, dextrose-saline combinations, amikacin sulfate, aminophylline, ascorbic acid injection, bretylium tosylate, cephapirin sodium, chloramphenicol sodium succinate, corticotropin, dimenhydrinate, erythromycin gluceptate, heparin sodium, hydrocortisone sodium succinate, lidocaine HCl, methicillin sodium, norepinephrine bitartrate, penicillin G potassium/sodium, phenobarbital sodium, potassium chloride, tobramycin sulfate, vancomycin HCl, verapamil and vitamin B-complex with C.

Calcium gluconate **compatibility information conflicts** or is dependent on diluent or concentration factors with the following drugs or solutions: phosphate salts, oxytetracycline HCl, prochlorperazine edisylate, and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography) for more specific information.

Calcium gluconate is reportedly **incompatible** with the following solutions or drugs: intravenous fat emulsion, amphotericin B, cefamandole naftate, cephalothin sodium, dobutamine HCl, methylprednisolone sodium succinate, and metoclopramide HCl.

**Pharmacology –** Calcium is an essential element that is required for many functions within the body, including proper nervous and musculoskeletal system function, cell-membrane and capillary permeability, and activation of enzymatic reactions.

**Uses/Indications** - Calcium salts are used for the prevention or treatment of hypocalcemic conditions.

**Pharmacokinetics** - Calcium is absorbed in the small intestine in the ionized form only. Presence of vitamin D (in active form) and an acidic pH is necessary for oral absorption. Parathormone (parathyroid hormone) increases with resultant increased calcium absorption in calcium deficiency states and decreases as serum calcium levels rise. Dietary factors (high fiber, phytates, fatty acids), age, drugs (corticosteroids, tetracyclines), disease states (steatorrhea, uremia, renal osteodystrophy, achlorhydria), or decreased serum calcitonin levels may all cause reduced amounts of calcium to be absorbed.

After absorption, ionized calcium enters the extracellular fluid and then is rapidly incorporated into skeletal tissue. Calcium administration does not necessarily stimulate bone formation. Approximately 99% of total body calcium is found in bone. Of circulating calcium, approximately 50% is bound to serum proteins or complexed with anions and 50% is in the ionized form. Total serum calcium is dependent on serum protein

concentrations. Total serum calcium changes by approximately 0.8 mg/dl for every 1.09 g/dl change in serum albumin. Calcium crosses the placenta and is distributed into milk.

Calcium is eliminated primarily in the feces, contributed by both unabsorbed calcium and calcium excreted into the bile and pancreatic juice. Only small amounts of the drug are excreted in the urine, as most of the cation filtered by the glomeruli is reabsorbed by the tubules and ascending loop of Henle. Vitamin D, parathormone, and thiazide diuretics decrease the amount of calcium excreted by the kidneys. Loop diuretics (*e.g.,* furosemide), calcitonin, and somatotropin increase calcium renal excretion.

**Contraindications/Precautions/Reproductive Safety** - Calcium is contraindicated in patients with ventricular fibrillation or with hypercalcemia. Parenteral calcium should not be administered to patients with above normal serum calcium levels. Calcium should be used very cautiously in patients receiving digitalis glycosides, or with cardiac or renal disease. Calcium chloride, because it can be acidifying, should be used with caution in patients with respiratory failure, respiratory acidosis, or renal disease.

Although parenteral calcium products have not been proven to be safe to use during pregnancy, they are often used before, during, and after parturition in cows, ewes, bitches, and queens to treat parturient paresis secondary to hypocalcemia.

**Adverse Effects/Warnings** - Hypercalcemia can be associated with calcium therapy, particularly in patients with cardiac or renal disease; animals should be adequately monitored. Other effects that may be seen include GI irritation and/or constipation after oral administration, mild to severe tissue reactions after IM or SQ administration of calcium salts and venous irritation after IV administration. Calcium chloride may be more irritating than other parenteral salts and is more likely to cause hypotension. Too rapid intravenous injection of calcium can cause hypotension, cardiac arrhythmias and cardiac arrest.

Should calcium salts be infused perivascularly, first stop the infusion. Ttreatment may then include: infiltrate the affected area with normal saline, corticosteroids administered locally, apply heat and elevate the area, and infiltrate affected area with 1% procaine and hyaluronidase.

**Overdosage/Acute Toxicity** - Unless other drugs are given concurrently that enhance the absorption of calcium, oral overdoses of calcium containing products are unlikely to cause hypercalcemia. Hypercalcemia can occur with parenteral therapy or oral therapy in combination with vitamin D or increased parathormone levels. Hypercalcemia should be treated by withholding calcium therapy and other calcium elevating drugs (*e.g.,* vitamin D analogs). Mild hypercalcemias generally will resolve without further intervention when renal function is adequate.

More serious hypercalcemias (>12 mg/dl) should generally be treated by hydrating with IV normal saline and administering a loop diuretic (*e.g.,* furosemide) to increase both sodium and calcium excretion. Potassium and magnesium must be monitored and replaced as necessary. ECG should also be monitored during treatment. Corticosteroids, and in humans, calcitonin and hemodialysis have also been employed in treating hypercalcemia.

**Drug Interactions** - Patients on **digitalis** therapy are more apt to develop arrhythmias if receiving IV calcium—use with caution. Calcium may antagonize the effects of **verapamil (and other calcium-channel blocking agents)**. **Thiazide diuretics** used in conjunction with large doses of calcium may cause hypercalcemia. Oral **magnesium** products with oral calcium may lead to increased serum magnesium and/or calcium, particularly in patients with renal failure.

Parenteral calcium can neutralize the effects of hypermagnesemia or magnesium toxicity secondary to parenteral **magnesium sulfate**. Parenteral calcium may reverse the effects of nondepolarizing **neuromuscular blocking agents** (*e.g.,* metubine, gallamine, pancuronium, atracurium, & vecuronium).

To Drug Monograph Index To Ophthalmic Product Index

Calcium has been reported to prolong or enhance the effects of **tubocurarine**. Oral calcium can reduce the amount of **phenytoin** or **tetracyclines** absorbed from the GI tract. Patients receiving both parenteral calcium and **potassium** supplementation may have an increased chance of developing cardiac arrhythmias—use cautiously.

Excessive intake of **vitamin A** may stimulate calcium loss from bone and cause hypercalcemia. Concurrent use of large doses of **vitamin D** or its analogs may cause enhanced calcium absorption and induce hypercalcemia.

**Drug/Laboratory Interactions** - Parenteral calcium may cause false-negative results for serum and urinary **magnesium** when using the Titan yellow method of determination.

**Doses** -
**Horses**:

For hypocalcemia:

a) Calcium gluconate injection: 150 - 250 mg/kg IV slowly to effect (intraperitoneal route may also be used). Monitor respirations and cardiac rate and rhythm during administration. (USPC 1990)
b) Calcium gluconate 23% injection: 250 - 500 ml IV slowly, or IM or SQ (divided and given in several locations, with massage at sites of injection). (Label directions; Calcium Gluconate Injection 23%—TechAmerica)
c) For lactation tetany: 250 ml per 450 kg body weight of a standard commercially available solution that also contains magnesium and phosphorous IV slowly while ascultating heart. If no improvement after 10 minutes, repeat. Intensity in heart sounds should be noted, with only an infrequent extrasystole. Stop infusion immediately if a pronounced change in rate or rhythm is detected. (Brewer 1987)

**Elephants:**

a) An Asian cow (~ 3750 kg) in dystocia was given an IV infusion of 750 ml Ca-Mg-borogluconate containing 12 g calcium borogluconate. Schaftenaar,W. 1996. **Vaginal vestibulotomy in an Asian elephant (*Elephas maximus*)**. Proceedings American Association of Zoo Veterinarians. Pages: 434-439

b) Calcium borogluconate: 50-900 ml / animal IV; as a peristaltic, calcium pantothenate, 35-50 g / animal IV Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

**Monitoring Parameters** -

1) Serum calcium
2) Serum magnesium, phosphate, and potassium when indicated
3) Serum PTH (parathormone) if indicated
4) Renal function tests initially and as required
5) ECG during intravenous calcium therapy if possible
6) Urine calcium if hypercalcuria develops

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products** (not necessarily a complete list)
Parenteral Products:

Calcium Gluconate (as calcium borogluconate) 23% [230 mg/ml; 20.7 mg (1.06 mEq) calcium per ml]; in 500 ml bottles; Generic; (Rx) Depending on the product, approved for use in cattle, horses, swine, sheep, cats, and dogs. No withdrawal times are required.

To Drug Monograph Index To Ophthalmic Product Index

Products are also available that include calcium, phosphorus, potassium and/or dextrose; refer to the individual product's labeling for specific dosage information. Trade names for these products include: *Norcalciphos*®—SKB, and *Cal-Dextro*® *Special, #2, C, & K*—Fort Dodge. They are legend (Rx) drugs.

Oral Products: No products containing only calcium (as a salt) are available commercially with veterinary labeling. There are several products (*e.g., Pet-Cal*® and *Osteoform*® *Improved*) that contain calcium with phosphorous and vitamin D (plus other ingredients in some preparations).

**Human-Approved Products** (not a complete list):

Parenteral Products:

Calcium Gluconate Injection 10% [100 mg/ml; 9 mg (0.47 mEq) calcium per ml] in 10 ml amps, 10 & 50 ml, 100 ml, & 200 ml vials; Generic; (Rx)

Calcium Chloride Injection 10% [100 mg/ml; 27.2 mg (1.36 mEq) calcium per ml] in 10 ml amps, vials, and syringes; Generic; (Rx)

Calcium Gluceptate Injection 1.1 g/5 ml in 5 ml amps and 5 ml fill in 10 ml vial; Calcium Gluceptate® (Abbott) (Rx)

Oral Products:

Calcium Gluconate (9% calcium) Tablets: 500 mg (45 mg of calcium), 650 mg (58.5 mg of calcium), 975 mg (87.75 mg calcium), 1 gram (90 mg of calcium); Generic; (OTC)

Calcium Lactate (13% calcium) Tablets: 325 mg (42.25 mg calcium), 650 mg (84.5 mg calcium); Generic; (OTC)

Also available are calcium glubionate syrup, calcium carbonate tablets, suspension & capsules, calcium citrate tablets, dibasic calcium phosphate dihydrate tablets, and tricalcium phosphate tablets.

**Camphorated Tincture of Opium — See Paregoric**

## CARFENTANIL CITRATE

### Elephants:

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

**SPECIAL NOTE REGARDING CARFENTANIL:** Opioid narcotics elevate blood pressure and have been implicated in the etiology of pink foam syndrome in wild African elephants. This emergency situation can be fatal. The syndrome manifests as pink froth from the trunk and is caused by pulmonary edema and capillary bleeding. Several authors recommend that azaperone be combined with opioid narcotics to counteract these hypertensive effects (see Hattingh and Knox, 1994 below). Also see azaperone monograph.

a) African elephants: 0.0021 mg/kg; supplement with 0.0005 mg/kg if needed; agitated or aggressive animals may require higher doses; reverse with 0.08 mg/kg naltrexone or nalmefene. Kreeger,T.J., Arnemo,J.M., and Raath,J.P., 2002. **Handbook of wildlife chemical immobilization**. Wildlife Pharmaceuticals Inc., Fort Collins, Colorado, U.S.A., pp.183-184.

To Drug Monograph Index To Ophthalmic Product Index

b) For wild African elephants the following doses of carfentanil are recommended:
Calves with shoulder heights of 90-115 cm: 1 mg
Calves with shoulder heights of 116-114 cm: 3 mg
Calves with shoulder heights of 141-165 cm: 5 mg
Calves with shoulder heights of 166-200 cm: 7 mg
Adult females: 10 mg
Adult males: 13 mg
These doses can be reduced by 25% for elephants in captivity. Raath,J.P. 1999. **Relocation of African elephants**. In: Fowler,M.E. and Miller,R.E. (Editors), Zoo and Wild Animal Medicine: Current Therapy 4. W.B. Saunders, Philadelphia, PA, USA pp. 525-533

c) A 5000 kg Asian elephant was given 10 mg carfentanil for surgical curettage of a foot abscess. Honeyman,V.L., Cooper,R.M., and Black,S.R. 1998. **A protected contact approach to anesthesia and medical management of an Asian elephant (*Elephas maximus*).** Proceedings AAZV and AAWV Joint Conference. Pages: 338-341

d) Thirty-seven wild African elephants were immobilized as follows: Calves (4-6 years; n=4) were immobilized with 1 mg carfentanil and adults with 3 mg carfentanil mixed with 1500 IU of hyaluronidase. All animals were reversed with naltrexone at a rate of 100 mg for every mg of carfentanil used. For 15 elephants, mean minutes elapsed for initial effect of standing still, recumbency, and recovery following reversal were 5.0 ±1.6, 10.7±3.9, and 5.9±3.9 respectively. Karesh,W.B., Smith,K.H., Smith,F., Atalia,M., Morkel,P., Torres,A., House,C., Braselton,W.E., and Dierenfeld,E.S. 1997. **Elephants, buffalo, kob, and rhinoceros: immobilization, telemetry, and health evaluations.** Proceedings American Association of Zoo Veterinarians. Pages: 296-230

e) Asian elephants: 0.002-0.004 mg/kg (total dose 5-12 mg); African elephants: 0.002 mg/kg (total dose 3-12 mg). Fowler,M.E., 1995. **Elephants**. In: Restraint and handling of wild and domestic animals. Iowa State University Press, Ames, Iowa, USA pp. 265-269

f) 2.4 µg/kg IM was given to captive juvenile African elephants. Schumacher,J., Heard,D.J., Caligiuri,R., Norton,T., and Jacobson,E.R. 1995. **Comparative effects of etorphine and carfentanil on cardiopulmonary parameters in juvenile African elephants (*Loxodonta africana*).** Journal of Zoo and Wildlife Medicine 26:(4):503-507. **Abstract:** Fourteen African elephants (Loxodonta africana) were immobilized with either etorphine hydrochloride (3.2 ± 0.5 µg/kg i.m.) or carfentanil citrate (2.4 µg/kg i.m.). Induction time with etorphine was significantly longer (30 ± 21 min) than with carfentanil (8 ± 2 min). Immediately following immobilization all elephants were placed in lateral recumbency and respiratory rate, heart rate, and rectal body temperature were monitored every 5 min throughout the immobilization period. Arterial blood samples, collected from an auricular artery, were taken 10 min after immobilization and every 15 min thereafter for up to 1 hr. At the first sampling, mean values for arterial blood gas variables for etorphine immobilized elephants were pHa, 7.29 ± 0.03; $PaCO_2$, 53.4 ± 5.2 mmHg; $PaO_2$, 71.8 ± 13.8 mmHg; standard base excess (SBE), -1.6 ± 2.9 mEq/L; and HCO3, 25.7 ± 2.7 mEq/L. After 1 hr of immobilization, mean arterial blood gas values were pHa, 7.32 ± 0.06; $PaCO_2$ , 57.2 ± 9.6 mm Hg; and $PaO_2$ , 53.8 ± 10.5 mm Hg; SBE, 2.7 ± 1.4 mEq/L; and $HCO_{3-}$, 30.6 ± 1.6 mEq/L.

For carfentanil immobilized elephants, blood gas values at the first time of collection were pHa, 7.28 ± 0.04; $PaCO_2$, 52.1 ± 2.8 mmHg; $PaO_2$, 78.3 ± 14.7 mmHg; SBE, -2.3 ± 24 mEq/L; and $HCO_{3-}$, 24.3 ± 2.1 mEq/L. Sixty minutes after the first sampling, blood gas values of one elephant were pHa, 7.38; $PaCO_2$, 48.7 mmHg; $PaO_2$, 52 mmHg; SBE, 3.4 mEq/L, and $HCO_{3-}$, 28.8 mEq/L. Over time there was a progressive decline in arterial PO2 in all elephants. It is concluded that elephants immobilized with either etorphine HCl or carfentanil developed hypoxemia ($PaO_2$ < 60 mmHg) after 30 min of immobilization. It is recommended that the administration of one of these opioid drugs be accompanied by supplemental oxygen, or followed by an inhalant anesthetic in 100% oxygen for prolonged procedures. Diprenorphine or nalmefene reversal was rapid and uneventful in both the etorphine and carfentanil group. No cases of renarcotization were

To Drug Monograph Index To Ophthalmic Product Index

noted. **Additional excerpt:** All elephants in the etorphine group (n=8) received diprenorphine at a mean dosage of 8.3 ± 1.1 µg/kg IV. Two elephants in the carfentanil group (n=6) were administered diprenorphine at a dosage of 8.9 µg/kg IV and IM. Three elephants in this group received nalmefene hydrochloride. One of the three elephants was given nalmefene 166.7 µg/kg both IV and SC. Two of the three elephants were given nalmefene IV and IM. The dosage was 88.9 µg/kg IV and IM in one elephant and 53.3 µg/kg IV and IM in the other. One elephant in the carfentanil group was administered nalmefene (88.9 µg/kg IV) followed by diprenorphine (8.9 µg/kg IM).

g) Carfentanil in combination with azaperone to reduce blood pressure. Hattingh,J. and Knox,C.M. 1994. **Arterial blood pressure in anesthetized African elephants**. South African Journal of Wildlife Research 24:(1/2): **Abstract:** A number of elephants previously captured in the Krueger National Park developed a pink frothy discharge from the external nares. Some of these elephants subsequently died and histopathological examinations indicated severe lung oedema. In view of the current hypothesis that high blood pressure could be a causative factor, arterial blood pressure was measured in elephants immobilized with etorphine alone (n=71) and with etorphine/azaperone (n=109) and with carfentanil/azaperone (n=26) mixtures. Arterial pressure was found to be significantly lower in the groups immobilized with azaperone mixtures than in the group immobilized with etorphine alone ($p < 0.05$). In addition, no cases of lung oedema were observed in animals immobilized with etorphine/azaperone and carfentanil/azaperone mixtures. It is strongly recommended, therefore, that azaperone be added to immobilization mixtures when elephants are subjected to herding prior to darting. Additional excerpt: all elephants in this study were juveniles 200 to 1300 kg. Group 1 (n=71) was immobilized with 4-8 mg etorphine; group 2 (n=109) was immobilized with 4-8 mg etorphine and 50-90 mg azaperone; and group 3 (n=26) was immobilized with 4-8 mg carfentanil and 50-90 mg azaperone

h) For African elephants (wild vs. captive not specified): 1-5 mg for juveniles (1-5 years); 6-8 mg for adult females; 9-10 mg for adult males .Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants**. In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441

i) One African elephant weighing 900 kg was immobilized with 2.3 µg/kg carfentanil IM (1.8 mg total dose), intubated and maintained on halothane and reversed uneventfully with 36 mg nalmefene IV and 36 mg SC. Another African elephant weighing 1,110 kg was immobilized at the same dosage (2.7 mg total dose), maintained on halothane and reversed with 90 mg nalmefene IV and 90 mg SC. Welsch,B., Jacobson,E.R., Kollias,G.V., Kramer,L., Gardner,H., and Page,C.D. 1989. **Tusk extraction in the African elephant (*Loxodonta africana*)**. Journal of Zoo and Wildlife Medicine 20:(4):446-453 **Abstract:** Unilateral dentoalveolar abscesses and/or tusk fractures were identified and tusk extractions performed in seven 3.5-21-yr-old African elephants (*Loxodonta africana*) of both sexes weighing 650-3,000 kg. Following immobilization with etorphine hydrochloride or carfentanil citrate, six of seven elephants were intubated and maintained on a 1-1.5% halothane in oxygen mixture; one elephant was maintained in lateral recumbency by multiple i.v. injections of etorphine. All elephants were positioned with the affected tusk up. For one elephant, two surgical procedures were required to remove the tusk. In six of seven elephants, the tusks were sectioned transversely and the tusk wall thinned by enlarging the pulp cavity with carbide burs. In those tusks with remaining pulp, the pulp was removed with stainless steel rods and hooks. Next, the tusk was sectioned longitudinally into three or four segments using a wood saw within the pulp chamber. bone gouges, osteotomes, and a mallet were used to free the outer epithelial and alveolar attachments from the tusk. Starting with the smallest segment, the sections were removed using long screwdriver-shaped stainless steel rods. The alveolar chamber was then periodically flushed postsurgically with a dilute organic iodine solution. For six of seven elephants, complete granulation of the alveolar chamber was evident by 4 mo postsurgery; the seventh elephant showed partial healing with granulation tissue at 2 mo following surgery.

j) Sixteen African elephants were immobilized with single IM injections of 2.3 ± 0.03 µg/kg IM carfentanil. Jacobson,E.R., Kollias,G.V., Heard,D.J., and Caligiuri,R. 1988. **Immobilization of African elephants with**

**carfentanil and antagonism with nalmefene and diprenorphine**. Journal of Zoo Animal Medicine 19:1-7 **Abstract:** Sixteen African elephants (*Loxodonta africana*) were immobilized with single i.m. injections of carfentanil citrate (2.1 ± 0.3 µg/kg body weight). All elephants were laterally recumbent in 10.1 ± 3.7 min. An additional elephant which received 1.4 µg /kg carfentanil did not become recumbent and additional carfentanil was required for immobilization. Following immobilization, nine elephants were maintained in lateral recumbency by administration of multiple i.v. injections of carfentanil, one elephant received a single i.v. dose of ketamine hydrochloride, and four were intubuted and administered 1-1.5% halothane in oxygen. Because a short duration of immobilization was desired, three elephants were not given additional drugs. The duration of immobilization ranged from 4 to 187 min. Following a variety of medical and surgical procedures, 13 elephants received nalmefene hydrochloride, two elephants received diprenorphine, and two elephants received both diprenorphine and nalmefene; antagonists were administered either i.v. and i.m. or i.v. and s.c. Sixteen of 17 elephants were standing in 2.9 ± 1.4 min; the standing time of one elephant was not recorded. See also nalmefene monograph.

k) Fourteen African elephants were immobilized with etorphine (2.9 ± 0.7 µg/kg ) or carfentanil (2.0 ± 0.2 µg/kg) and physiological effects compared. Jacobson,E.R., Heard,D.J., Caligiuri,R., and Kollias,G.V. 1987. **Physiologic effects of etorphine and carfentanil in African elephants**. Proc.1st.Intl.Conf.Zool.Avian Med. Pages: 525-527 **Abstract:** (Full text): The effects of etorphine hydrochloride and carfentanil citrate on blood pressure, heart rate, respiration and body temperature were determined in a group of captive African elephants (Loxodonta africana). Fourteen African elephants, weighing 450 kg to 4000 kg, divided into 2 groups of 6 and 8 elephants each, received either etorphine hydrochloride (2.9 ± 0.7 µg/kg of body weight; mean ± SD) or carfentanil citrate (2.0 ± 0.2 µg/kg of body weight) respectively. The mean time for lateral recumbency in elephants which received etorphine was 31 ± 9.1 minutes while the mean time for lateral recumbency in elephants which received carfentanil was 10.3 ± 4.1 minutes. Following immobilization, a 18 gauge catheter was inserted into an auricular artery, the catheter connected to a pressure transducer system and systolic, diastolic, and mean arterial pressures were monitored by use of a multichannel oscilloscope. Systolic, diastolic, mean arterial pressures, heart rate, respiration, and temperature were recorded every 5 minutes over a 45 to 60 minute period. Elephants were maintained in lateral recumbency over the period of monitoring by intravenous injections of either etorphine or carfentanil.

Following immobilization with etorphine, mean physiological values for elephants were: systolic pressure, 229 ± 33 mm Hg; diastolic pressure, 141 ± 30 mm Hg; mean arterial pressure, 177 ± 30 mm Hg; heart rate 64 ± 10 beats/minute; respiratory rate 10 ± 4 breaths/minute; body temperature, 97 ± 2°F. Mean physiological values at the final time period of monitoring prior to antagonism were: systolic pressure, 217 ± 40 mm Hg; diastolic pressure, 147 ± 36 mm Hg; mean arterial pressure, 176 ± 38mm Hg; heart rate 77 ± 13 beats/minute; respiratory rate 12 ± 1 breaths/minute; body temperature, 98 ± 2°F. Immediately following the last recording, all 8 elephants received the experimental opioid antagonist, nalmefene hydrochloride, administered at 38 ± 11 µg/kg of body weight given both subcutaneously and intravenously. The mean standing time following administration of nalmefene was 1.4 ± 0.7 minutes.

Immediately following immobilization with carfentanil, mean physiological values for elephants were: systolic pressure, 232 ± 28 mm Hg; diastolic pressure, 148 ± 14 mm Hg; mean arterial pressure, 183 ± 24 mm Hg; heart rate 57 ± 11 beats/minute; respiratory rate 11 ± 3 breaths/minute; body temperature, 99 ± 1°F. Mean physiological values at the final time period of monitoring prior to antagonism were: systolic pressure, 224 ± 29 mm Hg; diastolic pressure, 146 ± 13 mm Hg; mean arterial pressure, 179 ± 18mm Hg; heart rate 65 ± 11 beats/minute; respiratory rate 12 ± 1 breaths/minute; body temperature, 99 ± 1°F. Immediately following the last recording, all 6 elephants received the opioid antagonist, nalmefene hydrochloride administered at 62 ± 17 µg/kg of body weight given both subcutaneously and intravenously. The mean standing time following administration of nalmefene was 2.6 ± 1.6 minutes.

The results of this study indicated that both etorphine and carfentanil resulted in high blood pressure over the duration of the period of monitoring. Based upon these findings, both etorphine hydrochloride and

To Drug Monograph Index To Ophthalmic Product Index

carfentanil citrate are not recommended as the primary agent in performing major invasive surgical procedures in African elephants.

## CARPROFEN

**Chemistry** - A propionic acid derivative non-steroidal antiinflammatory agent, carprofen occurs as a white crystalline compound. It is practically insoluble in water and freely soluble in ethanol at room temperature.

**Storage/Stability/Compatibility** - The commercially available caplets should be stored at room temperature (15-30°C).

**Pharmacology** - Like other NSAIDs, carprofen exhibits analgesic, anti-inflammatory, and antipyretic activity probably through its inhibition of cyclooxygenase, phospholipase $A_2$ and inhibition of prostaglandin synthesis.

**Uses/Indications** - Carprofen is indicated for the relief of pain and inflammation in dogs. It may also prove to be of benefit in other species as well, but data are scant to support its safe use at this time. In Europe, carprofen is reportedly registered for single dose use in cats, but there have been reported problems (e.g., vomiting) with cats receiving more than a single dose.

**Pharmacokinetics** - When administered orally to dogs, carprofen is approximately 90% bioavailable. Peak serum levels occur between 1-3 hours post dosing. The drug is highly bound to plasma proteins (99%) and has a low volume of distribution (0.12 - 0.22 l/kg). Carprofen is extensively metabolized in the liver primarily via glucuronidation and oxidative processes. About 70-80% of a dose is eliminated in the feces; 10-20% eliminated in the urine. Some enterohepatic recycling of the drug occurs. Elimination half-life of carprofen in the dog is approximately 8-12 hours.

**Contraindications/Precautions/Reproductive Safety -** Carprofen is contraindicated in dogs with bleeding disorders (*e.g.,* Von Willebrand's), those that have had prior serious reactions to it or other propionic-class antiinflammatory agents. It should be used with caution in geriatric patients or those with preexisting chronic diseases (*e.g.*, inflammatory bowel disease, renal or hepatic insufficiency).

**Adverse Effects/Warnings** - Although adverse effects appear to be uncommon with carprofen use in dogs, they can occur. Mild gastrointestinal effects are the most likely to appear, but serious effects (hepatocellular damage and/or renal disease; hematologic and serious gastrointestinal effects) have been reported. Geriatric dogs or dogs with chronic diseases (*e.g.*, inflammatory bowel disease, renal or hepatic insufficiency) may be at greater risk for developing toxicity while taking this drug. Although not proven to be statistically significant, Labrador Retrievers have been associated with 1/3 of the initial cases associated with the reported hepatic syndrome. Before initiating therapy, pre-treatment patient evaluation and discussion with the owner regarding the potential risks versus benefits of therapy are strongly advised.

**Overdosage** - In dog toxicologic studies, repeated doses of up to 10X resulted in little adversity. Some dogs exhibited hypoalbuminemia, melena or slight increases in ALT. However, post-marketing surveillance suggests that there may be significant interpatient variability in response to acute or chronic overdoses.

**Drug Interactions** - Note: Although the manufacturer does not list any specific drug interactions in the package insert, it does caution to avoid or closely monitor carprofen's use with other ulcerogenic drugs (*e.g.*, corticosteroids or other NSAIDs). In humans, there are many interactions possible with NSAIDs. Because clinical experience is limited in dogs, the following may or may not be clinically significant: Because carprofen is highly bound to plasma proteins (99%) it may displace other highly bound drugs. Increased serum levels and duration of actions of **phenytoin, valproic acid, oral anticoagulants**, other

**anti-inflammatory agents, salicylates, sulfonamides**, and the **sulfonylurea antidiabetic agents** may occur.
When **aspirin** is used concurrently with carprofen, plasma levels of carprofen could decrease and an increased likelihood of GI adverse effects (blood loss) could occur. Concomitant administration of aspirin with carprofen cannot be recommended. **Probenecid** may cause a significant increase in serum levels and half-life of carprofen. Serious toxicity has occurred when NSAIDs have been used concomitantly with **methotrexate**; use together with extreme caution.
Carprofen may reduce the saluretic and diuretic effects of **furosemide** and increase serum levels of **digoxin**. Use with caution in patients with severe cardiac failure.

**Doses** -
**Dogs:**

As an antiinflammatory/analgesic:

a) 2.2 mg/kg PO twice daily; round dose to nearest half caplet increment (Package Insert; *Rimadyl*®—Pfizer)
b) For surgical pain: 4 mg/kg IV initially once; 2.2 mg/kg PO, IV, subQ or IM, repeat in 12 hours if needed.

For chronic pain: 2.2 mg/kg PO q12h (Johnson 1996)

**Monitoring Parameters** - 1) Baseline (especially in geriatric dogs or dogs with chronic diseases or those where prolonged treatment is likely): physical exam, CBC, Serum chemistry panel (including liver and renal function tests), UA 2) Clinical efficacy 3) Signs of potential adverse reactions: inappetence, diarrhea, vomiting, melena, polyuria/polydipsia, anemia, jaundice, lethargy, behavior changes, ataxia or seizures 4) Chronic therapy: Consider repeating CBC, UA and serum chemistries on an ongoing basis

**Client Information -** Although rare, serious adverse effects have been reported with the use of this drug. Clients should be informed of the risks associated with its use and be alerted to monitor for signs of potential adverse effects (see above). Should these signs present, clients should stop the drug immediately and contact their veterinarian.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products**:

Carprofen 25 mg, 75 mg & 100 mg scored caplets in bottles of 100 or 250; *Rimadyl*® (Pfizer); (Rx). Approved for use in dogs.

## CEFAZOLIN SODIUM

For general information on the cephalosporins including adverse effects, contraindications, overdosage, drug interactions, and monitoring parameters, refer to the monograph: Cephalosporins, General Information.

**Chemistry** - An injectable, semi-synthetic cephalosporin antibiotic, cefazolin sodium occurs as a practically odorless or having a faint odor, white to off-white, crystalline powder or lyophilized solid. It is freely soluble in water and very slightly soluble in alcohol. Each gram of the injection contains 2 mEq of sodium. After reconstitution, the solution for injection has a pH of 4.5 - 6 and has a light yellow to yellow color. May also be known as cephazolin sodium in the U.K. and other countries.

**Storage/Stability/Compatibility** - Cefazolin sodium powder for injection and solutions for injection should be protected from light. The powder for injection should be stored at room temperature (15-30°C); avoid

temperatures above 40°C. The frozen solution for injection should be stored at temperatures no higher than -20°C.

After reconstitution, the solution is stable for 24 hours when kept at room temperature and 96 hours if refrigerated. If after reconstitution, the solution is immediately frozen in the original container, the preparation is stable for at least 12 weeks when stored at -20°C.

The following drugs or solutions are reportedly **compatible** with cephapirin: Amino acids 4.25%/dextrose 25%, $D_5W$ in Ringer's, $D_5W$ in Lactated Ringer's, $D_5W$ in sodium chloride 0.2% - 0.9%, $D_5W$, $D_{10}W$, Ringer's Injection, Lactated Ringer's Injection, normal saline, metronidazole, verapamil HCl and vitamin B-complex.

The following drugs or solutions are reportedly **incompatible** or only compatible in specific situations with cefazolin: amikacin sulfate, amobarbital sodium, ascorbic acid injection, bleomycin sulfate, calcium chloride/gluconate, cimetidine HCl, erythromycin gluceptate, kanamycin sulfate, lidocaine HCl, oxytetracycline HCl, pentobarbital sodium, polymyxin B sulfate, tetracycline HCl and vitamin B-complex with C injection.

Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology/Spectrum of Activity** - A first generation cephalosporin, cefazolin exhibits activity against the bacteria usually covered by this class. Because MIC's occasionally differ for cefazolin when compared to either cephalothin/cephapirin, some clinical microbiologists recommend also testing bacterial susceptibilities for this antibiotic. For more specific information, refer to the monograph, Cephalosporins, General Information.

**Uses/Indications** - In the United States, there are no cefazolin products approved for veterinary species, but it has been used clinically in several species when an short-acting injectable first generation cephalosporin is indicated.

**Pharmacokinetics (specific)** - Cefazolin is not appreciably absorbed after oral administration and must be given parenterally to achieve therapeutic serum levels. Absorbed drug is excreted unchanged by the kidneys into the urine. Elimination half-lives may be significantly prolonged in patients with severely diminished renal function. Pharmacokinetic parameters for dogs and horses follow:

In dogs, peak levels occur in about 30 minutes after IM administration. The apparent volume of distribution at steady state is 700 ml/kg, total body clearance of 10.4 ml/min/kg with a serum elimination half-life of 48 minutes. Approximately 64% of the clearance can be attributed to renal tubular secretion. The drug is approximately 16-28% bound to plasma proteins in dogs.

In horses, the apparent volume of distribution at steady state is 190 ml/kg, total body clearance of 5.51 ml/min/kg with a serum elimination half-life of 38 minutes when given IV and 84 minutes after IM injection (gluteal muscles). Cefazolin is about 4-8% bound to equine plasma proteins. Because of the significant tubular secretion of the drug, it would be expected that probenecid administration would alter the kinetics of cefazolin. One study performed in horses (Donecker, Sams, and Ashcroft 1986), did not show any effect, but the author's concluded that the dosage of probenecid may have been sub-therapeutic in this species.

In calves, the volume of distribution is 165 ml/kg, and had a terminal elimination half-life of 49-99 minutes after IM administration.

To Drug Monograph Index To Ophthalmic Product Index

**Doses** -
**Horses**:

For susceptible infections:

a) Respiratory tract: 11 mg/kg IV or IM q12h (Beech 1987a)
b) 11 mg/kg IV or IM *qid* (Robinson 1987)
c) Foals: 20 mg/kg IV q8-12h (Caprile and Short 1987)

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Cefazolin Sodium Powder for Injection 250 mg (of cefazolin), 500 mg, 1, 5, 10, & 20g; *Ancef*® (SKF); *Kefzol*® (Lilly); *Zolicef*® (Apothecon);*Cefazolin Sodium*® (Apothecon). (Rx)

Cefazolin Sodium for Injection (IV infusion) 500 mg in 5% Dextrose in Water (of cefazolin), 1 g in 5% Dextrose in Water, 1 g in 10 ml vials; *Ancef*® (SKB), *Kefzol*® (Lilly); (Rx)

## CEFOPERAZONE SODIUM

**Chemistry** - A third generation cephalosporin, cefoperazone sodium contains a piperazine side chain giving it antipseudomonal activity. It occurs as white, crystalline powder and is freely soluble in water and poorly soluble in alcohol. At room temperature, cefoperazone sodium has a maximum solubility in compatible IV solutions of 475 mg/ml (at concentrations >333 mg/ml vigorous and prolonged shaking may be required). Reconstituted solutions of the drug have a pH from 4.5 - 6.5. One gram contains 1.5 mEq of sodium.

**Storage/Stability/Compatibility** - The sterile powder for injection should be stored at temperatures less than 25°C and protected from light. Once reconstituted, solutions do not need to be protected from light.

After reconstitution, cefoperazone sodium is generally stable for 24 hours at room temperature and 5 days when refrigerated in a variety of IV solutions (*e.g.*, sterile or bacteriostatic water for injection, dextrose in water/saline/LRS solutions, lactated Ringer's injection, Normasol R, and saline IV solutions). When frozen at -2 to -10°C in dextrose, sodium chloride or sterile water for injection, cefoperazone sodium is stable for 3 weeks (dextrose solutions) to 5 weeks (water or saline solutions).

Cefoperazone sodium is reportedly **compatible** with cimetidine HCl, clindamycin phosphate, furosemide and heparin sodium, acyclovir sodium, cyclophosphamide, esmolol HCl, famotidine, hydromorphone HCl, magnesium sulfate, and morphine sulfate. It is reportedly **incompatible** with some TPN mixtures, doxapram HCl, gentamicin sulfate, hetastarch, labetolol HCl, meperidine HCl, odansetron HCl, perphenazine, promethazine, and sargostim. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography) for more specific information.

**Pharmacology** - Cefoperazone is a third generation injectable cephalosporin agent. For more information, refer to the monograph: Cephalosporins, General Information.

**Uses/Indications** - Cefoperazone is used to treat serious infections, particularly against susceptible *Enterobacteriaceae* not susceptible to other less expensive agents or when aminoglycosides are not indicated (due to their potential toxicity).

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacokinetics** - Cefoperazone is not absorbed after oral administration and must be given parenterally. It is widely distributed throughout the body; CSF levels are low if meninges are not inflamed. Cefoperazone crosses the placenta and enters maternal milk in low concentrations; no documented adverse effects to offspring have been noted. Unlike most cephalosporins, cefoperazone is principally excreted in the bile and elimination half-lives are approximately 2 hours in humans. Dosage adjustments generally are not required for patients with renal insufficiency.

**Contraindications/Precautions/Reproductive Safety** - Only prior allergic reaction to cephalosporins contraindicates cefoperazone's use. In humans documented hypersensitive to penicillin, up to 16% may also be allergic to cephalosporins. The veterinary significance of this is unclear. Because cefoperazone is excreted in the bile, patients with significant hepatic disease or biliary obstruction may have their serum half-lives increase 2 - 4 times above normal. Dosage adjustment may be necessary. Cefoperazone should be used with caution in patients with preexisting bleeding disorders. It contains a thiomethyltetrazole side-chain which has been associated with causing coagulation abnormalities.

No teratogenic effects were demonstrated in studies in pregnant mice, rats, and monkeys given up to 10 times labeled doses of cefoperazone.

**Adverse Effects/Warnings** - Cefoperazone is a relatively safe agent. Rarely, hypersensitivity reactions could potentially occur in animals. Because of its thiomethyltetrazole side-chain it may also rarely cause hypoprothrombinemia. Diarrhea secondary to changes in gut flora have been reported. Some human patients demonstrate mild, transient increases in liver enzymes, serum creatinine and BUN. Clinical significance of these effects is in doubt. If administered via the IM route, pain at the injection site has also been noted.

**Overdosage/Acute Toxicity** - No specific antidotes are available. Overdoses should be monitored and treated symptomatically and supportively if required.

**Drug Interactions** - A disulfiram-like reaction (anorexia, nausea, vomiting) has been reported in humans who have ingested **alcohol** with 48-72 hours of receiving beta-lactam antibiotics with a thiomethyltetrazole side-chain (*e.g.,* cefamandole, cefoperazone, moxalactam, cefotetan). Because these antibiotics have been associated with bleeding, they should be used cautiously in patients receiving **oral anticoagulants**. Synergism against some Enterobacteriaceae (*e.g*., *Pseudomonas aeruginosa*) may be attained if using cefoperazone with a beta-lactamase inhibitor such as **clavulanic acid** or with an **aminoglycoside (*e.g.*, gentamicin, amikacin).** Do not mix cefoperazone in same syringe or IV bag with aminoglycosides as inactivation may occur. Synergy may be unpredictable however and although there have been no reports of additive nephrotoxicity with cefoperazone, some cephalosporins may increase the nephrotoxic potential of aminoglycosides. Probenecid does not have an effect on cefoperazone elimination.

**Laboratory Considerations -** When using Kirby-Bauer disk diffusion procedures for testing susceptibility, a specific 75 micrograms cefoperazone disk should be used. A cephalosporin-class disk containing cephalothin should not be used to test for cefoperazone susceptibility. An inhibition zone of 21 mm or more indicates susceptibility; 16-20 mm, intermediate; and 15 mm or less, resistant.

When using a dilution susceptibility procedure, an organism with a MIC of 16 micrograms/ml or less is considered susceptible and 64 micrograms/ml or greater is considered resistant. With either method, infections caused by organisms with intermediate susceptibility may be effectively treated if the infection is limited to tissues where the drug is concentrated (*e.g*., urine, bile) or if a higher than normal dose is used.

In some human patients receiving cefoperazone, a positive direct antiglobulin (**Coombs'**) test has been reported.

To Drug Monograph Index To Ophthalmic Product Index

Cefoperazone, like most other cephalosporins, may cause a **false-positive urine glucose determination** when using the cupric sulfate solution test (*e.g.*, *Clinitest*®).

**Doses** -
**Horses**:
For susceptible infections: 30 - 50 mg/kg q8-12h IV or IM (Note: This is a human dose and should be used as a general guideline only) (Walker 1992)

**Monitoring Parameters** - 1) Efficacy; 2) PT's, CBC if bleeding occurs

**Client Information** - Because cefoperazone use is generally associated with inpatient therapy, little client monitoring is required. They should be alert to either bleeding problems or symptoms associated with hypersensitivity.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:
Cefoperazone Sodium Powder for Injection in 1g, 2g vials. Also available in 1 or 2 gram piggyback containers and in pre-mixed frozen in 50 ml plastic containers *Cefobid*® (Roerig); (Rx)

## CEFOTAXIME SODIUM

For general information on the cephalosporins including adverse effects, contraindications, overdosage, drug interactions, and monitoring parameters, refer to the monograph: Cephalosporins, General Information.

**Chemistry** - A semisynthetic, 3rd generation, aminothiazolyl cephalosporin, cefotaxime sodium occurs as an odorless, white to off-white crystalline powder with a $pK_a$ of 3.4. It is sparingly soluble in water and slightly soluble in alcohol. Potency of cefotaxime sodium is expressed in terms of cefotaxime. One gram of cefotaxime (sodium) contains 2.2 mEq of sodium.

**Storage/Stability/Compatibility** - Cefotaxime sodium sterile powder for injection should be stored at temperatures of less than 30°C; protect from light. The commercially available frozen injection should be stored at temperatures no greater than -20°C. Depending on storage conditions, the powder or solutions may darken which may indicate a loss in potency.

All commonly used IV fluids and the following drugs are reportedly **compatible** with cefotaxime: metronidazole and verapamil. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology/Spectrum of Activity** - Cefotaxime has a relatively wide spectrum of activity against both gram positive and gram negative bacteria. While less active against *Staphylococcus spp.* than the first generation agents, it still has significant activity against those and other gram positive cocci. Cefotaxime, like the other 3rd generation agents, has extended coverage of gram negative aerobes particularly in the family Enterobacteriaceae, including *Klebsiella sp., E. coli, Salmonella, Serratia marcesans, Proteus sp.*, and *Enterobacter sp..* Cefotaxime's *in vitro* activity against *Pseudomonas aeruginosa* is variable and results are usually disappointing when the drug is used clinically against this

organism. Many anaerobes are also susceptible to cefotaxime, including strains of *Bacteroides fragilis*, *Clostridium sp*., *Fusobacterium sp*., *Peptococcus sp*., and *Peptostreptococcus sp*..

Because 3rd generation cephalosporins exhibit specific activities against bacteria, a 30 micrograms cefotaxime disk should be used when performing Kirby-Bauer disk susceptibility tests for this antibiotic.

**Uses/Indications** - In the United States, there are no cefotaxime products approved for veterinary species, but it has been used clinically in several species when an injectable 3rd generation cephalosporin may be indicated.

**Pharmacokinetics (specific)** - Cefotaxime is not appreciably absorbed after oral administration and must be given parenterally to attain therapeutic serum levels. After administration, the drug is widely distributed in body tissues, including bone, prostatic fluid (human), aqueous humor, bile, ascitic and pleural fluids. Cefotaxime crosses the placenta and activity in amniotic fluid either equals or exceeds that in maternal serum. Cefotaxime also is distributed into milk in low concentrations. In humans, approximately 13-40% of the drug is bound to plasma proteins.

Unlike the first generation cephalosporins (and most 2nd generation agents), cefotaxime will enter the CSF in therapeutic levels (at high dosages) when the patient's meninges are inflamed.

Cefotaxime is partially metabolized by the liver to desacetylcefotaxime which exhibits some antibacterial activity. Desacetylcefotaxime is partially degraded to inactive metabolites by the liver. Cefotaxime and its metabolites are primarily excreted in the urine. Because tubular secretion is involved in the renal excretion of the drug, probenecid has been demonstrated in several species to prolong the serum half-life of cefotaxime.

Pharmacokinetic parameters in certain veterinary species follow: In dogs, the apparent volume of distribution at steady state is 480 ml/kg, and a total body clearance of 10.5 ml/min/kg after intravenous injection. Serum elimination half-lives of 45 minutes when given IV, 50 minutes after IM injection, and 103 minutes after SQ injection have been noted. Bioavailability is about 87% after IM injection and approximately 100% after SQ injection.

In cats, total body clearance is approximately 3 ml/min/kg after intravenous injection and the serum elimination half-life is about 1 hour. Bioavailability is about 93-98% after IM injection.

**Doses** -
**Horses**:

For susceptible infections:

a) Foals: 20 - 30 mg/kg IV q6h (Caprile and Short 1987)

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Cefotaxime Sodium Powder for Injection; 500 mg, 1 g (as cefotaxime), 2 g, 10 g; *Claforan*® (Hoechst Marion Roussel); (Rx)

Cefotaxime Sodium for Injection in 5% dextrose bags (50 ml)—frozen; 1 g, 2 g; *Claforan*® (Hoechst Marion Roussel); (Rx)

To Drug Monograph Index To Ophthalmic Product Index

## CEFOXITIN SODIUM

For general information on the cephalosporins including adverse effects, contraindications, overdosage, drug interactions, and monitoring parameters, refer to the monograph: Cephalosporins, General Information.

**Chemistry** - Actually a cephamycin, cefoxitin sodium is a semisynthetic antibiotic that is derived from cephamycin C which is produced by *Streptomyces lactamdurans*. It occurs as a white to off-white, somewhat hygroscopic powder or granules with a slight characteristic odor. It is very soluble in water and slightly soluble in alcohol. Each gram of cefoxitin sodium contains 2.3 mEq of sodium.

**Storage/Stability/Compatibility** - Cefoxitin sodium powder for injection should be stored at temperatures less than 30°C and should not be exposed to temperatures greater than 50°C. The frozen solution for injection should be stored at temperatures no higher than -20°C.

After reconstitution, the solution is stable for 24 hours when kept at room temperature and from 48 hours to 1 week if refrigerated. If after reconstitution the solution is immediately frozen in the original container, the preparation is stable up to 30 weeks when stored at -20°C. Stability is dependent on the diluent used and the reader should refer to the package insert or other specialized references for more information. The powder or reconstituted solution may darken, but this apparently does not affect the potency of the product.

All commonly used IV fluids and the following drugs are reportedly **compatible** with cefoxitin: amikacin sulfate, cimetidine HCl, gentamicin sulfate, kanamycin sulfate, mannitol, metronidazole, mutivitamin infusion concentrate, sodium bicarbonate, tobramycin sulfate and vitamin B-complex with C. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology/Spectrum of Activity** - Although not a true cephalosporin, cefoxitin is usually classified as a 2nd generation agent. Cefoxitin has activity against gram positive cocci, but less so on a per weight basis than the 1st generation agents. Unlike the first generation agents, it has good activity against many strains of *E. coli*, *Klebsiella* and *Proteus* that may be resistant to the first generation agents. In human medicine, cefoxitin's activity against many strains of *Bacteroides fragilis* has placed it in a significant therapeutic role. While *Bacteroides fragilis* has been isolated from anerobic infections in veterinary patients, it may not be as significant a pathogen in veterinary species as in humans.

Because 2nd generation cephalosporins exhibit specific activities against bacteria, a 30-micrograms cefoxitin disk should be used when performing Kirby-Bauer disk susceptibility tests for this antibiotic

**Uses/Indications** - In the United States, there are no cefoxitin products approved for veterinary species, but it has been used clinically in several species when an injectable second generation cephalosporin may be indicated.

**Pharmacokinetics (specific)** - Cefoxitin is not appreciably absorbed after oral administration and must be given parenterally to achieve therapeutic serum levels. The absorbed drug is primarily excreted unchanged by the kidneys into the urine via both tubular secretion and glomerular filtration. In humans, approximately 2% of a dose is metabolized to descarbamylcefoxitin, which is inactive. Elimination half-lives may be significantly prolonged in patients with severely diminished renal function.

In horses, the apparent volume of distribution at steady state is 110 ml/kg, total body clearance of 4.32 ml/min/kg with a serum elimination half-life of 49 minutes.

In calves, the volume of distribution is 318 ml/kg, and has a terminal elimination half-life of 67

To Drug Monograph Index To Ophthalmic Product Index

minutes after IV dosing, and 81 minutes after IM administration. Cefoxitin is approximately 50% bound to calf plasma proteins. Probenecid (40 mg/kg) has been demonstrated to significantly prolong elimination half-lives.

**Doses –**
**Horses**:
For susceptible infections:
a) Foals: 20 mg/kg IV q4-6h (Caprile and Short 1987)

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:
Cefoxitin Sodium Powder for Injection 1 g (of cefoxitin), 2 g, 10 g
*Mefoxin*® (Merck); (Rx)
Cefoxitin Sodium in Dextrose 5% (Frozen) 1 g (20 mg/ml), 2 g (40 mg/ml)
*Mefoxin*® (Merck); (Rx)

## CEFTIOFUR SODIUM - PK
## CEFTIOFUR HCL

For general information on the cephalosporins including adverse effects, contraindications, overdosage, drug interactions, and monitoring parameters, refer to the monograph: Cephalosporins, General Information.

**Chemistry** - Ceftiofur sodium and HCl are semisynthetic 3rd generation cephalosporins.

**Storage/Stability/Compatibility** - Unreconstituted ceftiofur sodium powder for reconstitution should be stored in the refrigerator (2°-8°C). Protect from light. Color of the cake may vary from off-white to tan, but this does not affect potency. After reconstitution with bacteriostatic water for injection or sterile water for injection, the solution is stable for up to 7 days when refrigerated and for 12 hours at room temperature (15-30°C). According to the manufacturer, if a precipitate should form while being stored refrigerated during this time, the product may be used if it goes back into solution after warming. If not, contact the manufacturer. Frozen reconstituted solutions are stable for up to 8 weeks. Thawing may be done at room temperature or by swirling the vial under running warm or hot water.

The HCl product should be stored at controlled room temperature (20°-25°C; 68°-77°F) and protected from freezing. It should be shaken well before use.

**Pharmacology/Spectrum of Activity** - Ceftiofur inhibits cell wall synthesis (at stage three) of susceptible multiplying bacteria. Ceftiofur exhibits a spectrum of activity similar to that of cefotaxime. It has a broad range of in vitro activity against a variety of pathogens, including many species of Pasturella, Streptococcus, Staphylococcus, Salmonella, and E.coli.

**Uses/Indications** - Ceftiofur sodium/HCl is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Pasturella hemolytica, Pasturella multocida* and *Haemophilus somnus* in lactating or non-lactating cattle and ceftiofur sodium is indicated in horses for respiratory disease associated with *Strep zooepidimicus*:. Ceftiofur HCl is also approved for foot rot in cattle.

To Drug Monograph Index To Ophthalmic Product Index

Ceftiofur could potentially be of usefulness in small animal infections as well, but little published data is available to recommend its use.

**Pharmacokinetics (specific)** - In cattle, ceftiofur sodium and HCl have practically equivalent pharmacokinetic parameters. Peak levels of ceftiofur are slightly higher after IM injection of Naxcel®, but areas under the curve are practically equal as well as elimination half-lives (approx. 9-12 hours).

**Doses** -
**Cattle**:

For labeled indications:

a) Naxcel®: 1.1 - 2.2 mg/kg IM once daily for 3 treatments; may give additional doses on 4th and 5th day if response is not satisfactory. Reconstitute 1 g vial with 20 ml and the 4 g vial with 80 ml of either Bacteriostatic Water for Injection or Sterile Water for Injection. (Package Insert; *Naxcel*®—Upjohn)

b) Excenel®: 1.1 - 2.2 mg/kg IM or SQ once daily for 3 treatments; may give additional doses on 4th and 5th day if response is not satisfactory. For BRD only: May inject 2.2 mg/kg IM or SQ every other day (days 1 and 3; 48 hour interval). Do not inject more than 15 ml pe IM injection site. (Package Insert; *Excenel*®—Pharmacia/Upjohn)

**Horses**:

For respiratory disease associated with *Strep zooepidimicus*::

a) Naxcel®: 2.2 - 4.4 mg/kg (2 - 4 ml reconstituted sterile solution per 100 lb. of body weight) with a maximum of 10 ml administered per injection site. Repeat treatment at 24 hour intervals, continued for 48 hours after symptoms have disappeared. Do not exceed 10 days of treatment. (Package Insert; *Naxcel*®—Upjohn)

**Elephants:**

a) 2.2 – 4.4 mg/kg. Houck, R: Senior Veterinarian, Ringling Brothers and Barnum and Bailey Circus, 8607 Westwood Center Drive, Vienna, Virginia, 22182, personal communication, 1986. In: Olsen,J.H., 1999. **Antibiotic therapy in elephants**. In: Fowler,M.E. and Miller R.E. (Editors), **Zoo and Wild Animal Medicine: Current Therapy 4.** W.B. Saunders, Philadelphia, PA,USA p. 538

b) 1.1 mg/kg IM. Schmidt, M.J: Senior Research Veterinarian, Washington Park Zoo, Portland, Oregon, personal communication, 1986. In: Olsen,J.H., 1999. **Antibiotic therapy in elephants**. In: Fowler,M.E. and Miller R.E. (Editors), **Zoo and Wild Animal Medicine: Current Therapy 4.** W.B. Saunders, Philadelphia, PA,USA p. 538

Note: Naxcel can be reconstituted with less diluent than the package recommendations (25 to 35 ml vs 80 ml) and injections are well-tolerated (Mikota).

c) 1.1 mg/kg IM BID or TID or 1.1 mg/kg IV SID depending on the MIC of the pathogen (Dumonceaux, 2005). Dumonceaux, G, Isaza, R. Koch, D.E., and Hunter, R.P. 2005. Pharmacokinetics and i.m. bioavailability of ceftiofur in Asian elephants (Elephas maximus). J Vet Pharmacol Ther. 28(5):441-6.

Captive elephants are prone to infections of the feet, lungs, and skin. Often treatment regimens are established with no pharmacokinetic data on the agents being used for treatment in these species. A pharmacokinetic study using ceftiofur (1.1 mg/kg) was conducted in four adult female captive Asian elephants (Elephas maximus) at Busch Gardens in Tampa, Florida. Elephants were given both i.v. and i.m. administrations in a complete crossover design with a 3-week washout period between treatments. Blood samples were collected prior to drug administration and at 0.33, 0.67, 1, 1.5, 2, 4, 8, 12, 24, 48 and 72 h postadministration. Ceftiofur analysis was performed using a validated liquid chromatography/mass

To Drug Monograph Index To Ophthalmic Product Index

spectrophotometric (LC/MS) assay. Plasma concentrations for the i.m. samples were lower than expected. The mean C(max) following i.m. administration was 1.63 microg/mL with a corresponding T(max) of 0.55 h. Following i.v. administration, the median V(d(ss)) was 0.51 L/kg and a median Cl(p) of 0.069 L/kg/h. Mean i.m. bioavailability was 19%. The results indicate that ceftiofur used at 1.1 mg/kg i.m. could be useful in elephants when given two to three times a day or alternatively, 1.1 mg/kg i.v. once daily, depending upon the MIC of the pathogen.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Ceftiofur Sodium Powder for Injection 1 g, 4 g vials; *Naxcel*® (Pharmacia&Upjohn); (Rx) Approved for use in cattle and horses. No slaughter withdrawal or milk withholding time are required when administered as labeled.

Ceftiofur HCl Suspension for Injection 50 mg(of ceftiofur)/ml in 100 ml vials; *Excenel*® (Pharmacia&Upjohn); (Rx). Approved for use in cattle. Slaughter withdrawal=48 hours; no milk withholding time required when administered as labeled.

**Human-Approved Products**: None

## CEFTIOFUR LONG ACTING PK

**Pharmacokinetics of a long-acting ceftiofur crystalline-free acid formulation in Asian elephants (Elephas maximus).** M. J. Adkesson, R. E. Junge, M. C. Allender and T. Martin-Jimenez. Am J Vet Res 2012 Vol. 73 Issue 10 Pages 1512-8. Accession Number: 23013176 DOI: 10.2460/ajvr.73.10.1512

OBJECTIVE: To determine the pharmacokinetics of a long-acting formulation of ceftiofur, ceftiofur crystalline-free acid (CCFA), following SC injection to Asian elephants (Elephas maximus). ANIMALS: 11 adult Asian elephants. PROCEDURES: Each elephant received CCFA (6.6 mg/kg, SC) in the area caudoventral to the base of an ear. Blood samples were collected from an ear vein immediately prior to and at 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours after CCFA administration. Plasma concentrations of desfuroylceftiofur acetamide (the acetamide derivative of ceftiofur) were measured via ultrahigh-pressure liquid chromatography-tandem mass spectrometry. Data were analyzed via a noncompartmental pharmacokinetics approach. RESULTS: The mean +/- SD maximum plasma concentration of desfuroylceftiofur acetamide was 1.36 +/- 0.74 mug/mL and was detected at 4718 +/- 31.30 hours. The mean +/- SD area under the curve from time 0 to infinity was 2278 +/- 55.8 mug*h/mL, and the mean residence time from time 0 to infinity was 158.2 +/- 90.2 hours. The terminal elimination half-life associated with the slope of the terminal phase had a harmonic mean +/- pseudo-SD of 83.36 +/- 30.01 hours. CONCLUSIONS AND CLINICAL RELEVANCE: Elephants tolerated CCFA at a dose of 6.6 mg/kg, SC, well. Dosing recommendations will depend on the mean inhibitory concentration of ceftiofur for each bacterial pathogen. Desfuroylceftiofur acetamide concentrations remained > 0.25 mug/mL for the entire 168-hour study period, which suggested CCFA would provide clinically relevant antimicrobial activity against certain pathogens for 7 to 10 days.

## CEFTRIAXONE SODIUM CEFTIOFUR LONG ACTING

**Chemistry** - A third generation cephalosporin, ceftriaxone sodium occurs as white to yellowish-orange crystalline powder. It is soluble in water (400 mg/ml at 25°C). Potencies of commercial products are expressed in terms of ceftriaxone. One gram of ceftriaxone sodium contains 3.6 mEq of sodium.

**Storage/Stability/Compatibility** - The sterile powder for reconstitution should be stored at, or below 25°C and protected from light.

To Drug Monograph Index To Ophthalmic Product Index

After reconstituting with either 0.9% sodium chloride or $D_5W$, ceftriaxone solutions (at concentrations of approximately 100 mg/ml) are stable for 3 days at room temperature and for 10 days when refrigerated. Solutions of concentrations of 250 mg/ml are stable for 24 hours at room temperature and 3 days when refrigerated. At concentrations of 10-40 mg/ml solutions frozen at -20°C are stable for 26 weeks. The manufacturer does not recommend admixing any other anti-infective drugs with ceftriaxone sodium.

**Pharmacology** - Ceftriaxone is a third generation injectable cephalosporin agent. For more information, refer to the monograph: Cephalosporins, General Information.

**Uses/Indications** - Ceftriaxone is used to treat serious infections, particularly against susceptible *Enterobacteriaceae* that are not susceptible to other less expensive agents or when aminoglycosides are not indicated (due to their potential toxicity). Its long half life, good CNS penetration, and activity against *Borrelia burgdorferi* also has made it a potential choice for treating Lyme's disease.

**Pharmacokinetics** - Ceftriaxone is not absorbed after oral administration and must be given parenterally. It is widely distributed throughout the body; CSF levels are higher when meninges are inflamed. Ceftriaxone crosses the placenta and enters maternal milk in low concentrations; no documented adverse effects to offspring have been noted. Ceftriaxone is excreted by both renal and non-renal mechanisms and in humans, elimination half-lives are approximately 6-11 hours. Dosage adjustments generally are not required for patients with renal insufficiency (unless severely uremic) or with hepatic impairment.

**Contraindications/Precautions/Reproductive Safety** - Only prior allergic reaction to cephalosporins contraindicates ceftriaxone's use. In humans documented hypersensitive to penicillin, up to 16% may also be allergic to cephalosporins. The veterinary significance of this is unclear.

Although bleeding times have only been reported rarely in humans, ceftriaxone should be used with caution in patients with vitamin K utilization or synthesis abnormalities (*e.g.*, severe hepatic disease).

No teratogenic effects were demonstrated in studies in pregnant mice and rats given up to 20 times labeled doses of ceftriaxone.

**Adverse Effects/Warnings** - Because veterinary usage of ceftriaxone is very limited, an accurate adverse effect profile has not been determined. The following adverse effects have been reported in humans and may or may not apply to veterinary patients: hematologic effects, including eosinophilia (6%), thrombocytosis (5%), leukopenia (2%) and more rarely, anemia, neutropenia, lymphopenia and thrombocytopenia. Approximately 2-4% of humans get diarrhea. Very high dosages (100 mg/kg/day) in dogs have caused a "sludge" in bile. Hypersensitivity reactions (usually a rash) have been noted. Increased serum concentrations of liver enzymes, BUN, creatinine, and urine casts have been described in about 1-3% of patients. When given IM, pain may be noted at the injection site.

**Overdosage/Acute Toxicity** - Limited information available; overdoses should be monitored and treated symptomatically and supportively if required.

**Drug Interactions** - Synergism against some Enterobacteriaceae (*e.g.*, *Pseudomonas aeruginosa*) may be attained if using cefoperazone with an **aminoglycoside (*e.g.*, gentamicin, amikacin).** Organisms with a high degree of resistance to both ceftriaxone and the aminoglycoside are unlikely to be affected when the two drugs are used together.
Probenecid does not have an effect on ceftriaxone elimination.

**Laboratory Considerations -** When using Kirby-Bauer disk diffusion procedures for testing susceptibility, a specific 30 micrograms ceftriaxone disk should be used. A cephalosporin-class disk containing cephalothin

should not be used to test for ceftriaxone susceptibility. An inhibition zone of 18 mm or more indicates susceptibility; 14-17 mm, intermediate; and 13 mm or less, resistant.

When using a dilution susceptibility procedure, an organism with a MIC of 16 micrograms/ml or less is considered susceptible and 64 micrograms/ml or greater is considered resistant. With either method, infections caused by organisms with intermediate susceptibility may be effectively treated if the infection is limited to tissues where the drug is concentrated or if a higher than normal dose is used.

Ceftriaxone, like most other cephalosporins, may cause a **false-positive urine glucose** determination when using the cupric sulfate solution test (*e.g.*, *Clinitest*®).

Ceftriaxone in very high concentrations (50 micrograms/ml or greater) may cause falsely elevated serum creatinine levels when manual methods of testing are used. Automated methods do not appear to be affected.

**Doses** -
**Horses**:

For susceptible infections: 25 - 50 mg/kg q12h IV or IM (Note: This is a human dose and should be used as a general guideline only) (Walker 1992)

**Monitoring Parameters** - 1) Efficacy; 2) If long term therapy, occasional CBC, renal function (BUN, Serum Creatinine, urinalysis) and liver enzymes (AST, ALT) may be considered.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Ceftriaxone Powder for Injection 250 mg, 500 mg (as sodium), 1 g, 2g, 10 g; *Cefizox*® (Fujisawa) (Rx)

Ceftriaxone Injection in 5% dextrose in Water 1 g (as sodium) & 2 g frozen, premixed; *Cefizox*® (Fujisawa) (Rx)

## CEPHALEXIN

For general information on the cephalosporins including adverse effects, contraindications, overdosage, drug interactions, and monitoring parameters, refer to the monograph: Cephalosporins, General Information..

**Chemistry** - A semi-synthetic oral cephalosporin, cephalexin (as the monohydrate) occurs as a white to off-white, crystalline powder. It is slightly soluble in water and practically insoluble in alcohol.

**Storage/Stability/Compatibility** - Cephalexin tablets, capsules, and powder for oral suspension should be stored at room temperature (15-30°C) in tight containers. After reconstitution, the oral suspension is stable for 2 weeks.

**Pharmacology/Spectrum of Activity** - A first generation cephalosporin, cephalexin exhibits activity against the bacteria usually covered by this class. Refer to the monograph: Cephalosporins, General Information for more specific information.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - There are no approved cephalexin products for veterinary use in the United States. It has been used clinically in dogs, cats, horses and birds, however.

**Pharmacokinetics (specific)** - After oral administration, cephalexin is rapidly and completely absorbed in humans. Cephalexin (base) must be converted to the HCl before absorption can occur and, therefore, absorption can be delayed. There is a form of cephalexin HCl commercially available for oral use which apparently is absorbed more rapidly, but the clinical significance of this is in question.

In a study done in dogs and cats (Silley et al. 1988), peak serum levels reached 18.6 micrograms/ml about 1.8 hours after a mean oral dose of 12.7 mg/kg in dogs, and 18.7 micrograms/ml, 2.6 hours after an oral dose of 22.9 mg/kg in cats. Elimination half-lives ranged from 1-2 hours in both species. Bioavailability was about 75% in both species after oral administration.

In the U.K., an oily suspension of the sodium salt (*Ceporex® Injection*— Glaxovet) is apparently available for IM or SQ injection in animals. In calves, the sodium salt had a 74% bioavailability after IM injection and a serum half-life of about 90 minutes.

**Adverse Effects/Warnings** - In addition to the adverse effects listed in the general statement on the cephalosporins, cephalexin has reportedly caused salivation, tachypnea and excitability in dogs, and emesis and fever in cats. Nephrotoxicity occurs rarely during therapy with cephalexin, but patients with renal dysfunction, receiving other nephrotoxic drugs or are geriatric may be more susceptible. Interstitial nephritis, a hypersensitivity reaction, has been reported with many of the cephalosporins including cephalexin. The incidence of these effects is not known.

**Doses** -
**Horses**:

For susceptible infections:

a) 25 mg/kg PO *qid* (Robinson 1987)
b) 22 - 33 mg/kg PO q6h (Brumbaugh 1987)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Cephalexin (monohydrate) Capsules 250 mg, 500 mg and Tablets 250 mg, 500 mg and 1 gram; *Keflex®* (Dista); *Biocef®* (IEL); generic (Rx)

Cephalexin Oral Suspension 125 mg/5ml and 250 mg/5 ml in 100 and 200 ml and UD 5ml; *Keflex®* (Dista); *Biocef®* (IEL); generic (Rx)

CEPHALOSPORINS * ADVERSE EFFECT REPORTED

Note: There are presently over 20 different cephalosporin drugs available for either human or veterinary use. Ten separate monographs of cephalosporins that appear to have the most current veterinary use and/or applicability may be found by their generic name. For a more detailed review of cephalosporins in veterinary medicine, the reader is referred to the following article: Caprile, K.A. 1988. The Cephalosporin Antimicrobial Agents: A Comprehensive Review. J Vet Pharmacol Ther 11 (1):1-32.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - The cephalosporin antibiotics are comprised of several different classes of compounds with dissimilar spectrums of activity and pharmacokinetic profiles. All “true” cephalosporins are derived from cephalosporin C which is produced from *Cephalosporium acremonium*.

Cephalosporins are usually bactericidal against susceptible bacteria and act by inhibiting mucopeptide synthesis in the cell wall resulting in a defective barrier and an osmotically unstable spheroplast. The exact mechanism for this effect has not been definitively determined, but beta-lactam antibiotics have been shown to bind to several enzymes (carboxypeptidases, transpeptidases, endopeptidases) within the bacterial cytoplasmic membrane that are involved with cell wall synthesis. The different affinities that various beta-lactam antibiotics have for these enzymes (also known as penicillin-binding proteins; PBPs) help explain the differences in spectrums of activity of these drugs that are not explained by the influence of beta-lactamases. Like other beta-lactam antibiotics, cephalosporins are generally considered to be more effective against actively growing bacteria.

The cephalosporin class of antibiotics is usually divided into three classifications or generations. The so-called first generation of cephalosporins include (routes of administration in parentheses): cephalothin (IM/IV), cefazolin (IM/IV), cephapirin (IM/IV/Intramammary), cephradine (IM/IV/PO), cephalexin (PO) and cefadroxil (PO). While there may be differences in MIC’s for individual first generation cephalosporins, their spectrums of activity are quite similar. They possess generally excellent coverage against most gram-positive pathogens and variable to poor coverage against most gram negative pathogens. These drugs are very active *in vitro* against groups A beta-hemolytic and B *Streptococci*, non-enterococcal group D *Streptococci* (*S. bovis*), *Staphylococcus intermedius* and *aureas*, *Proteus mirabilis* and some strains of *E. coli*, *Klebsiella sp*., *Actinobacillus*, *Pasturella*, *Haemophilus equigenitalis*, *Shigella* and *Salmonella*. With the exception of *Bacteroides fragilis*, most anaerobes are very susceptible to the first generation agents. Most species of *Corynebacteria* are susceptible, but *C. equi* (*Rhodococcus*) is usually resistant. Strains of *Staphylococcus epidermidis* are usually sensitive to the parenterally administered 1st generation drugs, but may have variable susceptibilities to the oral drugs. The following bacteria are regularly resistant to the 1st generation agents: Group D *streptococci/enterococci* (*S. faecalis*, S*. faecium*), Methicillin-resistant *Staphylococci*, indole-positive *Proteus sp*., *Pseudomonas sp*., *Enterobacter sp*., *Serratia sp*. and *Citrobacter sp*..

The second generation cephalosporins include: cefaclor (PO), cefamandole (IM/IV), cefonicid (IM/IV), ceforanide (IM/IV) and cefuroxime (PO/IM/IV). Although not true cephalosporins (they are actually cephamycins), cefoxitin (IM/IV) and cefotetan (IM/IV) are usually included in this group, although some references categorize cefotetan as a 3rd generation agent. In addition to the gram positive coverage of the 1st generation agents, these agents have expanded gram negative coverage. Cefoxitin and cefotetan also have good activity against *Bacteroides fragilis*. Enough variation exists between these agents in regard to their spectrums of activity against most species of gram negative bacteria, that susceptibility testing is generally required to determine sensitivity. The second generation agents have not found widespread use in most veterinary practices, although cefoxitin has been used somewhat.

The third generation cephalosporins retain the gram positive activity of the first and second generation agents, but in comparison, have much expanded gram negative activity. Included in this group are: cefotaxime (IM/IV), moxalactam (actually a 1-oxa-beta-lacatam; IM/IV), cefoperazone (IM/IV), ceftizoxime (IM/IV), ceftazidime (IM/IV), ceftriaxone (IM/IV), ceftiofur (IM) and cefixime (PO). As with the 2nd generation agents, enough variability exists with individual bacterial sensitivities that susceptibility testing is necessary for most bacteria. Usually only ceftazidime and cefoperazone are active against most strains of *Pseudomonas aeruginosa*. Because of the excellent gram negative coverage of these agents and when compared to the aminoglycosides, their significantly less toxic potential, they have been used on an increasing basis in veterinary medicine. Ceftiofur is approved for use in beef cattle, but its use in other species is hindered by a lack of data on its spectrum of activity or availability of pharmacokinetic profiles.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - Cephalosporins have been used for a wide range of infections in various species. FDA-approved indications/species, as well as non-approved uses are listed in the Uses/Indications and Dosage sections for each individual drug.

**Pharmacokinetics (General)**- Until recently, only some first generation cephalosporins were absorbed appreciably after oral administration, but this has changed with the availability of cefuroxime axetil (2nd generation) and cefixime (3rd generation). Depending on the drug, absorption may be delayed, unaltered, or increased if administered with food. There are reported species variations in the oral bioavailability of some cephalosporins which are detailed under each individual drug's monograph.

Cephalosporins are widely distributed to most tissues and fluids, including bone, pleural fluid, pericardial fluid and synovial fluid. Higher levels are found in inflamed than in normal bone. Very high levels are found in the urine, but they penetrate poorly into prostatic tissue and aqueous humor. Bile levels can reach therapeutic concentrations with several of the agents as long as biliary obstruction is not present. With the exception of cefuroxime, no first or second generation cephalosporin enters the CSF (even with inflamed meninges) in therapeutically effective levels. Therapeutic concentrations of cefotaxime, moxalactam, cefuroxime, ceftizoxime, ceftazidime and ceftriaxone can be found in the CSF after parenteral dosing in patients with inflamed meninges. Cephalosporins cross the placenta and fetal serum concentrations can be 10% or more of those found in maternal serum. Cephalosporins enter milk in low concentrations. Protein binding of the drugs is widely variable and species specific. Cephalosporins tend to bind to equine and canine plasma proteins less so then to human plasma proteins.

Cephalosporins and their metabolites (if any) are excreted by the kidneys, via tubular secretion and/or glomerular filtration. Some cephalosporins (*e.g.,* cefotaxime, cefazolin, and cephapirin) are partially metabolized by the liver to desacetyl compounds that may have some antibacterial activity.

**Contraindications/Precautions/Reproductive Safety** - Cephalosporins are contraindicated in patients who have a history of hypersensitivity to them. Because there may be cross-reactivity, use cephalosporins cautiously in patients who are documented hypersensitive to other beta-lactam antibiotics (*e.g.,* penicillins, cefamycins, carbapenems).

Oral systemic antibiotics should not be administered in patients with septicemia, shock or other grave illnesses as absorption of the medication from the GI tract may be significantly delayed or diminished. Parenteral routes (preferably IV) should be used for these cases.

Cephalosporins have been shown to cross the placenta and safe use of them during pregnancy have not been firmly established, but neither have there been any documented teratogenic problems associated with these drugs. However, use only when the potential benefits outweigh the risks.

**Adverse Effects/Warnings** - Adverse effects with the cephalosporins are usually not serious and have a relatively low frequency of occurrence.

Hypersensitivity reactions unrelated to dose can occur with these agents and can be manifested as rashes, fever, eosinophilia, lymphadenopathy, or full-blown anaphylaxis. The use of cephalosporins in patients documented to be hypersensitive to penicillin-class antibiotics is controversial. In humans, it is estimated that up to 15% of patients hypersensitive to penicillins will also be hypersensitive to cephalosporins. The incidence of cross-reactivity in veterinary patients is unknown.

Cephalosporins can cause pain at the injection site when administered intramuscularly, although this effect is less so with cefazolin than other agents. Sterile abscesses or other severe local tissue reactions are also possible but are much less common. Thrombophlebitis is also possible after IV administration of these drugs.

To Drug Monograph Index To Ophthalmic Product Index

When given orally, cephalosporins may cause GI effects (anorexia, vomiting, diarrhea). Administering the drug with a small meal may help alleviate these symptoms. Because the cephalosporins may also alter gut flora, antibiotic-associated diarrhea can occur as well as the selection out of resistant bacteria maintaining residence in the colon of the animal.

While it has been demonstrated that the cephalosporins (particularly cephalothin) have the potential for causing nephrotoxicity, at clinically used doses in patients with normal renal function, risks for this adverse effect occurring appear minimal.

High doses or very prolonged use has been associated with neurotoxicity, neutropenia, agranulocytosis, thrombocytopenia, hepatitis, positive Comb's test, interstitial nephritis, and tubular necrosis. Except for tubular necrosis and neurotoxicity, these effects have an immunologic component.

Some cephalosporins (cefamandole, cefoperazone, moxalactam) that contain a thiomethyltetrazole side chain have been implicated in causing bleeding problems in humans. These drugs are infrequently used in veterinary species at the present time, so any veterinary ramifications of this effect are unclear.

**Overdosage/Acute Toxicity** - Acute oral cephalosporin overdoses are unlikely to cause significant problems other than GI distress, but other effects are possible (see Adverse effects section).

**Drug Interactions** - The concurrent use of parenteral **aminoglycosides** or other nephrotoxic drugs (*e.g.,* **amphotericin B**) with cephalosporins is controversial. Potentially, cephalosporins could cause additive nephrotoxicity when used with these drugs, but this interaction has only been well documented with cephaloridine (no longer marketed). Nevertheless, they should be used together cautiously. *In vitro* studies have demonstrated that cephalosporins can have synergistic or additive activity against certain bacteria when used with **aminoglycosides**, **penicillins**, or **chloramphenicol**. However, some clinicians do not recommend using cephalosporins concurrently with **bacteriostatic antibiotics** (*e.g.,* chloramphenicol), particularly in acute infections where the organism is proliferating rapidly. **Probenecid** competitively blocks the tubular secretion of most cephalosporins, thereby increasing serum levels and serum half-lives. A disulfiram-like reaction (anorexia, nausea, vomiting) has been reported in humans who have ingested **alcohol** with 48-72 hours of receiving beta-lactam antibiotics (*e.g.,* cefamandole, cefoperazone, moxalactam, cefotetan) with a thiomethyltetrazole side-chain. Because these antibiotics have been associated with bleeding, they should be used cautiously in patients receiving **oral anticoagulants**.

**Drug/Laboratory Interactions** - Except for cefotaxime, cephalosporins may cause false-positive **urine glucose determinations** when using cupric sulfate solution (Benedict's Solution, *Clinitest*®). Tests utilizing glucose oxidase (*Tes-Tape*®, *Clinistix*®) are not affected by cephalosporins.

When using the Jaffe reaction to measure **serum or urine creatinine**, cephalosporins (not ceftazidime or cefotaxime) in high dosages may falsely cause elevated values.

In humans, particularly with azotemia, cephalosporins have caused a false-positive direct **Combs' test**. Cephalosporins may also cause falsely elevated **17-ketosteroid** values in urine.

**Monitoring Parameters** - Because cephalosporins usually have minimal toxicity associated with their use, monitoring for efficacy is usually all that is required. Patients with diminished renal function, may require intensified renal monitoring. Serum levels and therapeutic drug monitoring are not routinely done with these agents.

**Elephants:**
a) **Adverse effect noted:** There are no published pharmacokinetic studies on cephalosporins in elephants. Potential side effects (renal and hepatic problems) have been noted when a second generation

To Drug Monograph Index To Ophthalmic Product Index

cephalosporin was used IV (specific drug not cited). Schmidt, M.J: Senior Research Veterinarian, Washington Park Zoo, Portland, Oregon, personal communication, 1986. In: Olsen,J.H., 1999. **Antibiotic therapy in elephants**. In: Fowler,M.E. and Miller R.E. (Editors), **Zoo and Wild Animal Medicine: Current Therapy 4.** W.B. Saunders, Philadelphia, PA,USA p. 538

See also Cetiofur sodium

## CEPHALOTHIN SODIUM

For general information on the cephalosporins including adverse effects, contraindications, overdosage, drug interactions, and monitoring parameters, refer to the monograph: Cephalosporins, General Information.

**Chemistry** - An injectable semi-synthetic cephalosporin antibiotic, cephalothin sodium occurs as a practically odorless, white to off-white, crystalline powder. It is freely soluble in water and very slightly soluble in alcohol. Each gram of the injection contains 2.8 mEq of sodium. After reconstitution the solution for injection has a pH of 6.0-8.5.

**Storage/Stability/Compatibility** - The sterile powder for injection and reconstitution should be stored at room temperature. After reconstituting with sterile water for injection, cephalothin sodium neutral is stable for 12 hours at room temperature and 96 hours when refrigerated. Precipitates may occur with refrigerated solutions, but can be redissolved with warming and agitation. Solutions may darken, particularly at room temperature, but this does not indicate any loss of potency. In the frozen state, cephalothin sodium solutions are relatively stable.

The following drugs or solutions are reportedly **compatible** with cephalothin: $D_{25}W$/Amino Acids 4.25%, $D_5W$ in Lactated Ringer's, $D_5W$ in sodium chloride 0.2% - 0.9%, $D_5W$, $D_{10}W$, Lactated Ringer's Injection, normal saline, ascorbic acid injection, chloramphenicol sodium succinate, clindamycin phosphate, cytarabine, fluorouracil, heparin sodium, hydrocortisone sodium succinate, magnesium sulfate, metaraminol bitartrate, methotrexate, nitrofurantoin sodium, oxacillin sodium, phytonadione, polymyxin B sulfate, potassium chloride, sodium bicarbonate and vitamin B-complex with C.

The following drugs or solutions are reportedly **incompatible** or only compatible in specific situations with cephalothin: amikacin sulfate, aminophylline, bleomycin sulfate, calcium chloride/gluconate, cimetidine HCl, dopamine HCl, doxorubicin HCl, erythromycin lactobionate, gentamicin sulfate, isoproterenol HCl, kanamycin sulfate, norepinephrine bitartrate, oxytetracycline HCl, penicillin G potassium/sodium, phenobarbital sodium, prochlorperazine edisylate and tetracycline HCl.

Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology/Spectrum of Activity** - A first generation cephalosporin, cephalothin exhibits activity against the bacteria usually covered by this class. Refer to the monograph: Cephalosporins, General Information for more specific information.

**Uses/Indications** - In the United States, there are no cephalothin products approved for veterinary species, but it has been used clinically in several species when a relatively short-acting, injectable, first generation cephalosporin is indicated.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacokinetics (specific)** - Cephalothin is not appreciably absorbed after oral administration and must be given parenterally to achieve therapeutic serum levels. Absorbed drug is partially metabolized by the liver and kidneys to desacetylcephalothin which is about 25% as active an antibacterial as the parent compound. In humans, about 60-95% of the drug is excreted unchanged into the urine and 27-54% of a dose is excreted as the desacetyl metabolite. Elimination half-lives may be significantly prolonged in patients with severely diminished renal function. Pharmacokinetic parameters for dogs and horses follow:

In dogs, the apparent volume of distribution at steady state is 435 ml/kg, total body clearance of 11.6 - 15 ml/min/kg with a serum elimination half-life of 42-51 minutes.
In horses, the apparent volume of distribution at steady state is 145 ml/kg, total body clearance of 13 ml/min/kg with a serum elimination half-life of 15 minutes when given IV and 49 minutes after IM injection. Cephalothin is about 20% bound to equine plasma proteins.

**Doses** - Note: IM injection may be very painful.
**Horses**:

For susceptible infections:

a) 11 - 18 mg/kg IM or IV *qid* (Robinson 1987)
b) Foals: 20 - 30 mg/kg IV q6h (Caprile and Short 1987)]
c) 18 mg/kg IM or IV q6h (Beech 1987b)

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Cephalothin Sodium Powder for Injection 1 g, 2 g in 10 ml vials and 100 ml piggyback vials and Faspak; *Keflin®, Neutral* (Lilly), generic (Rx)

Cephalothin Sodium Injection 1 g and 2 g in 5% dextrose premixed bags in 50 ml $D_5W$ (frozen); *Cephalothin Sodium®* (Baxter); (Rx)

## CEPHAPIRIN
## CEPHAPIRIN BENZATHINE

For general information on the cephalosporins including adverse effects, contraindications, overdosage, drug interactions, and monitoring parameters, refer to the monograph: Cephalosporins, General Information.

**Chemistry** - An injectable semi-synthetic cephalosporin antibiotic, cephapirin sodium occurs as a white to off-white, crystalline powder having a faint odor. It is very soluble in water and slightly soluble in alcohol. Each gram of the injection contains 2.36 mEq of sodium. After reconstitution the solution for injection has a pH of 6.5-8.5. May also be known as cefapirin sodium in the U.K. and other countries.

**Storage/Stability/Compatibility** - The sterile powder for injection and reconstitution should be stored at room temperature and is stable for 24 months in dry state. After reconstituting with sterile water for injection in concentrations of 50 - 400 mg/ml, cephapirin is stable for 12 hours at room temperature. After reconstituting with bacteriostatic water for injection in concentrations of 250 - 400 mg/ml, cephapirin is stable for 48 hours at room temperature. After reconstituting with sodium chloride 0.9% injection or dextrose 5% in water in concentrations of 20 - 100 mg/ml, cephapirin is stable for 24 hours at room temperature. All of the above solutions are stable for 10 days when stored at 4°C (refrigeration) and may be stable longer when solutions are frozen. Solutions may become yellow, but this does not indicate any loss of potency.

To Drug Monograph Index  To Ophthalmic Product Index

Cephapirin mastitis tubes should be stored at room temperature (15-30°C); avoid excessive heat.

The following drugs or solutions are reportedly **compatible** with cephapirin: $D_5W$ in Ringer's, $D_5W$ in Lactated Ringer's, $D_5W$ in sodium chloride 0.2% - 0.9%, $D_5W$, $D_{10}W$, $D_{20}W$, Ringer's Injection, Lactated Ringer's Injection, normal saline, bleomycin sulfate, calcium chloride/gluconate, chloramphenicol sodium succinate, diphenhydramine HCl, ergonovine maleate, heparin sodium, hydrocortisone sodium phosphate/succinate, metaraminol bitartrate, oxacillin sodium, penicillin G potassium/sodium, phenobarbital sodium, phytonadione, potassium chloride, sodium bicarbonate, succinylcholine chloride, verapamil HCl, vitamin B-complex with C and warfarin sodium.

The following drugs or solutions are reportedly **incompatible** or only compatible in specific situations with cephapirin: Mannitol 20%, amikacin sulfate, aminophylline, ascorbic acid injection, epinephrine HCl, erythromycin gluceptate, gentamicin sulfate, kanamycin sulfate, nitrofurantoin sodium, norepinephrine bitartrate, oxytetracycline HCl, phenytoin sodium, tetracycline HCl, and thiopental sodium.

Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology/Spectrum of Activity** - A first generation cephalosporin, cephapirin exhibits activity against the bacteria usually covered by this class. A cephalothin disk is usually used to determine bacterial susceptibility to this antibiotic when using the Kirby-Bauer method. Refer to the monograph: Cephalosporins, General Information for more specific information.

**Uses/Indications** - In the United States, there are no parenterally administered cephapirin products approved for veterinary species, but it has been used clinically in several species when a relatively short-acting injectable first generation cephalosporin is indicated.

An intramammary cephapirin sodium product (*Cefa-Lak*®—Fort Dodge) is approved for use in the treatment of mastitis in lactating dairy cows and cephapirin benzathine (*Cefa-Dri*®—Fort Dodge) is approved in dry cows.

**Pharmacokinetics (specific)** - Cephapirin is not appreciably absorbed after oral administration. In horses, the bioavailability is about 95% after IM injection. The apparent volumes of distribution have been reported as 0.32 L/kg in dogs, 0.335 - 0.399 L/kg in cattle and 0.17 - 0.188 L/kg in horses. The total body clearance of cephapirin is 8.9 ml/min/kg in dogs, 12.66 ml/min/kg in cattle and about 7.8 - 10 ml/min/kg in horses. Serum elimination half-life is about 25 minutes in dogs, 64 - 70 minutes in cattle and 25-55 minutes in horses. Probenecid has been demonstrated to reduce the renal clearance of the drug.

**Doses** -
**Horses**:

For susceptible infections:

a) 20 mg/kg IM q8h or q12h if administered with probenecid (50 mg/kg intragastrically). (Juzwiak et al. 1989)
b) Foals: 20 - 30 mg/kg IV q6h (Caprile and Short 1987)
c) 20 mg/kg IM q8h (Brumbaugh 1987)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times -**

**Veterinary-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Cephapirin Sodium Mastitis Tube; 200 mg cephapirin per 10 ml tube; *Cefa-Lak*® (Fort Dodge); (OTC) Approved for use in lactating dairy cattle. Milk withdrawal = 96 hours; Slaughter withdrawal = 4 days.

Cephapirin Benzathine Mastitis Tube; 300 mg cephapirin per 10 ml tube; *Cefa-Dri*® (Fort Dodge); (OTC) Approved for use in dry dairy cattle. Milk withdrawal = 72 hours after calving and must not be administered within 30 days of calving; Slaughter withdrawal = 42 days.

**Human-Approved Products**:

Cephapirin Sodium Powder for Injection 500 mg, 1 g, 2 g, 4 g, 20 g; *Cefadyl*® (Apothecon);*Cephapirin Sodium*® (Lyphomed); , generic; (Rx)

## CHARCOAL, ACTIVATED

**Chemistry** - Activated charcoal occurs as a fine, black, odorless, tasteless powder that is insoluble in water or alcohol. Commercially available activated charcoal products may differ in their adsorptive properties, but one gram must adsorb 100 mg of strychnine sulfate in 50 ml of water to meet USP standards. Activated charcoal has several synonyms including: active carbon, activated carbon, adsorbent charcoal, decolorizing carbon, or medicinal charcoal.

**Storage/Stability/Compatibility** - Store activated charcoal in well-closed glass or metal containers or in the manufacturer's supplied container.

**Pharmacology** - Activated charcoal adsorbs many chemicals and drugs in the upper GI tract thereby preventing or reducing their absorption. While activated charcoal also adsorbs various nutrients and enzymes from the gut, when used for acute poisonings, no clinical significance usually results. Activated charcoal reportedly is not effective in adsorbing cyanide, but this has been disputed in a recent study. It also is not very effective in adsorbing alcohols, ferrous sulfate, caustic alkalies, nitrates, sodium chloride/chlorate, petroleum distillates or mineral acids.

**Uses/Indications** - Activated charcoal is administered orally to adsorb certain drugs or toxins to prevent or reduce their systemic absorption.

**Pharmacokinetics** - Activated charcoal is not absorbed nor metabolized in the gut.

**Contraindications/Precautions/Reproductive Safety** - Charcoal should not be used for mineral acids or caustic alkalies as it is ineffective. Although not contraindicated for ethanol, methanol, or iron salts, activated charcoal is not very effective in adsorbing these products and may obscure GI lesions during endoscopy.

**Adverse Effects/Warnings** - Very rapid GI administration of charcoal can induce emesis. Charcoal can cause either constipation or diarrhea and feces will be black. Products containing sorbitol may cause loose stools and vomiting.
Charcoal powder is very staining and the dry powder tends to "float" covering wide areas.

**Overdosage/Acute Toxicity** - None reported when used for acute therapy; see Adverse Effects above for more information.

**Drug Interactions** - Separate by at least 3 hours administration of any other **orally administered therapeutic agents** from the charcoal dose. Charcoal should not be administered with **dairy products or mineral oil** as the adsorptive properties of the charcoal will be diminished. Do not administer (at the same time) with **syrup of ipecac** as the charcoal can adsorb the ipecac and reduce its efficacy.

To Drug Monograph Index To Ophthalmic Product Index

**Doses** -
**Horses**:

a) Foals: 250 grams (minimum). Adult horses: up to 750 grams. Make a slurry by mixing with up to 4 L (depending on animal's size) of warm water and administer via stomach tube. Leave in stomach for 20-30 minutes and then give a laxative to hasten removal of toxicants. (Oehme 1987b)

**Monitoring Parameters** - Monitoring for efficacy of charcoal is usually dependent upon the toxin/drug that it is being used for and could include the drug/toxin's serum level, clinical signs, etc.

**Client Information** - This agent should usually be used with professional supervision, depending on the potential severity of the toxin/overdose. Charcoal can be very staining to fabrics.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Activated charcoal 47.5%, Kaolin 10% granules (free flowing and wettable) in 1 lb bottles, and 5 kg pails *Toxiban® Granules* (Vet-A-Mix); (OTC) Indicated for use in both large and small animals.

Activated charcoal 10.4%, Kaolin 6.25% suspension in 240 ml bottles *Toxiban® Suspension* (Vet-A-Mix); (OTC) Indicated for use in both large and small animals.

Activated Charcoal Aqueous Suspension 50 g in unit dose tube *Liqui-Char-Vet Aqueous Suspension®* (Daniels); (OTC)

**Human-Approved Products**:

Activated Charcoal Powder in 15, 30, 40 , 120 , 240 g & UD 30 g (Activated charcoal is also available in bulk powder form); Generic, (OTC)

Activated Charcoal Suspension; 25 g in 120 ml bottles, and 50 g in 240 ml bottles; *Actidose-Aqua®* (Paddock) ; (OTC)

Activated Charcoal Suspension with sorbitol; 15 g in 120 ml bottles 25 g in 120 ml bottles, 30 g in 150 ml bottles, and 50 g in 240 ml bottles; *Actidose with Sorbitol®* (Paddock),*CharcoAid®* (Requa); (OTC)

Activated Charcoal Liquid 15 g & 50g with & without sorbitol in 120 ml and 240 ml bottles, 12.5 g in propylene glycol 60 ml bottles, and 25 g in propylene glycol 120 ml bottles; *CharcoAid 2000 ®* (Requa) (OTC) Generic; (OTC)

Activated Charcoal Liquid; 12.5 g in 60 ml bottles, 15 g in 75 ml bottles, 25 g in 120 ml bottles, 30 g in 120 ml bottles, & 50 g in 240 ml bottles; *Liqui-Char®* (Jones Medical); (OTC)

Activated Charcoal Granules 15 g in 120 ml bottles; *CharcoAid* 2000® (Requa) (OTC)

## CHLORAMBUCIL

**Chemistry** - A nitrogen mustard derivative antineoplastic agent, chlorambucil occurs as an off-white, slightly granular powder. It is very slightly soluble in water.

**Storage/Stability/Compatibility** - Chlorambucil tablets should be stored in light-resistant, well-closed containers at room temperature. An expiration date of one year after manufacture is assigned to the commercially available tablets.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Chlorambucil is a cell-cycle nonspecific alkylating antineoplastic/immunosuppressive agent. Its cytotoxic activity stems from cross-linking with cellular DNA.

**Uses/Indications** - Chlorambucil may be useful in a variety of neoplastic diseases, including lymphocytic leukemia, multiple myeloma, polycythemia vera, macroglobulinemia, and ovarian adenocarcinoma. It may also be useful as adjunctive therapy for some immune-mediated conditions (*e.g.*, glomerulonephritis, non-erosive arthritis, or immune-mediated skin disease).

**Pharmacokinetics** - In humans, chlorambucil is rapidly and nearly completely absorbed after oral administration. It is highly bound to plasma proteins. While it is not known whether it crosses the blood-brain barrier, neurological side effects have been reported. Chlorambucil crosses the placenta, but it is not known whether it enters maternal milk. Chlorambucil is extensively metabolized in the liver, primarily to phenylacetic acid mustard, which is active. Phenylacetic acid mustard is further metabolized to other metabolites that are excreted in the urine.

**Contraindications/Precautions/Reproductive Safety** - Chlorambucil is contraindicated in patients who are hypersensitive to it or have demonstrated resistance to its effects. It should be used with caution in patients with preexisting bone marrow depression or infection, or susceptible to bone marrow depression or infection.

Chlorambucil's teratogenic potential has not been well documented, but it may potentially cause a variety of fetal abnormalities. It is generally recommended to avoid the drug during pregnancy, but because of the seriousness of the diseases treated with chlorambucil, the potential benefits to the mother must be considered. Chlorambucil has been documented to cause irreversible infertility in male humans, particularly when given during pre-puberty and puberty.

**Adverse Effects/Warnings** - The most commonly associated major adverse effect seen with chlorambucil therapy is myelosuppression manifested by anemia, leukopenia, and thrombocytopenia. It may occur gradually with nadirs occurring usually within 7-14 days of the start of therapy. Recovery generally takes from 7-14 days. Severe bone marrow depression can result in pancytopenia that may take months to years for recovery. In humans, bronchopulmonary dysplasia with pulmonary fibrosis and uric acid nephropathy, have been reported. These effects are more uncommon and generally associated with chronic, higher dose therapy. Hepatotoxicity has been reported rarely in humans. Alopecia and delayed regrowth of shaven fur have been reported in dogs. Poodles or Kerry blues are more likely to be affected than other breeds.

**Overdosage/Acute Toxicity** - The oral $LD_{50}$ in mice is 123 mg/kg. There has been limited experiences with acute overdoses in humans. Doses of up to 5 mg/kg resulted in neurologic (seizures) toxicity and pancytopenia (nadirs at 1-6 weeks post ingestion). All patients recovered without long term sequelae. Treatment should consist of gut emptying when appropriate (beware of rapidly changing neurologic status if inducing vomiting). Monitoring of CBC's several times a week for several weeks should be performed after overdoses and blood component therapy may be necessary.

**Drug Interactions** - The principal concern should be the concurrent use with other drugs that are also myelosuppressive, including many of the **other antineoplastics and other bone marrow depressant drugs (*e.g.*, chloramphenicol, flucytosine, amphotericin B, or colchicine)**. Bone marrow depression may be additive. Use with other **immunosuppressant drugs (*e.g.*, azathioprine, cyclophosphamide, corticosteroids)** may increase the risk of infection.

**Laboratory Considerations -** Chlorambucil may raise serum **uric acid** levels. Drugs such as **allopurinol** may be required to control hyperuricemia in some patients.

**Doses** -

To Drug Monograph Index To Ophthalmic Product Index

**Horses**:

For adjunctive therapy in treating lymphoma using the LAP protocol: Cytosine arabinoside 200 - 300 mg/m2 SubQ or IM once every 1-2 weeks; Chlorambucil 20 mg/$m^2$ PO every 2 weeks (alternating with cytosine arabinoside) and Prednisone 1.1 - 2.2 mg/kg PO every other day. If this protocol is not effective (no response seen in 2-4 weeks) add vincristine at 0.5 mg/$m^2$ IV once a week. Side effects are rare. (Couto 1994)

**Monitoring Parameters** - 1) Efficacy; 2) CBC, Platelets once weekly (or once stable every other week) during therapy; 3) Uric acid, liver enzymes; if warranted

**Client Information** - Clients must understand the importance of both administering chlorambucil as directed and to report immediately any signs associated with toxicity (*e.g.*, abnormal bleeding, bruising, urination, depression, infection, shortness of breath, etc.).

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Chlorambucil Oral Tablets 2 mg; *Leukeran*® (Glaxo Wellcome); (Rx)

## CHLORAMPHENICOL
## CHLORAMPHENICOL PALMITATE
## CHLORAMPHENICOL SODIUM SUCCINATE

**Chemistry** - Originally isolated from *Streptomyces venezuelae*, chloramphenicol is now produced synthetically. It occurs as fine, white to grayish, yellow white, elongated plates or needle-like crystals with a $pK_a$ of 5.5. It is freely soluble in alcohol and about 2.5 mg are soluble in 1 ml of water at 25°C.

Chloramphenicol palmitate occurs as a bland mild tasting, fine, white, unctuous, crystalline powder having a faint odor. It is insoluble in water and sparingly soluble in alcohol.
Chloramphenicol sodium succinate occurs as a white to light yellow powder. It is freely soluble in both water or alcohol. Commercially available chloramphenicol sodium succinate for injection contains 2.3 mEq of sodium per gram of chloramphenicol.

**Storage/Stability/Compatibility** - Chloramphenicol capsules and tablets should be stored in tight containers at room temperature (15-30°C). The palmitate oral suspension should be stored in tight containers at room temperature and protected from light or freezing.

The sodium succinate powder for injection should be stored at temperatures less than 40°, and preferably between 15-30°C. After reconstituting the sodium succinate injection with sterile water, the solution is stable for 30 days at room temperature and 6 months if frozen. The solution should be discarded if it becomes cloudy.

The following drugs and solutions are reportedly **compatible** with chloramphenicol sodium succinate injection: all commonly used intravenous fluids, amikacin sulfate, aminophylline, ampicillin sodium (in syringe for 1 hr.) ascorbic acid, calcium chloride/gluconate, cephalothin sodium, cephapirin sodium, colistimethate sodium, corticotropin, cyanocobalamin, dimenhydrinate, dopamine HCl, ephedrine sulfate, heparin sodium, hydrocortisone sodium succinate, hydroxyzine HCl, kanamycin sulfate, lidocaine HCl,

magnesium sulfate, metaraminol bitartrate, methicillin sodium, methyldopate HCl, methylprednisolone sodium succinate, metronidazole w/ or w/o sodium bicarbonate, nafcillin sodium, oxacillin sodium, oxytocin, penicillin G potassium/sodium, pentobarbital sodium, phenylephrine HCl w/ or w/o sodium bicarbonate, phytonadione, plasma protein fraction, potassium chloride, promazine HCl, ranitidine HCl, sodium bicarbonate, thiopental sodium, verapamil HCl, and vitamin B-complex with C.

The following drugs and solutions are reportedly **incompatible** (or compatibility data conflicts) with chloramphenicol sodium succinate injection: chlorpromazine HCl, glycopyrrolate, metoclopramide HCl, oxytetracycline HCl, polymyxin B sulfate, prochlorperazine edislyate/mesylate, promethazine HCl, tetracycline HCl, and vancomycin HCl.

Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Chloramphenicol usually acts as a bacteriostatic antibiotic, but at higher concentrations or against some very susceptible organisms it can be bactericidal. Chloramphenicol acts by binding to the 50S ribosomal subunit of susceptible bacteria, thereby preventing bacterial protein synthesis. Erythromycin, clindamycin, lincomycin, tylosin, etc., also bind to the same site, but unlike them, chloramphenicol appears to also have an affinity for mitochondrial ribosomes of rapidly proliferating mammalian cells (*e.g.,* bone marrow) which may result in a reversible bone marrow suppression.

Chloramphenicol has a wide spectrum of activity against many gram positive and negative organisms. Gram positive aerobic organisms that are generally susceptible to chloramphenicol include many streptococci and staphylococci. It is also effective against some gram negative aerobes including *Neissiera*, *Brucella*, *Salmonella*, *Shigella*, and *Haemophilus*. Many anaerobic bacteria are sensitive to chloramphenicol, including *Clostridum, Bacteroides* (including *B. fragilis*), *Fusobacterium*, and *Veillonella*. Chloramphenicol also has activity against *Nocardia*, *Chlamydia, Mycoplasma,* and *Rickettsia*.

**Uses/Indications** - Chloramphenicol is used for a variety of infections in small animals and horses, particularly those caused by anaerobic bacteria. Because of the human public health implications, the use of chloramphenicol in animals used for food production is banned by the FDA.

**Pharmacokinetics** - Chloramphenicol is rapidly absorbed after oral administration with peak serum levels occurring approximately 30 minutes after dosing. The palmitate oral suspension produces significantly lower peak serum levels when administered to fasted cats. The sodium succinate salt is rapidly and well absorbed after IM or SQ administration in animals and, contrary to some recommendations, need not be administered only intravenously. The palmitate and sodium succinate is hydrolyzed in the GI tract and liver to the base.

Chloramphenicol is widely distributed throughout the body. Highest levels are found in the liver and kidney, but the drug attains therapeutic levels in most tissues and fluids, including the aqueous and vitreous humor, and synovial fluid. CSF concentrations may be up tp 50% of those in the serum when meninges are uninflamed and higher when meninges are inflamed. A 4-6 hour lag time before CSF peak levels to occur may be seen. Chloramphenicol concentrations in the prostate are approximately 50% of those in the serum. Because only a small amount of the drug is excreted unchanged into the urine in dogs, chloramphenicol may not be the best choice for lower urinary tract infections in that species. The volume of distribution of chloramphenicol has been reported as 1.8 L/kg in the dog, 2.4 L/kg in the cat, and 1.41 L/kg in horses. Chloramphenicol is about 30-60% bound to plasma proteins, enters milk and crosses the placenta.

In most species, chloramphenicol is eliminated primarily by hepatic metabolism via glucuronidative mechanisms. Only about 5-15% of the drug is excreted unchanged in the urine. The cat, having little ability to glucuronidate drugs, excretes 25% or more of a dose as unchanged drug in the urine.

To Drug Monograph Index  To Ophthalmic Product Index

The elimination half-life has been reported as 1.1-5 hours in dogs, <1 hour in foals & ponies, and 4-8 hours in cats. The elimination half-life of chloramphenicol in birds is highly species variable, ranging from 26 minutes in pigeons to nearly 5 hours in bald eagles and peafowl.
The usual serum therapeutic range for chloramphenicol is 5-15 micrograms/ml.

**Contraindications/Precautions/Reproductive Safety** - Chloramphenicol is contraindicated in patients hypersensitive to it. Because of the potential for hematopoietic toxicity, the drug should be used with extreme caution, if at all, in patients with preexisting hematologic abnormalities, especially a preexisting non-regenerative anemia. The drug should only be used in patients in hepatic failure when no other effective antibiotics are available. Chloramphenicol should be used with caution in patients with impaired hepatic or renal function as drug accumulation may occur. Those patients may need dosing adjustment, and monitoring of blood levels should also be considered in these patients.

Chloramphenicol should be used with caution in neonatal animals, particularly in young kittens. In neonates (humans), circulatory collapse (so-called “Gray-baby syndrome”) has occurred with chloramphenicol, probably due to toxic levels accumulating secondary to an inability to conjugate the drug or excrete the conjugate effectively. Because chloramphenicol is found in milk at 50% of serum levels (in humans), the drug should be given with caution to nursing bitches or queens, particularly within the first week after giving birth.

One manufacturer (Osborn) states that chloramphenicol “should not be administered to dogs maintained for breeding purposes”. Chloramphenicol has not been determined to be safe for use during pregnancy. The drug may decrease protein synthesis in the fetus, particularly in the bone marrow. It should only be used when the benefits of therapy clearly outweigh the risks.

**Adverse Effects/Warnings** - While the toxicity of chloramphenicol in humans has been much discussed, the drug is considered by most to have a low order of toxicity in adult companion animals when appropriately dosed.

The development of aplastic anemia reported in humans, does not appear to be a significant problem for veterinary patients. However, a dose-related bone marrow suppression (reversible) is seen in all species, primarily with long-term therapy. Early signs of bone marrow toxicity can include vacuolation of the many of the early cells of the myeloid and erythroid series, lymphocytopenia, and neutropenia.

Other effects that may be noted include, anorexia, vomiting, diarrhea and depression.
It has been said that cats tend to be more sensitive to developing adverse reactions to chloramphenicol than dogs, but this is probably more as a result of the drug’s longer half-life in the cat. It is true that cats dosed at 50 mg/kg q12h for 2-3 weeks do develop a high incidence of adverse effects and should be closely monitored when prolonged high-dose therapy is necessary.

**Overdosage/Acute Toxicity** - Because of the potential for serious bone marrow toxicity, large overdoses of chloramphenicol should be handled by emptying the gut using standard protocols. For more information on the toxicity of chloramphenicol, refer to the Adverse Effects section above.

**Drug Interactions** - Chloramphenicol can inhibit the hepatic metabolism of several drugs, including **phenytoin, primidone, phenobarbital, pentobarbital,** and **cyclophosphamide**. Chloramphenicol has been demonstrated to prolong the duration of pentobarbital anesthesia by 120% in dogs, and 260% in cats. Phenobarbital may also decrease the plasma concentrations of chloramphenicol. In dogs receiving both chloramphenicol and primidone, anorexia and CNS depression may occur. Serum monitoring of the affected drugs should be considered if any of these drugs are to be used concurrently with chloramphenicol. The hematologic response to **iron salts** and **Vitamin $B_{12}$** can be decreased when concomitantly administered with chloramphenicol. Chloramphenicol should be used with extreme caution, if at all, with other **drugs that**

To Drug Monograph Index To Ophthalmic Product Index

**can cause myelosuppression** (*e.g.,* cyclophosphamide). **Penicillin** may slightly increase the serum half-life of chloramphenicol. Chloramphenicol may antagonize the bactericidal activity of the **penicillins** or **aminoglycosides**. This antagonism has not been demonstrated *in vivo*, and these drug combinations have been used successfully many times clinically. **Rifampin** may decrease serum chloramphenicol levels. Other antibiotics that bind to the 50S ribosomal subunit of susceptible bacteria (**erythromycin, clindamycin, lincomycin, tylosin**, etc.) may potentially antagonize the activity of chloramphenicol or vice versa, but the clinical significance of this potential interaction has not been determined. Chloramphenicol may suppress antibody production if given prior to an antigenic stimulus and may affect responses to **vaccinations**. If administered after the antigen challenge, immune response may not be altered. Immunizations should be postponed, if possible, in animals receiving chloramphenicol.

**Drug/Laboratory Interactions** - False-positive **glucosuria** has been reported, but the incidence is unknown.

**Doses** -
**Horses**:

For susceptible infections:

a) 10 - 50 mg/kg PO *qid*. If using palmitate salt, give 20 - 50 mg/kg PO *qid*. For sodium succinate: 20 - 50 mg/kg IM or IV *qid*. (Robinson 1987)
b) Chloramphenicol sodium succinate: 25 mg/kg IM q8h (Baggot and Prescott 1987)
c) Foals: Chloramphenicol sodium succinate: 50 mg/kg IV q6-8h (use longer dosage interval in premature foals and those less than 2 days old). (Caprile and Short 1987)
d) 45 - 60 mg/kg PO q8h; 45 - 60 mg/kg IM, SQ or IV q6-8h (USPC 1990)

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects; chronic therapy should be associated with routine CBC monitoring

**Client Information** - Must not be used in any animal to be used for food production. There is evidence that humans exposed to chloramphenicol have an increased risk of developing a fatal aplastic anemia. Products should be handled with care. Do not inhale powder and wash hands after handling tablets. Crushed tablets or capsule contents are very bitter tasting and animals may not accept the drug if presented in this manner.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**:
Note: The oral suspension (palmitate salt) has reportedly been discontinued and the availability of any veterinary-labeled oral dosage form has been sporadic at best.

Chloramphenicol Oral Tablets 100 mg, 250 mg, 500 mg, 1 gram; Approved for use in dogs only.

Veterinary-labeled chloramphenicol capsules may also be commercially available.

**Human-Approved Products**:

Chloramphenicol Capsules 250 mg; *Chloromycetin Kapseals*® (Parke-Davis), generic; (Rx)

Chloramphenicol Sodium Succinate Powder for Injection 100 mg/ml (as sodium succinate) when reconstituted 1 g vials; *Chloromycetin*® *Sodium Succinate* (Parke-Davis), generic; (Rx)

Topical, otic and ophthalmic preparations are also available.

## CHLORPHENIRAMINE MALEATE

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - A propylamine (alkylamine) antihistaminic agent, chlorpheniramine maleate occurs as an odorless, white, crystalline powder with a melting point between 130 - 135° C and a $pK_a$ of 9.2. One gram is soluble in about 4 ml of water, or 10 ml of alcohol. The pH of the commercially available injection is between 4 - 5.2.

**Storage/Stability/Compatibility** - Chlorpheniramine tablets and sustained-release tablets should be store in tight containers. The sustained-release capsules should be stored in well-closed containers. The oral solution and injectable products should be stored in light-resistant containers; avoid freezing. All chlorpheniramine products should be stored at room temperature (15-30°C).

Chlorpheniramine for injection is reportedly **compatible** with most commonly used IV solutions and the following drugs: amikacin sulfate, diatrizoate meglumine 52%/diatrizoate sodium 8% (Renografin-60®), diatrizoate meglumine 34.3%/diatrizoate sodium 35% (*Renovist*®), diatrizoate sodium 75% (*Hypaque*®), iothalamate meglumine 60% (*Conray*®), and iothalamate sodium 80% (*Angio-Conray*®).

Chlorpheniramine is reportedly **incompatible** with: calcium chloride, kanamycin sulfate, norepinephrine bitartrate, pentobarbital sodium, and iodipamide meglumine 52% (*Cholographin*®). Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** - Antihistamines ($H_1$-receptor antagonists) competitively inhibit histamine at $H_1$ receptor sites. They do not inactivate or prevent the release of histamine, but can prevent histamine's action on the cell. Besides their antihistaminic activity, these agents all have varying degrees of anticholinergic and CNS activity (sedation). Some antihistamines have antiemetic activity (*e.g.,* diphenhydramine) or antiseritonin activity (*e.g.,* cyproheptadine, azatadine).

**Uses/Indications** - Antihistamines are used in veterinary medicine to reduce or help prevent histamine mediated adverse effects.

**Pharmacokinetics** - Chlorpheniramine pharmacokinetics have not been described in domestic species. In humans, the drug is well absorbed after oral administration, but because of a relatively high degree of metabolism in the GI mucosa and the liver, only about 25-60% of the drug is available to the systemic circulation.

Chlorpheniramine is well distributed after IV injection, the highest distribution of the drug (in rabbits) occurs in the lungs, heart, kidneys, brain, small intestine and spleen. In humans, the apparent steady-state volume of distribution is 2.5 - 3.2 L/kg and it is about 70% bound to plasma proteins. It is unknown if chlorpheniramine is excreted into the milk.

Chlorpheniramine is metabolized in the liver and practically all the drug (as metabolites and unchanged drug) is excreted in the urine. In human patients with normal renal and hepatic function, the terminal serum half-life the drug ranges from 13.2-43 hours.

**Contraindications/Precautions** - Chlorpheniramine is contraindicated in patients who are hypersensitive to it or other antihistamines in its class. Because of their anticholinergic activity, antihistamines should be used with caution in patients with angle closure glaucoma, prostatic hypertrophy, pyloroduodenal or bladder neck obstruction, and COPD if mucosal secretions are a problem. Additionally, they should be cautiously used in patients with hyperthyroidism, cardiovascular disease or hypertension.

**Adverse Effects/Warnings** - Most commonly seen adverse effects are CNS depression (lethargy, somnolence) and GI effects (diarrhea, vomiting, anorexia). The sedative effects of antihistamines may

To Drug Monograph Index To Ophthalmic Product Index

diminish with time. Anticholinergic effects (dry mouth, urinary retention) are a possibility. The sedative effects of antihistamines may adversely affect the performance of working dogs.

**Overdosage** - Overdosage may cause CNS stimulation (excitement to seizures) or depression (lethargy to coma), anticholinergic effects, respiratory depression, and death. Treatment consists of emptying the gut if the ingestion was oral using standard protocols. Induce emesis if the patient is alert and CNS status is stable. Administration of a saline cathartic and/or activated charcoal may be given after emesis or gastric lavage. Treatment of other symptoms should be performed using symptomatic and supportive therapies. Phenytoin (IV) is recommended in the treatment of seizures caused by antihistamine overdose in humans; barbiturates and diazepam are avoided.

**Drug Interactions** - Increased sedation can occur if chlorpheniramine is combined with **other CNS depressant drugs**. Antihistamines may partially counteract the anticoagulation effects of **heparin** or **warfarin**.

**Laboratory Interactions** - Antihistamines can decrease the wheal and flare response to **antigen skin testing**. In humans, it is suggested that antihistamines be discontinued at least 4 days before testing.

**Doses** - Note: Contents of sustained-release capsules may be placed on food, but should not be allowed to dissolve before ingestion.
**Dogs**:

a) 4 - 8 mg PO q12h (Kirk 1986)
b) 2 - 4 mg PO *bid-tid* (Morgan 1988)

**Elephants:**

As an antihistamine:
a) Pheniramine: 1700-2300 mg/animal in Asian elephants; author's personal experience. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

**Monitoring Parameters** -

1) Clinical efficacy and adverse effects

**Client Information/FDA Approval Status** - Except in the combination products listed below, no veterinary-approved product is available. Chlorpheniramine is approved for use in humans; the oral dosage forms are either prescription or non-prescription agents, depending on the product's labeling. The injectable products are prescription only.

**Dosage Forms/Preparations** -

**Veterinary-Approved Products**:. None None as a single entity. This compound is also found in the veterinary-approved (dogs, cats, horses) products *Diathal*® (Schering) and *Azimycin*® (Schering). *Diathal*® contains: chlorpheniramine maleate 10 mg/ml, procaine penicillin G 200,000 U/ml, dihydrostreptomycin sulfate 250 mg/ml and diphemanil methylsulfate 25 mg/ml. *Azimycin*® contains: chlorpheniramine maleate 10 mg/ml, procaine penicillin G 200,000 U/ml, dihydrostreptomycin sulfate 250 mg/ml, dexamethasone 0.5 mg/ml, and procaine HCl 20 mg/ml.

**Human-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Chlorpheniramine Maleate Oral Tablets 2 mg (chewable), 4 mg, 8 mg (timed release), 12 mg (timed release) (OTC)

Chlorpheniramine Maleate Oral Syrup 2 mg/5 ml in 118 ml btls (OTC)

Chlorpheniramine Maleate Injection 10 mg/ml in 30 ml vials & 100 mg/ml in 10 ml vials; (Rx)

There are many registered trade names for chlorpheniramine; a commonly known product is *Chlor-Trimeton*® (Schering). Many combination products are available that combine chlorpheniramine with decongestants, analgesics, and/or antitussives.

## CHLORPROMAZINE HCL

**Chemistry** - A propylamino phenothiazine derivative, chlorpromazine is the prototypic phenothiazine agent. It occurs as a white to slightly creamy white, odorless, bitter tasting, crystalline powder. One gram is soluble in 1 ml of water and 1.5 ml of alcohol. The commercially available injection is a solution of chlorpromazine HCl in sterile water at a pH of 3-5.

**Storage/Stability/Compatibility** - Protect from light and store at room temperature; avoid freezing the oral solution and injection. Dispense oral solution in amber bottles. Store oral tablets in tight containers. Do not store in plastic syringes or IV bags for prolonged periods of time as the drug may adsorb to plastic.

Chlorpromazine will darken upon prolonged exposure to light; do not use solutions that are darkly colored or if precipitates have formed. A slight yellowish color will not affect potency or efficacy. Alkaline solutions will cause the drug to oxidize.

The following products have been reported to be **compatible** when mixed with chlorpromazine HCl injection: all usual intravenous fluids, ascorbic acid, atropine sulfate, butorphanol tartrate, diphenhydramine, droperidol, fentanyl citrate, glycopyrrolate, heparin sodium, hydromorphone HCl, hydroxyzine HCl, lidocaine HCl, meperidine, metoclopramide, metaraminol bitartrate, morphine sulfate, pentazocine lactate, promazine HCl, promethazine, scopolamine HBr, & tetracycline HCl.

The following products have been reported as being **incompatible** when mixed with chlorpromazine: aminophylline, amphotericin B, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, methicillin sodium, methohexital sodium, nafcillin sodium, penicillin g potassium, pentobarbital sodium, phenobarbital sodium, and thiopental sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Once the principle phenothiazine used in veterinary medicine, chlorpromazine has been largely supplanted by acepromazine. It has similar pharmacologic activities as acepromazine, but is less potent and has a longer duration of action. For further information refer to the acepromazine monograph.

**Uses/Indications** - The clinical use of chlorpromazine as a neuroleptic agent has diminished, but the drug is still used for its antiemetic effects in small animals and occasionally as a preoperative medication and tranquilizer. As an antiemetic, chlorpromazine will inhibit apomorphine-induced emesis in the dog but not the cat. It will also inhibit the emetic effects of morphine in the dog. It does not inhibit emesis caused by copper sulfate, or digitalis glycosides.

**Pharmacokinetics** - Chlorpromazine is absorbed rapidly after oral administration, but undergoes extensive first pass metabolism in the liver. The drug is also well absorbed after IM injection, but onsets of action are slower than after IV administration.

To Drug Monograph Index To Ophthalmic Product Index

Chlorpromazine is distributed throughout the body and brain concentrations are higher than those in the plasma. Approximately 95% of chlorpromazine in plasma is bound to plasma proteins (primarily albumin).

The drug is extensively metabolized principally in the liver and kidneys, but little specific information is available regarding its excretion in dogs and cats.

**Contraindications/Precautions** - Chlorpromazine causes severe muscle discomfort and swelling when injected IM into rabbits; use IV only in this species. See other contraindications/precautions in the acepromazine monograph found earlier in this section.

**Adverse Effects/Warnings** - In addition to the possible effects listed in the acepromazine monograph, chlorpromazine may cause extrapyrimidal symptoms in the cat when used at high dosages. These symptoms can include tremors, shivering, rigidity & loss of the righting reflexes. Lethargy, diarrhea, and loss of anal sphincter tone may also be seen.

Horses may develop an ataxic reaction with resultant excitation and violent consequences. These ataxic periods may cycle with periods of sedation. Because of this effect, chlorpromazine is rarely used in equine medicine today.

**Overdosage** - Refer to the information listed in the acepromazine monograph.

**Drug Interactions** - Phenothiazines should not be given within one month of worming with an **organophosphate agent** as their effects may be potentiated. **Physostigmine** toxicity may be enhanced by chlorpromazine. Toxicity of the herbicide **paraquat** is increased by chlorpromazine. **Other CNS depressant agents (barbiturates, narcotics, anesthetics**, etc.) may cause additive CNS depression if used with phenothiazines. **Quinidine** given with phenothiazines can cause additive cardiac depression. **Antidiarrheal mixtures** (*e.g.,* Kaolin/pectin, bismuth subsalicylate mixtures) and **antacids** may cause reduced GI absorption of oral phenothiazines. Increased blood levels of both drugs may result if **propranolol** is administered with phenothiazines. Phenothiazines block alpha-adrenergic receptors, if **epinephrine** is then given, unopposed beta-activity causing vasodilation and increased cardiac rate can occur. **Phenytoin** metabolism may be decreased if given concurrently with phenothiazines. **Procaine** activity may be enhanced by phenothiazines. **Dipyrone** used with chlorpromazine has been reported to cause serious hypothermia.

**Doses -**
**Horses**: Note: Because of side effects (ataxia, panic reaction) this drug is not recommended for use in horses; use acepromazine or promazine if phenothiazine therapy is desired.

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

a) Chlorpromazine 2000 mg orally BID was given to an adult Asian bull elephant. See text below Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1992. **A case of ochlophobia in a tusker**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India p. 176 **Full text:** An adult captive tusker to be used for ceremonial purpose could not tolerate crowd (ochlophobia - fear of the crowd). The animal was put on 2000 mg of chlorpromazine twice daily orally and

behaved normally during the entire festival season of 6 months. The animal again showed symptoms of fear of the crowd when the owner withdrew the drug. So the animal was put on 100 mg haloperidol twice daily orally. This relieved the symptoms very well but without sedation compared to chlorpromazine hydrochloride.

**Monitoring Parameters** -

1) Cardiac rate/rhythm/blood pressure if indicated and possible to measure
2) Degree of tranquilization/anti-emetic activity if indicated
3) Body temperature (especially if ambient temperature is very hot or cold)

**Client Information** - Avoid getting solutions on hands or clothing as contact dermatitis may develop. May discolor the urine to a pink or red-brown color; this is not abnormal.

**Dosage Forms/Preparations** -

**Veterinary-Approved Products:** None

**Human-approved Products:**

Chlorpromazine Tablets 10 mg, 25 mg, 50 mg, 100 mg, 200 mg; *Thorazine*® (SKF); Generic; (Rx)

Chlorpromazine Extended-release Capsules 30 mg, 75 mg, 150 mg, 200 mg, 300 mg; *Thorazine*® *Spansule*®(SKF); (Rx)

Chlorpromazine Oral Solutions: 2 mg/ml (syrup) in 120 ml bottles; 30 mg/ml (concentrate) in 120 ml bottles, gallons; 100 mg/ml (concentrate) in 60 and 240 ml bottles*Thorazine*® (SKF) ; Generic; (Rx)

Rectal suppositories 25 mg, 100 mg (as base); *Thorazine*® (SKF); (Rx)

Injection 25 mg/ml in 1 & 2 ml amps and cartridges and 10 ml vials; *Thorazine*® (SKF);*Ormazine*® (Hauck); Generic; (Rx)

## CHORIONIC GONADOTROPIN

**Chemistry** - A gonad-stimulating polypeptide secreted by the placenta, chorionic gonadotropin is obtained from the urine of pregnant women. It occurs as a white or practically white, amorphous, lyophilized powder. It is soluble in water and practically insoluble in alcohol. One International Unit of HCG is equal to one USP unit. There are at least 1500 USP Units per mg.
Chorionic gonadotropin has many synonyms, including human chorionic gonadotropin, HCG, hCG, CG, chorionic gonadotrophin, pregnancy-urine hormone, and PU.

**Storage/Stability/Compatibility** - Chorionic gonadotropin powder for injection should be stored at room temperature (15-30°C) and protected from light. After reconstitution, the resultant solution is stable for 30-90 days (depending on the product) when stored at 2-15°C.

**Pharmacology** - HCG mimics quite closely the effects of luteinizing hormone (LH), but also has some FSH-like activity. In males, HCG can stimulate the differentiation of, and androgen production by, testicular interstitial (Leydig) cells. It may also stimulate testicular descent when no anatomical abnormality is present.

In females, HCG will stimulate the corpus luteum to produce progesterone, and can induce ovulation (possibly also in patients with cystic ovaries). In the bitch, HCG will induce estrogen secretion.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications -** The veterinary product's labeled indication is for "parenteral use in cows for the treatment of nymphomania (frequent or constant heat) due to cystic ovaries." It has been used for other purposes in several species, refer to the Dosage section for more information.

**Pharmacokinetics** - HCG is destroyed in the GI tract after oral administration, so it must be given parenterally. After IM injection, peak plasma levels occur in about 6 hours. HCG is distributed primarily to the ovaries in females and to the testes in males, but some may also be distributed to the proximal tubules in the renal cortex.

HCG is eliminated from the blood in biphasic manner. The initial elimination half-life is about 11 hours and the terminal half-life is approximately 23 hours.

**Contraindications/Precautions** - In humans, HCG is contraindicated in patients with prostatic carcinoma or other androgen-dependent neoplasias, precocious puberty or having a previous hypersensitivity reaction to HCG. No labeled contraindications for veterinary patients were noted, but the above human contraindications should be used as guidelines. Antibody production to this hormone has been reported after repetitive use, resulting in diminished effect.

**Adverse Effects/Warnings** - Potentially, hypersensitivity reactions are possible with this agent. HCG may cause abortion in mares prior to the 35th day of pregnancy, perhaps due to increased estrogen levels. No other reported adverse reactions were noted for veterinary patients.
In humans, HCG has caused pain at the injection site, gynecomastia, headache, depression, irritability and edema.

**Overdosage** - No overdosage cases have been reported with HCG.

**Drug Interactions** - No interactions have apparently been reported with HCG.

**Doses** -
**Horses**:

For cryptorchidism:

a) Foal: 1000 Units injected twice weekly for 4-6 weeks (McDonald 1988) (Note: Many clinicians believe that medical treatment is unwarranted and that surgery should be performed.)

To induce ovulation in early estrus when one, large dominant follicle that is palpable with a diameter >35 mm is present:

a) HCG: 2000 - 3000 IU IV (preferable to treat mare 6 hours before mating) (Hopkins 1987)

For treatment of persistent follicles during the early transition period:

a) 1000 - 5000 IU (results are variable). (Van Camp 1986)

To hasten ovulation and reduce variability of estrus after prostaglandin synchronization:

a) HCG: 1500 - 3300 IU 5-6 days after the second prostaglandin treatment or on the first or second day of estrus. (Bristol 1986)

To induce ovulation after estrus has commenced:

a) 2500 - 4000 IU IM or SQ; ovulation generally occurs in 24-48 hours (Roberts 1986b)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** - All HCG products are prescription (Rx).

Chorionic Gonadotropin (HCG) Powder for Injection 5,000 Units per vial with 10 ml of diluent to make 500 Units/ml

Chorionic Gonadotropin (HCG) Powder for Injection 10,000 Units per vial with 10 ml of diluent to make 1000 Units/ml

To Drug Monograph Index To Ophthalmic Product Index

Chorionic Gonadotropin (HCG) Powder for Injection 20,000 Units per vial with 10 ml of diluent to make 2000 Units/ml

There are several products available with a variety of trade names, as well as many generically labeled products. Two commonly known products are *A.P.L*® (Wyeth-Ayerst) and *Follutein*® (Squibb). Veterinary-Approved Products are known to be available from Solvay (*Follutein*®) and LyphoMed (generically labeled). There are chorionic gonadotropin products approved for use in dairy cattle and beef cattle. There are no withdrawal times for either milk or meat.

## CIMETIDINE
## CIMETIDINE HCL

**Chemistry** - An $H_2$- receptor antagonist, cimetidine occurs as a white to off-white, crystalline powder. It has what is described as an "unpleasant" odor and a $pK_a$ of 6.8. Cimetidine is sparingly soluble in water and soluble in alcohol. Cimetidine HCl occurs as white, crystalline powder and is very soluble in water and soluble in alcohol. It has a $pK_a$ of 7.11 and the commercial injection has a pH of 3.8-6.

**Storage/Stability/Compatibility** - Cimetidine products should be stored protected from light and kept at room temperature. Do not refrigerate the injectable product as precipitation may occur. Oral dosage forms should be stored in tight containers.

The cimetidine injectable product is **compatible** with the commonly used IV infusions solutions, including amino acid (TPN) solutions, but should be used within 48 hours of dilution. Cimetidine is also reported to be compatible with the following drugs: acetazolamide sodium, amikacin sulfate, atropine sulfate, carbenicillin disodium, cefoxitin sodium, chlorothiazide sodium, clindamycin phosphate, colistimethate sodium, dexamethasone sodium phosphate, digoxin, epinephrine, erythromycin lactobionate, furosemide, gentamicin sulfate, heparin sodium, insulin (regular), isoproterenol HCl, lidocaine HCl, lincomycin HCl, methylprednisolone sodium succinate, nafcillin sodium, norepinephrine bitartrate, penicillin G potassium/sodium, phytonadione, polymyxin B sulfate, potassium chloride, protamine sulfate, quinidine gluconate, sodium nitroprusside, tetracycline HCl, vancomycin HCl, verapamil HCl, and vitamin B complex (w/ or w/o C).

The following drugs are reported to be either **incompatible** with cimetidine or data are conflicting: amphotericin B, ampicillin sodium, cefamandole naftate, cefazolin sodium, cephalothin sodium, and pentobarbital sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - At the $H_2$ receptors of the parietal cells, cimetidine competitively inhibits histamine, thereby reducing gastric acid output both during basal conditions and when stimulated by food, pentagastrin, histamine or insulin. Gastric emptying time, pancreatic or biliary secretion, and lower esophageal pressures are not altered by cimetidine. By decreasing the amount of gastric juice produced, cimetidine also decreases the amount of pepsin secreted.

Cimetidine has an apparent immunomodulating effect as it has been demonstrated to reverse suppressor T cell-mediated immune suppression. It also possesses weak anti-androgenic activity.

**Uses/Indications -** In veterinary medicine, cimetidine has been used for the treatment and/or prophylaxis of gastric, abomasal and duodenal ulcers, uremic gastritis, stress-related or drug-induced erosive gastritis, esophagitis, duodenal gastric reflux and esophageal reflux. It has also been employed to treat

hypersecretory conditions associated with gastrinomas and systemic mastocytosis. Cimetidine has also been used investigationally as a immunomodulating agent (see doses) in dogs.

**Pharmacokinetics** - Pharmacokinetic data for veterinary species is limited for this agent. In dogs, the oral bioavailability is reported to be approximately 95%, serum half-life is 1.3 hours and volume of distribution is 1.2 L/kg.

In humans, cimetidine is rapidly and well absorbed after oral administration, but a small amount is metabolized in the liver before entering the systemic circulation (first-pass effect). The oral bioavailability is 70-80%. Food may delay absorption and slightly decrease the amount absorbed, but when given with food, peak levels occur when the stomach is not protected by the buffering capabilities of the ingesta.

Cimetidine is well distributed in body tissues and only 15-20% is bound to plasma proteins. The drug enters milk and crosses the placenta.

Cimetidine is both metabolized in the liver and excreted unchanged by the kidneys. More drug is excreted by the kidneys when administered parenterally (75%) than when given orally (48%). The average serum half-life is 2 hours in humans, but can be prolonged in elderly patients and in those with renal or hepatic disease. Peritoneal dialysis does not appreciably enhance the removal of cimetidine from the body.

**Contraindications/Precautions** - Cimetidine is contraindicated in patients with known hypersensitivity to the drug.

Cimetidine should be used cautiously in geriatric patients and in patients with significantly impaired hepatic or renal function. In humans meeting these criteria, increased risk of CNS (confusion) effects may occur; dosage reductions may be necessary.

**Adverse Effects/Warnings** - Adverse effects appear to be very rare in animals at the dosages generally used. Potential adverse effects (documented in humans) that could be seen, include mental confusion, headache (upon discontinuation of the drug), gynecomastia and decreased libido. Rarely, agranulocytosis may develop and if given rapidly IV, transient cardiac arrhythmias may be seen. Pain at the injection site may be noted after IM administration.

Cimetidine does inhibit microsomal enzymes in the liver and may alter the metabolic rates of other drugs (see Drug Interactions below).

**Overdosage** - Clinical experience with cimetidine overdosage is limited. In laboratory animals, very high dosages have been associated with tachycardia and respiratory failure. Respiratory support and beta-adrenergic blockers have been suggested for use should these symptoms occur.

**Drug Interactions** - Cimetidine may inhibit the hepatic microsomal enzyme system and thereby reduce the metabolism, prolong serum half-lives, and increase the serum levels of several drugs. It may also reduce the hepatic blood flow and reduce the amount of hepatic extraction of drugs that have a high first-pass effect. The following drugs may be affected: beta**-blockers** (*e.g.,* **propranolol**), **lidocaine, calcium channel blockers** (*e.g.,* **verapamil**), **diazepam (and other benzodiazepines), ethanol, metronidazole, phenytoin, quinidine, theophylline, and warfarin.** Dosage adjustment or increased therapeutic monitoring may be necessary.
Cimetidine may decrease the renal clearance of **procainamide**. Cimetidine may exacerbate leukopenias when used with other agents that can cause this problem. Stagger doses (separate by 2 hours if possible) of cimetidine with **antacids, metoclopramide, sucralfate, digoxin,** and **ketoconazole**.

**Drug/Laboratory Interactions -** Cimetidine may cause small increases in plasma **creatinine** concentrations early in therapy. These increases are generally mild, non-progressive, and have

disappeared when therapy is discontinued. Histamine$_2$ blockers may antagonize the effects of histamine and pentagastrin in the **evaluation gastric acid secretion**. After using **allergen extract skin tests**, histamine$_2$ antagonsits may inhibit histamine responses. It is recommended that histamine$_2$ blockers be discontinued at least 24 hours before performing either of these tests.

**Doses** -
**Horses**:

For foals:

a) 1000 mg divided *bid* or *tid* PO, IV or IM (Robinson 1987)
b) 300 - 600 mg PO or IV 4 times a day (Clark and Becht 1987)

**Monitoring Parameters** -

1) Clinical efficacy (dependent on reason for use); monitored by decrease in symptomatology, endoscopic examination, blood in feces, etc.
2) Adverse effects if noted

**Client Information** - To maximize the benefit of this medication, it must be administered as prescribed by the veterinarian; symptoms may reoccur if dosages are missed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Cimetidine Tablets 100 mg, 200 mg, 300 mg, 400 mg, 800 mg; *Tagamet*® HB (SKBeecham) (OTC); *Tagamet*® (SK-Beecham) (Rx); generic (Rx)

Cimetidine HCl Liquid 300 mg (as HCl) per 5 ml; *Tagamet*® (SK-Beecham) (Rx); *Cimetidine Oral Solution*® (Barre-National) (Rx)

Cimetidine HCl for Injection 150 mg/ml in 2 ml vials and 8 ml multiple-dose vials and 8 ml vials; 300 mg (as HCl) in 50 ml 0.9% sodium chloride in premixed single-dose containers; *Tagamet*® (SK-Beecham) (Rx);*Cimetidine*® (Endo) (Rx)

## CISAPRIDE

**Chemistry** - An oral GI prokinetic agent, cisapride is a substituted piperidinyl benzamide and is structurally, but not pharmacologically, related to procainamide. It is available commercially as a monohydrate, but potency is expressed in terms of the anhydrate.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, store cisapride tablets in tight, light-resistant containers at room temperature.

**Pharmacology** - Cisapride increases lower esophageal peristalsis and sphincter pressure and accelerates gastric emptying. The proposed mechanism of action is that it enhances the release of acetylcholine at the myenteric plexus, but does not induce nicotinic or muscarinic receptor stimulation. Acetylcholinesterase activity is not inhibited. Cisapride blocks dopaminergic receptors to a lesser extent than does metoclopramide and does not increase gastric acid secretion.

**Uses/Indications** - Cisapride is a new agent. Proposed uses for it in small animals include esophageal reflux and treatment of primary gastric stasis disorders.

To Drug Monograph Index  To Ophthalmic Product Index

**Pharmacokinetics** - Human data: After oral administration, cisapride is rapidly absorbed with an absolute bioavailability of 35-40%. The drug is highly bound to plasma proteins and apparently extensively distributed throughout the body. Cisapride is extensively metabolized and its elimination half life is about 8-10 hours.

**Contraindications/Precautions/Reproductive Safety** - Cisapride is contraindicated in patients in whom increased gastrointestinal motility could be harmful (*e.g.*, perforation, obstruction, GI hemorrhage) or those who are hypersensitive to the drug.

Cisapride at high dosages (> 40 mg/kg/day) caused fertility impairment in female rats. At doses 12 to 100 times the maximum recommended, cisapride was embryotoxic and fetotoxic in rabbits and rats. Its use during pregnancy should occur only when the benefits outweigh the risks. Cisapride is excreted in maternal milk in low levels; use with caution in nursing mothers.

**Adverse Effects/Warnings** - Usage in small animal medicine has been limited to this point and an adverse effect profile has not been determined. As expected in humans, the primary adverse effects are gastrointestinal related with diarrhea and abdominal pain most commonly reported.
Dosage may need to be decreased in patients with severe hepatic impairment.

**Overdosage/Acute Toxicity** - In one reported human overdose of 540 mg, the patient developed GI distress and urinary frequency. $LD_{50}$ doses in various lab animals range from 160 - 4000 mg/kg. Significant overdoses should be handled using standard gut emptying protocols when appropriate; supportive therapy should be initiated when required.

**Drug Interactions** - Because cisapride can decrease GI transit times, absorption of other drugs given orally may be affected. **Oral drugs with a narrow therapeutic index** may need serum levels monitored more closely when adding or discontinuing cisapride. Use of **anticholinergic agents** may diminish the effects of cisapride. **Cimetidine** (not ranitidine) may increase cisapride serum levels and cisapride may accelerate **cimetidine** and **ranitidine** absorption thereby enhancing their effects. Cisapride may enhance **anticoagulants'** effects; additional monitoring and anticoagulant dosage adjustments may be required. Cisapride may enhance the sedative effects of **alcohol** or **benzodiazepines**. Elevated concentrations of cisapride with resultant ventricular arrhythmias may result if coadministered with **ketoconazole**, **itraconazole**, IV **miconazole** or **troleandomycin**. At present, the manufacturer states that cisapride should not be used with these drugs.

**Doses** -
**Horses**:

As a promotility agent:

a) Preliminary study: Author states that 0.1 mg/kg was superior to other doses used. No mention of dosage route or frequency was noted. (Roussel 1992)

**Monitoring Parameters** - Efficacy and adverse effects profile.

**Client Information** - Because cisapride is a "new" drug, inform client to watch carefully for and report any adverse effects noted.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Cisapride Oral Tablets 10 mg & 20 mg; *Propulsid*® (Janssen); *Prepulsid*® in Canada, New Zealand, etc. (Rx)

Cisapride Suspension: 1 mg/ml in 450 ml bottles; *Propulsid*®(Janssen) (Rx)

## CLENBUTEROL HCL

**Chemistry, Storage/Stability** - A beta-2-adrenergic agonist, clenbuterol HCl's chemical name is 1-(4-Amino-3,5-dichlorophenyl)-2-tert-butyl aminoethanol HCl. The commercially available syrup is colorless and should be stored at room temperature (avoid freezing). The manufacturer warns to replace the safety cap on the bottle when not in use.

**Pharmacology** - Like other beta-2 agonists, clenbuterol is believed to act by stimulating production of cyclic AMP through the activation of adenyl cyclase. By definition, Beta-2 agonists have more smooth muscle relaxation activity (bronchial, vascular and uterine smooth muscle) versus its cardiac effects (Beta 1).

**Uses/Indications** - Clenbuterol is approved for use in horses as a bronchodilator in the management of airway obstruction, such as chronic obstructive pulmonary disease (COPD).
It has been used as a partitioning agent in food producing animals, but its use for this purpose is banned in the USA as relay toxicity in humans has been documented.

**Pharmacokinetics** - After oral administration to horses, peak plasma levels of clenbuterol occur 2 hours after administration and the average half life is about 10 hours. The manufacturer states that the duration of effect varies from 6-8 hours.

**Contraindications/Precautions/Reproductive Safety -** The drug is contraindicated in food producing animals (legal ramifications). It should not be used in pregnant mares near full term as it antagonizes the effects of dinoprost (prostaglandin $F_2$alpha) and oxytocin and can diminish normal uterine contractility. The label states that the drug should not be used in horses suspected of having cardiovascular impairment as tachycardia may occur. Clenbuterol's safety in breeding stallions and brood mares has not been established.

**Adverse Effects/Warnings** - Muscle tremors, sweating, restlessness, urticaria and tachycardia may be noted, particularly early in the course of therapy. Creatine kinase elevations have been noted in some horses and rarely ataxia can occur.

Clenbuterol has been touted in some body building circles as an alternative to anabolic steroids for muscle development and body fat reduction, however its safe use for this purpose is in serious question. Be alert for scams to divert legitimately obtained clenbuterol for this purpose.

**Overdosage** - Some case reports of clenbuterol overdoses have been reported in various species. Depending on dosage and species, emptying gut may be appropriate; otherwise supportive therapy and administration of parenteral beta blockers to control heart rate and rhythm, and elevated blood pressure may be considered.

**Drug Interactions** - Concomitant administration with **other sympathomimetic amines** (e.g., terbutaline) may enhance the adverse effects of clenbuterol. **Beta blockers** (e.g. propranolol) may antagonize clenbuterol's effects. **Tricyclic antidepressants or monoamine oxidase inhibitors** may potentiate the vascular effects of clenbuterol. Use with inhalation anesthetics (*e.g.*, **halothane, isoflurane, methoxyflurane**), may predispose the patient to ventricular arrhythmias, particularly in patients with

preexisting cardiac disease—use cautiously. Use with **digitalis** glycosides may increase the risk of cardiac arrhythmias. Clenbuterol may antagonize the effects of **dinoprost** (prostaglandin $F_2$alpha) and **oxytocin**.

**Doses** -
**Horses**:

As a bronchodilator:

Initially, 0.8 micrograms/kg (practically: 0.5 ml of the commercially available syrup/100 lb. BW) twice daily for 3 days; if no improvement increase to 1.6 micrograms/kg (practically: 1 ml of the commercially available syrup/100 lb. BW) twice daily for 3 days; if no improvement increase to 2.4 micrograms/kg (practically: 1.5 ml of the commercially available syrup/100 lb. BW) twice daily for 3 days; if no improvement increase to 3.2 micrograms/kg (practically: 2 ml of the commercially available syrup/100 lb. BW) twice daily for 3 days; if no improvement discontinue therapy. Recommended duration of therapy is 30 days; then withdraw therapy and reevaluate. If signs return, reinitiate therapy as above. (Package Insert; Ventipulmin®)

**Monitoring Parameters** - 1) Clinical efficacy; 2) Adverse effects (primarily cardiac rate)

**Client Information** - Clients should be instructed on the restricted use requirements of this medication and to keep it secure from children or those who may "abuse" it. The drug may prohibited from use by various equine associations (*e.g.*, racing or show).

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products**:

Clenbuterol HCl Oral Syrup 72.5 mcg/ml in 100 ml and 330 ml bottles; *Ventipulmin® Syrup* (Boehringer Ingelheim Vetmedica); (Rx). Approved for use in horses not intended for use as food. Extralabel clenbuterol use is prohibited by federal (USA) law.

**Human-Approved Products**: None

## CLIOQUINOL

**Chemistry** - Also known as iodochlorhydroxyquin, clioquinol possesses antibacterial, antifungal and amoebicidal activity. It occurs as a tasteless, voluminous, yellowish white to brownish yellow powder that has a slight characteristic odor. The drug is practically insoluble in water and alcohol.

**Storage/Stability/Compatibility** - Unless otherwise directed, store clioquinol boluses at room temperature and protect from light.

**Pharmacology** - Information on the mechanism of action of clioquinol was not located, but its action is probably due to its iodine content. It is reportedly active against some cocci, *E. coli*, yeasts, and some protozoal parasites, particularly *Trichomonas sp*..

**Uses/Indications** - Clioquinol boluses are approved for oral use in horses to treat diarrheas that have failed to respond to regular forms of treatment, particularly if caused by some protozoal organisms. Clioquinol was once used orally in humans to treat diarrhea, but severe neurotoxic reactions have eliminated its use in humans, except as a topical antifungal.

**Pharmacokinetics** - The drug is only minimally absorbed after oral administration in horses. No other information was noted.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions/Reproductive Safety** - Not to be used in horses intended for food. No other information located.

**Adverse Effects/Warnings** - The manufacturer does not list any adverse effects for this product when used orally in horses. In humans, subacute myelo-opticoneuropathy was seen in many patients taking the drug orally for prolonged periods of time. It is unknown if the drug causes neurotoxic effects in horses. Topical administration for 28 days of the 3% topical preparation has caused toxicity in dogs.

**Overdosage/Acute Toxicity** - No specific information located regarding overdosage in horses. Iodism or potentially neurotoxic reactions (see Adverse effects above) could result.

**Drug Interactions**; **Drug/Laboratory Interactions** - None located, but the iodine component of the drug may affect some thyroid function tests.

**Doses** -
**Horses**:

For chronic diarrhea in horses:

a) 1 bolus (10 g) for a 1000 lb horse PO daily until feces become formed. Then reduce dose and give daily or reduce dose and give on alternate days or even less frequently. (Package insert; *Rheaform® Boluses*—Solvay)

**Monitoring Parameters** -

1) Clinical efficacy
2) Occasional neurological evaluations recommended with prolonged therapy

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: Note: Current marketing status is unknown.

Clioquinol Oral Boluses 10 g; *Rheaform® Boluses* (Fort Dodge); (Rx) Approved for use in horses.

**Human-Approved Products**: No systemic products approved in the United States. Topical formulations are available.

## CLOPROSTENOL SODIUM

**Chemistry** - A synthetic prostaglandin of the F class, cloprostenol sodium occurs as a white or almost white, amorphous, hygroscopic powder. It is freely soluble in water and alcohol. Potency of the commercially available product is expressed in terms of cloprostenol.

**Storage/Stability/Compatibility** - Cloprostenol sodium should be stored at room temperature (15-30°C); protect from light.

**Pharmacology** - Prostaglandin F□alpha and its analogues cloprostenol and fluprostenol are powerful luteolytic agents. They cause rapid regression of the corpus luteum and arrest its secretory activity. These prostaglandins also have direct stimulating effect on uterine smooth muscle causing contraction and a relaxant effect on the cervix.
In normally cycling animals, estrus will generally occur 2-5 days after treatment. In pregnant cattle treated between 10-150 days of gestation, abortion will usually occur 2-3 days after injection.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications -** Cloprostenol (*Estrumate*®—Miles) is approved for use in beef or dairy cattle to induce luteolysis. It is recommended by the manufacturer for unobserved or undetected estrus in cows cycling normally, pyometra or chronic endometritis, expulsion of mummified fetus, luteal cysts, induced abortions after mismating and to schedule estrus and ovulation for controlled breeding.

**Pharmacokinetics** - No information was located on the pharmacokinetics of cloprostenol.

**Contraindications/Precautions** - Cloprostenol is contraindicated in pregnant animals when abortion or induced parturition is not desired.

**Adverse Effects/Warnings** - The manufacturer does not list any adverse effects for this product when used as labeled. If used after the 5th month of gestation, increased risk of dystocia and decreased efficacy occur.

Do not administer IV.

Women of child-bearing age, persons with asthma or other respiratory diseases should use extreme caution when handling cloprostenol as the drug may induce abortion or acute bronchoconstriction. Cloprostenol is readily absorbed through the skin and must be washed off immediately with soap and water.

**Overdosage** - The manufacturer states that at doses of 50 and 100 times those recommended, cattle may show symptoms of uneasiness, slight frothing and milk let-down.
Overdoses of cloprostenol or other synthetic prostaglandin $F_{2alpha}$ analogs in small animals reportedly can result in shock and death.

**Drug Interactions** - Other **oxytocic agents**' activity may be enhanced by cloprostenol.

**Doses** -
**Horses**:
To cause abortion prior to the twelfth day of gestation:
a) 100 micrograms IM, most effective day 7 or 8 post estrus. Mare will usually return to estrus within 5 days. (Lofstedt 1986)

**Client Information** - Cloprostenol should be used by individuals familiar with its use and precautions. Pregnant women, asthmatics or other persons with bronchial diseases should handle this product with extreme caution. Any accidental exposure to skin should be washed off immediately.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Cloprostenol Sodium Injection Equiv. to 250 micrograms/ml cloprostenol in 10 ml or 20 ml vials;
*Estrumate*® (Bayer); (Rx) Approved for use in beef and dairy cattle. No preslaughter withdrawal nor milk withdrawal is required; no specific tolerance for cloprostenol residues have been published.

**Human-Approved Products**: None

## CLORSULON

**Chemistry** - A benzenesulfonamide, clorsulon has a chemical name of 4-amino-6-trichloroethenyl-1,3-benzenedisulfonamide.

To Drug Monograph Index To Ophthalmic Product Index

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, clorsulon should be stored at room temperature (15-30°C).

**Pharmacology** - In susceptible flukes, clorsulon inhibits the glycolytic enzymes 3-phosphoglycerate kinase and phosphoglyceromutase, thereby blocking the Emden-Myerhof glycolytic pathway. The fluke is deprived of its main metabolic energy source and dies.

**Uses/Indications** - Clorsulon is approved for use in the treatment of immature and adult forms of *Fasciola hepatica* (Liver fluke) in cattle. It is not effective against immature flukes less than 8 weeks old. It also has activity against *Fasciola gigantica*. Although not approved, the drug has been used in practice in various other species (*e.g.,* sheep, llamas). It has activity against *F. magna* in sheep, but is not completely effective in eradicating the organism after a single dose, thereby severely limiting its clinical usefulness against this parasite. Clorsulon is also not effective against the rumen fluke (*Paramphistomum*).

**Pharmacokinetics** - After oral administration to cattle, the drug is absorbed rapidly with peak levels occurring in about 4 hours. Approximately 75% of the circulating drug is found in the plasma and 25% in erythrocytes. At 8-12 hours after administration, clorsulon levels peak in the fluke.

**Contraindications/Precautions/Reproductive Safety** - No milk withdrawal time has been determined, and the drug is labeled not to be used in female dairy cattle of breeding age.
Clorsulon is considered to be safe to use in pregnant or breeding animals.

**Adverse Effects/Warnings** - When used as directed adverse effects are unlikely to occur with this agent.

**Overdosage/Acute Toxicity** - Clorsulon is very safe when administered orally to cattle or sheep. Doses of up to 400 mg/kg have not produced toxicity in sheep. A dose that is toxic in cattle has also not been determined.

**Drug Interactions & Drug/Laboratory Interactions** - None identified.

**Doses** -
**Cattle**:
For *Fasciola hepatica* infections:
a) 7 mg/kg PO; deposit suspension over the back of the tongue. (Label directions; *Curatrem*®—MSD-AgVet)

**Llamas**:
For *Fasciola hepatica* infections:
a) 7 mg/kg PO. (Fowler 1989)

**Elephants:**

a) Darunee Tuntasuvan B.Sc., D.V.M., Ph.D. (personal communication) 2003. In an unpubublished study, Dr. Tantasuvan found a mixture of 1% ivermectin and 10% Clorsulon (Ivomec – F) administered subcutaneously at a dose of 0.1 mg/kg to be 100 % effective against helminths. Flotation and sedimentation techniques were performed and eggs / gram determined at 0, 1, and 2 days and at weekly intervals for 6 weeks. This dose was not effective against flukes.

**Monitoring Parameters** -
1) Clinical efficacy

**Client Information** - Shake well before using.

To Drug Monograph Index  To Ophthalmic Product Index

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

Clorsulon 8.5% (85 mg/ml) Oral Drench in quarts or gallons; *Curatrem*® (Rhone Merieux); (OTC) Approved for use in beef and non-lactating dairy cattle. Slaughter withdrawal= 8 days.

## CLOXACILLIN
## CLOXACILLIN BENZATHINE

For general information on the penicillins, including adverse effects, contraindications, overdosage, drug interactions and monitoring parameters, refer to the monograph: Penicillins, General Information.

**Chemistry** - An isoxazolyl-penicillin, cloxacillin sodium is a semisynthetic penicillinase-resistant penicillin. It is available commercially as the monohydrate sodium salt which occurs as an odorless, bitter-tasting, white, crystalline powder. It is freely soluble in water and soluble in alcohol and has a $pK_a$ of 2.7. One mg of cloxacillin sodium contains not less than 825 micrograms of cloxacillin.

Cloxacillin sodium may also be known as sodium cloxacillin, chlorphenylmethyl isoxazolyl penicillin sodium or methylchlorophenyl isoxazolyl penicillin sodium.
Cloxacillin benzathine occurs as white or almost white powder that is slightly soluble in water and alcohol. A 1% (10 mg/ml) suspension has a pH from 3-6.5.

**Storage/Stability/Compatibility** - Cloxacillin sodium capsules and powder for oral solution should be stored at temperatures less than 40°C and preferably at room temperature (15-30°C). After reconstituting, refrigerate any remaining oral solution and discard after 14 days. If stored at room temperature, the oral solution is stable for 3 days.

Unless otherwise instructed by the manufacturer, cloxacillin benzathine mastitis syringes should be stored at temperatures less than 25°C in tight containers.

**Pharmacology/Uses/Indications** - Cloxacillin, dicloxacillin and oxacillin have nearly identical spectrums of activity and can be considered therapeutically equivalent when comparing *in vitro* activity. These penicillinase-resistant penicillins have a more narrow spectrum of activity than the natural penicillins. Their antimicrobial efficacy is aimed directly against penicillinase-producing strains of gram positive cocci, particularly *Staphylococcal* species. They are sometimes called anti-staphylococcal penicillins. There are documented strains of Staphylococcus that are resistant to these drugs (so-called methicillin-resistant *Staph*), but these strains have not as yet been a major problem in veterinary species. While this class of penicillins do have activity against some other gram positive and gram negative aerobes and anaerobes, other antibiotics (penicillins and otherwise) are usually better choices. The penicillinase-resistant penicillins are inactive against *Rickettsia*, mycobacteria, fungi, *Mycoplasma* and viruses.

The veterinary use of these agents has been primarily in the treatment of bone, skin, and other soft tissue infections in small animals when penicillinase-producing *Staphylococcus* species have been isolated, or in the treatment of mastitis with cloxacillin in dairy cattle.

**Pharmacokinetics (specific)** - Cloxacillin is only available in oral and intramammary dosage forms. Cloxacillin sodium is resistant to acid inactivation in the gut, but is only partially absorbed. The bioavailability after oral administration in humans has been reported to range from 37-60%, and if given with food, both the rate and extent of absorption is decreased.

To Drug Monograph Index  To Ophthalmic Product Index

The drug is distributed to the liver, kidneys, bone, bile, pleural fluid, synovial fluid and ascitic fluid. Only minimal amounts are distributed into the CSF, as with the other penicillins. In humans, approximately 90-95% of the drug is bound to plasma proteins.

Cloxacillin is partially metabolized to both active and inactive metabolites. These metabolites and the parent compound are rapidly excreted in the urine via both glomerular filtration and tubular secretion mechanisms. A small amount of the drug is also excreted in the feces via biliary elimination. The serum half-life in humans with normal renal function ranges from about 24-48 minutes. In dogs, 30 minutes has been reported as the elimination half-life.

**Doses** - Author's (Plumb) note: Injectable form is not available in the U.S.A.
**Cattle**:

For mastitis (treatment or prophylaxis) caused by susceptible organisms:

a) Lactating cow (using lactating cow formula; *Dari-Clox*®): After milking out and disinfecting teat, instill contents of syringe; massage. Repeat q12h for 3 total doses.
Dry (non-lactating) cows (using dry cow formula; benzathine): After last milking (or early in the dry period), instill contents of syringe and massage into each quarter. (Package inserts; *Dari-Clox*®, *Orbenin-DC*®—Beecham; *Dri-Clox*®—Fort Dodge)

**Client Information** - Unless otherwise instructed by the veterinarian, this drug should be given orally on an empty stomach, at least 1 hour before feeding or 2 hours after. Keep oral solution in the refrigerator and discard any unused suspension after 14 days.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Cloxacillin Benzathine 500 mg (of cloxacillin) in a peanut-oil gel; 10 ml syringe for intramammary infusion

*Orbenin-DC*® (Pfizer), *Dry-Clox*® (Fort Dodge); (Rx) Approved for use in dairy cows during the dry period (immediately after last milking or early in the dry period). Do not use within 30 days prior to calving (28 days for *Orbenin-DC*®). Slaughter withdrawal = 30 days (28 days for *Orbenin-DC*®). A tolerance of 0.01 ppm has been established for negligible residues in uncooked edible meat and milk from cattle.

Cloxacillin Sodium 200 mg (of cloxacillin) in vegetable oils; 10 ml syringe for intramammary infusion

*Dari-Clox*® (Pfizer); (Rx) Approved for use in lactating dairy cows. Milk withdrawal = 48 hours; Slaughter withdrawal = 10 days.

**Human-Approved Products**:

Cloxacillin Sodium Capsules 250 mg, 500 mg; *Tegopen*® (Apothecon) (Rx),*Cloxapen*® (SK-Beecham) (Rx), generic; (Rx)

Cloxacillin Sodium Powder for Oral Solution 125 mg/5 ml in 100 & 200 ml bottles; *Tegopen*® (Apothecon) (Rx), generic; (Rx)

## CORTICOTROPIN

**Chemistry** - A 39 amino acid polypeptide, corticotropin is secreted from the anterior pituitary. The first 24 amino acids (from the N-terminal end of the chain) define its biologic activity. While human, sheep, cattle and swine corticotropin have different structures, the first 24 amino acids are the same and, therefore,

biologic activity is thought to be identical. Commercial sources of ACTH generally are obtained from porcine pituitaries. One USP unit of corticotropin is equivalent to 1 mg of the international standard.

Corticotropin is available commercially as corticotropin for injection, repository corticotropin for injection, and corticotropin zinc hydroxide suspension. Corticotropin is commonly called ACTH (abbreviated from adrenocorticotropic hormone). Repository corticotropin is often called ACTH gel and is the most commonly used ACTH product in veterinary medicine.

**Storage/Stability/Compatibility** - Corticotropin for injection (aqueous) can be stored at room temperature (15-30°C) before reconstitution. After reconstitution, it should be refrigerated and used within 24 hours. Repository corticotropin injection should be stored in the refrigerator (2-8°C). To allow ease in withdrawing the gel into a syringe, the vial may be warmed with warm water prior to use.

**Pharmacology** - ACTH stimulates the adrenal cortex (principally the zona fasiculata) to stimulate the production and release of glucocorticoids (primarily cortisol in mammals and corticosterone in birds). ACTH release is controlled by corticotropin-releasing factor (CRF) activated in the central nervous system and via a negative feedback pathway, whereby either endogenous or exogenous glucocorticoids suppresses ACTH release.

**Uses/Indications -** In veterinary medicine, an ACTH product (*Adrenomone*®—Summit Hill) is approved for use in dogs, cats, and beef or dairy cattle for stimulation of the adrenal cortex when there is a deficiency of ACTH, and as a therapeutic agent in primary bovine ketosis. In practice however, it tends to be used most often in the diagnosis of hyper- or hypoadrenocorticism (ACTH-stimulation test) and to monitor the response to mitotane therapy in Cushing's syndrome.

ACTH has been used for several purposes in human medicine for its corticosteroid stimulating properties, but as it must be injected, it is not commonly employed.

**Pharmacokinetics** - Because it is rapidly degraded by proteolytic enzymes in the gut, ACTH cannot be administered PO. It is not effective if administered topically to the skin or eye. After IM injection in humans, repository corticotropin injection is absorbed over 8-16 hours. The elimination half-life of circulating ACTH is about 15 minutes, but because of the slow absorption after IM injection of the gel, effects may persist up to 24 hours.

**Contraindications/Precautions** - When used for diagnostic purposes, it is unlikely that increases in serum cortisol levels induced by ACTH will have significant deleterious effects on conditions where increased cortisol levels are contraindicated (*e.g.,* systemic fungal infections, osteoporosis, peptic ulcer disease, etc.). ACTH gel should not be used in patients hypersensitive to porcine proteins.

ACTH should only be used during pregnancy when the potential benefits outweigh the risks. It may be embryocidal. Neonates born from mothers receiving ACTH should be observed for signs of adrenocortical insufficiency.

**Adverse Effects/Warnings** - Prolonged use may result in fluid and electrolyte disturbances and other adverse effects. If using on a chronic basis, refer to the human literature for an extensive listing of potential adverse reactions. The veterinary manufacturer suggests giving potassium supplementation with chronic therapy. Do not administer the repository form (gel) IV.

**Overdosage** - When used for diagnostic purposes, acute inadvertent overdoses are unlikely to cause any significant adverse effects. Monitor as required and treat symptomatically if necessary.

To Drug Monograph Index To Ophthalmic Product Index

**Drug Interactions** - Glucocorticoids may alter the insulin requirements of diabetics. When used chronically, there are several potential interactions with ACTH including **barbiturates, phenytoin, rifampin, cyclophosphamide, estrogens, ulcerogenic drugs (*e.g.,* ASA, NSAIDs), potassium-depleting diuretics/drugs (*e.g.,* amphotericin B) and oral anticoagulants**. If the drug is to be used for purposes other than diagnostic purposes and the animal is receiving or will receive one of drugs listed above, refer to an appropriate reference (see bibliography) for further information.

**Drug/Laboratory Interactions -** ACTH may decrease **$^{131}$I uptake** by the thyroid gland. ACTH may suppress **skin test reactions** and interfere with **urinary estrogen** determinations.

**Doses** - Obtain specific information from the laboratory on sample handling and laboratory normals for cortisol when doing ACTH stimulation tests. ACTH is quite unstable in unfrozen plasma.
**Horses**:

ACTH Stimulation Test:

a) Draw baseline blood sample for cortisol determination and administer 1 Unit/kg IM of ACTH gel. Draw second sample 8 hours later. Normal stimulation will result in serum cortisol levels will increase 2-3 times. Horses with pituitary tumors will increase cortisol fourfold after ACTH. (Beech 1987b)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Corticotropin, Repository for Injection; 40 Units/ml and 80 Units/ml in 5 ml an d10 ml vials; ACTH Gel (Anthony); *Adrenomone*® (Summit Hill) (Rx) Approved for use in dogs, cats, and beef or dairy cattle.

**Human-Approved Products**:

Corticotropin Powder for Injection; 25 Units per vial, and 40 Units per vial

*Acthar*® (Rorer) (Rx) *ACTH* ®(Parke-Davis); (Rx); generic (Rx)

Corticotropin, Repository for Injection; 40 Units/ml and 80 Units/ml in 1 ml and 5 ml vials

*H.P. Acthar*® *Gel* (Rorer) (Rx), *ACTH-80*®(Various); (Rx)

## DANTROLENE SODIUM

**Chemistry** - A hydantoin derivative which is dissimilar structurally and pharmacologically from other skeletal muscle relaxant drugs, dantrolene sodium is a weak acid with a $pK_a$ of 7.5. It occurs as an odorless, tasteless, orange, fine powder that is slightly soluble in water. It rapidly hydrolyzes in aqueous solutions to the free acid form which precipitates out of solution.

**Storage/Stability/Compatibility** - Dantrolene capsules should be stored in well-closed containers at room temperature. Dantrolene powder for injection should be stored at temperatures less than 30°C and protected from prolonged exposure to light. After reconstitution, the powder for injection should be used within 6 hours when stored at room temperature and should be protected from direct light. It is not compatible with either normal saline or $D_5W$ injection.

**Pharmacology** - Dantrolene exhibits muscle relaxation activity by direct action on muscle. While the exact mechanism is not well understood, it probably acts on skeletal muscle by interfering with the release of calcium from the sarcoplasmic reticulum. It has no discernible effects on the respiratory or cardiovascular systems, but can drowsiness and dizziness. The reasons for these CNS effects are not known.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - In humans, oral dantrolene is indicated primarily for the treatment associated with upper motor neuron disorders (*e.g.,* multiple sclerosis, cerebral palsy, spinal cord injuries, etc.). In veterinary medicine, its proposed indications include the prevention and treatment of malignant hyperthermia syndrome in various species, the treatment of functional urethral obstruction due to increased external urethral tone in dogs and cats, the prevention and treatment of equine post-anesthetic myositis (PAM) and equine exertional rhabdomyolysis. It has also been recommended to be used in the treatment of bites from Black Widow Spiders in small animals and in the treatment of porcine stress syndrome.

**Pharmacokinetics** - The bioavailability of dantrolene after oral administration in humans is only about 35% and after intragastric administration to horses, approximately 39%. The drug is fairly slowly absorbed, with peak levels occurring about 5 hours after oral administration (humans) and 1.5 hours in horses. The drug is substantially bound to plasma proteins (principally albumin), but many drugs may displace it from such (see Drug Interactions).

Dantrolene is rapidly eliminated from the horse ($t_{1/2}$≈130 minutes). The elimination half-life in humans is approximately 8 hours. Dantrolene is metabolized in the liver and the metabolites are excreted in the urine. Only about 1% of the parent drug is excreted unchanged in the urine and bile.

**Contraindications/Precautions** - Because dantrolene can cause hepatotoxicity, it should be used with extreme caution in patients with preexisting liver disease. It should be used with caution in patients with severe cardiac dysfunction or pulmonary disease. The safe use of dantrolene during pregnancy has not been determined.

**Adverse Effects/Warnings** - The most significant adverse reaction with dantrolene therapy is hepatotoxicity. In humans, it is most commonly associated with high dose chronic therapy, but may also be seen after short high dose therapy. The incidence of this reaction is unknown in veterinary medicine, but must be monitored for.

More common, but less significant are the CNS associated signs of sedation, dizziness, headache, etc. and GI effects (nausea, vomiting, constipation). Also seen are increased urinary frequency, and possibly hypotension.

**Overdosage** - There is no specific antidotal therapy to dantrolene overdoses, therefore remove the drug from the gut if possible and treat supportively.

**Drug Interactions** - Dantrolene may be displaced from plasma proteins by **warfarin** with increased effects or adverse reactions resulting. Diazepam, phenytoin or phenylbutazone have not been demonstrated to alter the plasma protein binding of dantrolene.

Increased risks of hepatotoxicity from dantrolene have been seen in women >35 years of age who are also receiving **estrogen** therapy. The veterinary significance is unknown for this potential interaction. Increased sedation may be seen if **tranquilizing agents** are used concomitantly with dantrolene.

**Doses** -
**Horses**:

For treatment of acute rhabdomyolosis:

a) 15 - 25 mg/kg slow IV *qid* (Robinson 1987)

For prevention of rhabdomyolysis:

a) 2 mg/kg PO once daily (Robinson 1987)

For prevention of post-anesthetic myositis (PAM):

a) 10 mg/kg PO (intragastric) 1.5 hours before surgery. This should give peak levels at the time surgery begins and maintain postulated therapeutic levels for an additional 2 hours. The

intragastric preparation was made by dissolving/suspending the contents of oral capsules into 500 ml of normal saline. Should further doses be warranted, additional doses of 2.5 mg/kg PO (intragastric) q60 minutes can be given.
Alternatively, IV doses of 1.9 mg/kg loading will give therapeutic levels but will only persist for about 20 minutes. An IV dose of 4 mg/kg will maintain therapeutic levels for about 2 hours but peak levels will be quite high. (Court et al. 1987)

**Monitoring Parameters** -
Depending on the reason for use:

1) Baseline and periodic liver function tests (ALT, AST, Alk Phos, etc) if projecting to be used chronically or using high dosages
2) Body temperature (malignant hyperthermia)
3) Urine volume, frequency, continence

**Client Information** - This drug should only be used by professionals familiar with its use.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Dantrolene Sodium 25 mg, 50 mg, 100 mg capsules; *Dantrium*® (Procter & Gamble Pharm.) (Rx)

Dantrolene Sodium for Injection 20 mg per vial (with mannitol 3 g.); *Dantrium*® *Intravenous* (Procter & Gamble Pharm.) (Rx)

Note: Because of the expense, minimum order quantity, and non-returnable nature of the commercially available intravenous product, it is not well suited for veterinary use.

## DECOQUINATE

**Chemistry** - A coccidiostat, decoquinate occurs as a cream to buff-colored fine amorphous powder having a slight odor. It is insoluble in water.

**Storage/Stability/Compatibility** - Decoquinate is reportedly incompatible with strong bases or oxidizing material. Follow label storage directions; store in a cool, dry place. *Deccox*® is labeled as being compatible (and cleared for use) with bacitracin zinc (with or without roxarsone), chlortetracycline, and lincomycin.

**Pharmacology** - Decoquinate is 4-hydroxy quinolone agent that has anticoccidial activity. Decoquinate act on the sporozoite stage of the life cycle. The sporozoite apparently can still penetrate the host intestinal cell, but further development is prevented. The mechanism of action for decoquinate is to disrupt electron transport in the mitochondrial cytochrome system of coccidia.

**Uses/Indications** - Decoquinate is labelled for use in cattle for the prevention of coccidiosis in either ruminating or non-ruminating calves, cattle or young goats caused by the species *E. christenseni* or *E. ninakohlyakimoviae* . It is used for prevention of coccidiosis in broilers caused by *E. tenella, E. necatrix, E. acervulina, E. mivati, E. maxima* or *E. burnetti*.

**Pharmacokinetics** - No information located.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions/Reproductive Safety** - Decoquinate is not effective for treating clinical coccidiosis and has no efficacy against adult coccidia. Decoquinate is not approved for use in animals producing milk for food or in laying chickens.

**Adverse Effects/Warnings** - No adverse effects listed when given as directed.

**Overdosage/Acute Toxicity** - No specific information located. Decoquinate is considered to have a wide safety margin.

**Drug Interactions/Laboratory Considerations** - None located.

**Doses** -
**Dogs**:

For coccidiosis:

a) Prophylaxis: 50 mg/kg PO once daily (Matz 1995)

**Cattle:**

For prophylaxis of coccidiosis:

a) Using the 6% premix: 0.5 mg/kg per day in feed for at least 28 days**.** (Penzhorn and Swan 1993) (McDougald and Roberson 1988)

**Client Information** - Decoquinate should be used for at least 4 weeks when used for preventing coccidiosis outbreaks.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Decoquinate 6% (27.2 grams per lb.) Feed Additive (with corn meal, soybean oil, lecithin and silicon dioxide) in 50 LB bags; *Deccox*® (Rhone-Poulenc); (OTC) Approved for use in cattle (not lactating dairy cattle), goats (not lactating dairy goats) and poultry (not laying chickens).

Decoquinate 10X (2.271 grams per lb.) Feed Additive (with vitamins A, $D_3$, E) in 20 LB. buckets; *Deccox 10X*® (Vedco); (OTC) Approved for use in cattle (not lactating dairy cattle), goats (not lactating dairy goats).

Decoquinate 568 mg per pound Top Dress (with vitamins A, $D_3$, E) in 20 LB buckets; *Deccox Top Dress*® (Vedco); (OTC) Approved for use in cattle (not lactating dairy cattle), goats (not lactating dairy goats).

**Human-Approved Products**: None

## DETOMIDINE HCL

**Chemistry** - An imidazoline derivative alpha$_2$-adrenergic agonist, detomidine HCl occurs as a white crystalline substance that is soluble in water.

**Storage/Stability/Compatibility** - Detomidine HCl for injection should be stored at room temperature (15-30°C) and be protected from light.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Detomidine, like xylazine is an alpha$_2$-adrenergic agonist that produces a dose-dependent sedative and analgesic effect, but also has cardiac and respiratory effects. For more information refer to the xylazine monograph or the adverse effects section below.

**Uses/Indications** - At the present time detomidine is only approved for use as a sedative analgesic in horses, but it also has been used clinically in other species.

**Pharmacokinetics** - Detomidine is well absorbed after oral administration, but is used only parenterally at the present time. The drug is apparently rapidly distributed into tissues, including the brain after parenteral administration and is extensively metabolized and then excreted primarily into the urine.

**Contraindications/Precautions/Reproductive Safety** - Detomidine is contraindicated in horses with preexisting AV or SA heart block, severe coronary insufficiency, cerebrovascular disease, respiratory disease or chronic renal failure. It should be used with caution in animals with endotoxic or traumatic shock or approaching shock, and advanced hepatic or renal disease. Horses who are stressed due to temperature extremes, fatigue, or high altitude should also receive the drug with caution.

Although animals may appear to be deeply sedated, some may respond to external stimuli; use appropriate caution. The manufacturer recommends allowing the horse to stand quietly for 5 minutes prior to injection and for 10-15 minutes after injection to improve the effect of the drug. After administering detomidine, protect the animal from temperature extremes.

**Adverse Effects/Warnings** - Detomidine can cause an initial rise in blood pressure which is then followed by bradycardia and heart block. Atropine at 0.02 mg/kg IV has been successfully used to prevent or correct the bradycardia that may be seen when the detomidine is used at labeled dosages. Also, piloerection, sweating, salivation, slight muscle tremors, and penile prolapse may all be noted after injection.

**Overdosage/Acute Toxicity** - The manufacturer states that detomidine is tolerated by horses at doses 5 times (0.2 mg/kg) the high dose level (0.04 mg/kg). Doses of 0.4 mg/kg given daily for 3 consecutive days produced microscopic foci of myocardial necrosis in 1 of 8 horses tested. Doses of 10-40 times those recommended can cause severe respiratory and cardiovascular changes which can become irreversible and cause death. Yohimbine theoretically could be used to reverse some or all of the effects of the drug, but not enough clinical experience has been reported to make any recommendations for its use at this time.

**Drug Interactions** - The manufacturer warns against using this agent with intravenous **potentiated sulfonamides (e.g., trimethoprim/sulfa)** as fatal dysrhythmias may occur, and to use with extreme caution in combination with **other sedative or analgesic drugs**. Because this is a relatively new drug, more interactions may be forthcoming; refer to the xylazine monograph for more information on interactions with alpha$_2$-adrenergic agonists.

**Doses** -
**Horses**:

For sedation/analgesia:

a) 20 - 40 micrograms/kg (0.02 - 0.04 mg/kg) IV or IM (IV only for analgesia). Effects generally occur within 2-5 minutes. Lower dose will generally provide 30-90 minutes of sedation and 30-45 minutes of analgesia. The higher dose will generally provide 90-120 minutes of sedation and 45-75 minutes of analgesia. Allow animal to rest quietly prior to and after injection. (Package insert; *Dormosedan*®—SKB)

**Monitoring Parameters** -

1) Level of sedation, analgesia
2) Cardiac rate/rhythm; blood pressure if indicated

To Drug Monograph Index To Ophthalmic Product Index

**Client Information** - This drug should be used in a professionally supervised setting by individuals familiar with its properties.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Detomidine HCl for Injection 10 mg/ml in 5 and 20 ml vials
*Dormosedan*® (Pfizer); (Rx) Approved for use in horses.
The trade name, *Domosedan*® may be used in countries outside of the United States.

**Human-Approved Products**: None

## DEXAMETHASONE
## DEXAMETHASONE SODIUM PHOSPHATE
## DEXAMETHASONE 21-ISONICOTINATE

Note: For more information refer to the monograph: Glucocorticoids, General Information.

**Chemistry** - A synthetic glucocorticoid, dexamethasone occurs as an odorless, white to practically white, crystalline powder that melts with some decomposition at about 250°C. It is practically insoluble in water and sparingly soluble in alcohol. Dexamethasone sodium phosphate occurs as an odorless or having a slight odor, white to slightly yellow, hygroscopic powder. One gram of is soluble in about 2 ml of water; it is slightly soluble in alcohol. Dexamethasone 21-isonicotinate occurs as a nearly odorless and tasteless, white to slight yellow, crystalline powder.

1.3 mg of dexamethasone sodium phosphate is equivalent to 1 mg of dexamethasone; 4 mg/ml of dexamethasone sodium phosphate injection is approximately equivalent to 3 mg/ml of dexamethasone.

**Storage/Stability/Compatibility** - Dexamethasone is heat labile and should be stored at room temperature (15-30°C) unless otherwise directed by the manufacturer. Dexamethasone sodium phosphate injection should be protected from light. Dexamethasone tablets should be stored in well-closed containers.

Dexamethasone sodium phosphate for injection is reportedly **compatible** with the following drugs: amikacin sulfate, aminophylline, bleomycin sulfate, cimetidine HCl, glycopyrrolate, lidocaine HCl, nafcillin sodium, netilmicin sulfate, prochlorperazine edisylate and verapamil.

It is reportedly **incompatible** with: daunorubicin HCl, doxorubicin HCl, metaraminol bitartrate, and vancomycin. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Contraindications/Precautions** - Because dexamethasone has negligible mineralocorticoid effect, it should generally not be used alone in the treatment of adrenal insufficiency. For more information refer to the Glucocorticoid monograph.

**Doses** -
**Cattle**:
For adjunctive therapy of insect bites or stings:
a) 2 mg/kg IM or IV q4h (use epinephrine if anaphylaxis develops) (Fowler 1993)

To Drug Monograph Index To Ophthalmic Product Index

For adjunctive therapy of cerebral edema secondary to polioencephalomalacia:

a) 1 - 2 mg/kg intravenously (Dill 1986)

For adjunctive therapy of radial nerve injury, or femoral nerve paralysis:

a) Adult cattle (400-800 kg and not pregnant): 20 - 40 mg IM or IV; Calves: 10 mg IM or IV. Taper or discontinue therapy in 2-3 days. Many cases require only a single dose. (Rebhun 1986)

For adjunctive therapy of obturator nerve paralysis:

a) 10 - 40 mg parenterally once daily for 2-3 days then discontinue. (Rebhun 1986)

For adjunctive therapy of peroneal nerve injuries:

a) 10 - 30 mg parenterally for acute cases when not contraindicated due to pregnancy or infection. (Rebhun 1986)

For elective inducement of parturition or termination of pregnancy:

a) For abortion: 25 mg parenterally with 25 mg prostaglandin $F_{2\alpha}$ after 150 days of gestation. For inducement or parturition from 8th month of gestation on: 20 mg IM. (Drost 1986)
b) For inducement of parturition when given within 2 weeks of normal term: 20 - 30 mg IM (Barth 1986)

For adjunctive therapy of aseptic laminitis:

a) 5 - 20 mg IM or IV; continue therapy for 2-3 days (Berg 1986)

For primary bovine ketosis:

a) 5 - 20 mg IV or IM (Package Insert; *Azium*®— Schering)

**Horses**:

For glucocorticoid therapy:

a) 0.05 - 0.2 mg/kg once daily IV, IM or PO (Robinson 1987)

Dexamethasone suppression test:

a) 20 mg IM. Normal values: Cortisol levels decrease 50% in 2 hours, 70% in 4 hours, and 80% at 6 hours. At 24 hours levels are still depressed about 30% of original value. (Beech 1987b)

For labeled indications (various inflammatory conditions associated with the musculoskeletal system) for dexamethasone 21-isonicotinate (*Voren*®):

a) 5 - 20 mg IM; may repeat. (Package Insert; *Voren*®— Bio-ceutic)

For labeled indications (anti-inflammatory/glucocorticoid agent) for dexamethasone injection (*Azium*®):

a) 2.5 - 5 mg IV or IM. (Package Insert; *Azium*®— Schering)

For labeled indications (anti-inflammatory/glucocorticoid agent) for dexamethasone sodium phosphate injection (*Azium*®-*SP*):

a) 2.5 - 5 mg IV. (Package Insert; *Azium*®— Schering)

**Llamas**:

For adjunctive therapy of anaphylaxis:

a) 2 mg/kg IV (Smith 1989)

**Elephants:**

a) For treatment of heatstroke: 1mg/5 kg body weight. Schmidt,M.J., 1986. **Proboscidea (Elephants)**. In: Fowler,M.E. (Editor), Zoo and wild animal medicine. W.B. Saunders, Philadelphia,PA, USA pp. 884-923

**Dosage Forms/Preparations/Approval Status/Withdrawal Times**-

**Veterinary-Approved Products**:

Dexamethasone Oral Tablets 0.25 mg; *Azium*® *Tablets* (Schering), generic; (Rx) Approved for use in dogs and cats

To Drug Monograph Index To Ophthalmic Product Index

Dexamethasone Chewable Tablets; *Pet-Derm III* ® (Pfizer) (Rx). 0.25 mg scored tablets. Approved for dogs only.

Dexamethasone Injection 2 mg/ml; *Azium*® *Solution* (Schering),*Dexameth-a-Vet*® (Anthony) (Rx) generic; (Rx) Approved for use in dogs, cats, horses and cattle. There are no withdrawal times required when used in cattle.

Dexamethasone Sodium Phosphate Injection 4 mg/ml (equivalent to 3 mg/ml dexamethasone); *Azium*® *SP Injection* (Schering), *Dex-A-Vet Injection* (Anthony), generic; (Rx) Approved for use in horses.

**Human-Approved Products**: All require a presecription (Rx); many different trade named products are available.

Tablets: 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, & 6 mg
Oral Elixir/Solution: 0.5 mg/5 ml, 0.5 mg/0.5 ml
Dexamethasone Acetate Injection: 8 mg/ml, 16 mg/ml
Dexamethasone Sodium Phosphate Injection: 4 mg/ml, 10 mg/ml, 20 mg/ml, 24 mg/ml

## DEXPANTHENOL
## D-PANTHENOL

**Chemistry** - The alcohol of D-pantothenic acid, dexpanthenol occurs as a slightly bitter-tasting, clear, viscous, somewhat hygroscopic liquid. It is freely soluble in water or alcohol.

**Storage/Stability/Compatibility** - Dexpanthenol should be protected from both freezing and excessive heat. It is incompatible with strong acids and alkalis.

**Pharmacology** - A precursor to pantothenic acid, dexpanthenol acts as a precursor to coenzyyme A which is necessary for acetylation reactions to occur during gluconeogenesis and in the production acetylcholine. It has been postulated that post-surgical ileus can be prevented by giving high doses of dexpanthenol by assuring adequate levels of acetylcholine. However, one study in normal horses (Adams, Lamar, and Masty 1984) failed to demonstrate any effect of dexpanthenol on peristalsis.

**Uses/Indications -** Dexpanthenol has been suggested for use in intestinal atony or distension, postoperative retention of flatus and feces, prophylaxis and treatment of paralytic ileus after abdominal surgery or traumatic injuries, equine colic (not due to mechanical obstruction) and any other condition when there is an impairment of smooth muscle function. Controlled studies are lacking with regard to proving the efficacy of the drug for any of these indications.

**Pharmacokinetics** - Dexpanthenol is rapidly converted to pantothenic acid *in vivo*, which is widely distributed throughout the body, primarily as coenzyme A.

**Contraindications/Precautions** - Dexpanthenol is contraindicated in ileus secondary to mechanical obstruction or in cases of colic caused by the treatment of cholinergic anthelmintics. It is also contraindicated in humans with hemophilia as it may exacerbate bleeding. Safety in use during pregnancy has not been established.

**Adverse Effects/Warnings** - Adverse reactions are reportedly rare. Hypersensitivity reactions have been reported in humans, but may have been due to the preservative agents found in the injectable product. Potentially, GI cramping and diarrhea are possible.

**Overdosage** - The drug is considered non-toxic even when administered in high doses.

To Drug Monograph Index  To Ophthalmic Product Index

**Drug Interactions** - The manufacturer's have recommended that dexpanthenol not be administered within 12 hours of **neostigmine** or other parasympathomimetic agents and within 1 hour of receiving **succinylcholine**. The clinical significance of these potential interactions have not been documented, however.

**Doses** -
**Horses**:

a) 2.5 grams IV or IM; repeat if indicated at 4-6 hour intervals (Rossoff 1974), (Label Instructions; d-Panthenol Injectable - Vedco)

**Monitoring Parameters** -

1) Clinical Efficacy

**Client Information** - Should be used in a professionally-monitored situation where gastrointestinal motility can be monitored.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Dexpanthenol Injection 250 mg/ml in 100 ml vials (Veterinary labeled)
Generic; (Rx) Approved for use in dogs, cats, and horses.

**Human-Approved Products**:

Dexpanthenol Injection 250 mg/ml in 2 ml amps, 2 ml & 10 ml vials, UD Stat-Pak 2 ml disp syringes; *Ilopan*® (Adria), Generic; (Rx)

## DEXTRAN 70

Note: Dextran is also available as Dextran 40 and Dextran 75. Because Dextran 70 is the most commonly version used in veterinary medicine, the following monograph is limited to it alone.

**Chemistry** - A branched polysaccharide used intravenously as a plasma volume expander, dextran 70 occurs as a white to light yellow amorphous powder. It is freely soluble in water and insoluble in alcohol. Dextran 70 contains (on average) molecules of 70,000 daltons. Each 500 ml of the commercially available 6% dextran 70 in normal saline provides 77 mEq of sodium.

**Storage/Stability/Compatibility** - Dextran 70 injection should be stored at room temperature; preferably in an area with little temperature variability. While only clear solutions should be used, dextran flakes can form but can be resolubolized by heating the solution in a boiling water bath until clear, or autoclaving at 110°C for 15 minutes. Dextran 70 is compatible with many other solutions and drugs; refer to specialized references (e.g. Trissel) for more information.

**Pharmacology** - Dextran 70 has osmotic effects similarly to albumin. Dextran's colloidal osmotic effect draws fluid into the vascular system from the interstitial spaces, resulting in increased circulating blood volume.

**Uses/Indications** - Dextran 70 is a relatively low cost colloid for the adjunctive treatment of hypovolemic shock.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacokinetics** - After IV infusion, circulating blood volume is increased maximally within one hour and effects can persist for 24 hours or more. Approximately 20-30% of a given dose remains in the intravascular compartment at 24 hours and it may be detected in the blood 4-6 weeks after dosing. Dextran 70 is slowly degraded to glucose by dextranase in the spleen and then metabolized to carbon dioxide and water. A small amount may be excreted directly into the gut and eliminated in the feces.

**Contraindications/Precautions/Reproductive Safety -** Patients overly susceptible to circulatory overload (severe heart or renal failure) should receive dextran 70 with great caution. Dextran 70 is contraindicated in patients with severe coagulopathies and should be used with caution in patients with thrombocytopenia as it can interfere with platelet function. Do not give dextran IM. Patients on strict sodium restriction should receive dextran cautiously as a 500 ml bag contains 77 mEq of sodium.

**Adverse Effects/Warnings** - Moderate to life threatening reactions appear to rare in the dog. Dextran 70 may increase bleeding time and decrease von Willebrand's factor antigen and factor VIII activity. This apparently does not usually cause clinical bleeding in dogs. Anaphylactoid reactions are not that rare in humans, but apparently are very rare in dogs. Dextran 70 has only been rarely associated with acute renal failure, unlike dextran 40. In humans, GI effects (abdominal pain, nausea/vomiting) have been reported with use of dextran 70.

**Overdosage** - The drug should be dosed and monitored carefully as volume overload may result.

**Drug Interactions** - Dextran reportedly has no drug interactions that are clinically significant.

**Lab Interactions** - Dextran 70 may interfere with **blood cross-matching** as it can cross-link with red blood cells and appear as rouleaux formation. Isotonic saline may be used to negate this effect. Blood **glucose** levels may be increased as dextran is degraded. Falsely elevated **bilirubin** levels may be noted; reason unknown.

**Doses** -
**Dogs:**

a) Up to 40 ml/kg/day; not to be infused faster than 5 ml/kg/hr (Haskins 1992)
b) 20 ml/kg; bolus to effect (Eastlake and Snyder 1998)

**Monitoring Parameters** - Other than the regular monitoring performed in patients that would require volume expansion therapy, there is no inordinate monitoring required specific to dextran therapy.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products**: None

**Human-Approved Products**:

6% Dextran-70 in normal saline (0.9% NaCl) in 500 ml; *Dextran 70* (McGaw); *Gentran® 70* (Baxter) *Macrodex*® (Medisan); (Rx)

6% Dextran-70 in $D_5W$ in 500 ml; *Macrodex*® (Medisan); (Rx)

## DIAZEPAM

**Chemistry** - A benzodiazepine, diazepam is a white to yellow, practically odorless crystalline powder with a melting point between 131°-135°C and $pK_a$ of 3.4. Diazepam is tasteless initially, but a bitter after-taste develops. One gram is soluble in 333 ml of water, 25 ml of alcohol, and it is sparingly soluble in propylene glycol. The pH of the commercially prepared injectable solution is adjusted with benzoic acid/sodium

To Drug Monograph Index To Ophthalmic Product Index

benzoate to 6.2-6.9. It consists of a 5 mg/ml solution with 40% propylene glycol, 10% ethanol, 5% sodium benzoate/benzoic acid buffer, and 1.5% benzyl alcohol as a preservative.

**Storage/Stability/Compatibility** - All diazepam products should be stored at room temperature (15°-30°C). The injection should be kept from freezing and protected from light. The oral dosage forms (tablets/capsules) should be stored in tight containers and protected from light.

Because diazepam may adsorb to plastic, it should not be stored drawn up into plastic syringes. The drug may also significantly adsorb to IV solution plastic (PVC) bags and to the infusion tubing. This adsorption appears to be dependent on several factors (temperature, concentration, flow rates, line length, etc.).

The manufacturers of injectable diazepam do not recommend the drug be mixed with any other medication or IV diluent. The drug has been successfully diluted to concentrations of 5 mg/50 ml or 5 mg/100 ml in normal saline, lactated Ringer's and $D_5W$. Differing results have occurred with different manufacturer's products. Do not administer if a precipitate forms and does not clear.

**Pharmacology** - The subcortical levels (primarily limbic, thalamic, and hypothalamic) of the CNS are depressed by diazepam and other benzodiazepines thus producing the anxiolytic, sedative, skeletal muscle relaxant, and anticonvulsant effects seen. The exact mechanism of action is unknown, but postulated mechanisms include: antagonism of serotonin, increased release of and/or facilitation of gamma-aminobutyric acid (GABA) activity, and diminished release or turnover of acetylcholine in the CNS. Benzodiazepine specific receptors have been located in the mammalian brain, kidney, liver, lung, and heart. In all species studied, receptors are lacking in the white matter.

**Uses/Indications** - Diazepam is used clinically for its anxiolytic, muscle relaxant, hypnotic, appetite stimulant, and anticonvulsant activities. Refer to the dosage section for those and other suggested indications and doses for each species.

**Pharmacokinetics** - Diazepam is rapidly absorbed following oral administration. Peak plasma levels occur within 30 minutes to 2 hours after oral dosing. The drug is slowly (slower than oral) and incompletely absorbed following IM administration.

Diazepam is highly lipid soluble and is widely distributed throughout the body. It readily crosses the blood-brain barrier and is fairly highly bound to plasma proteins. In the horse at a serum of concentration of 75 ng/ml, 87% of the drug is bound to plasma proteins. In humans, this value has been reported to be 98-99%.

Diazepam is metabolized in the liver to several metabolites, including desmethyldiazepam (nordiazepam), temazepam, and oxazepam, all of which are pharmacologically active. These are eventually conjugated with glucuronide and eliminated primarily in the urine. Because of the active metabolites, serum values of diazepam are not useful in predicting efficacy. Serum half-lives (approximated) have been reported for diazepam and metabolites in dogs, cats, and horses:

| | Dogs | Cats | Horses | Humans |
|---|---|---|---|---|
| Diazepam | 2.5 - 3.2 hrs | 5.5 hrs | 7 - 22 hrs | 20 - 50 hrs |
| Nordiazepam | 3 hrs | 21.3 hrs | | 30 - 200 hrs |

**Contraindications/Precautions** - Slowly inject intravenously. This is particularly true when using a small vein for access or in small animals. Diazepam may cause significant thrombophlebitis. Too rapid of an injection of intravenous diazepam in small animals or neonates, may cause cardiotoxicity secondary to the propylene glycol in the formulation. Intra-carotid artery injections must be avoided.

To Drug Monograph Index To Ophthalmic Product Index

Use cautiously in patients with hepatic or renal disease and in debilitated or geriatric patients. the drug should be administered to patients in coma, shock or with significant respiratory depression very cautiously. It is contraindicated in patients with known hypersensitivity to the drug. Benzodiazepines may impair the abilities of working animals. If administering the drug IV, be prepared to administer cardiovascular or respiratory support.

Diazepam has been implicated in causing congenital abnormalities in humans if administered during the first trimester of pregnancy. Infants born of mothers receiving large doses of benzodiazepines shortly before delivery have been reported to suffer from apnea, impaired metabolic response to cold stress, difficulty in feeding, hyperbilirubinemia, hypotonia, etc. Withdrawal symptoms have occurred in infants whose mothers chronically took benzodiazepines during pregnancy. The veterinary significance of these effects is unclear, but the use of these agents during the first trimester of pregnancy should only occur when the benefits clearly outweigh the risks associated with their use. Benzodiazepines and their metabolites are distributed into milk and may cause CNS effects in nursing neonates.

**Adverse Effects/Warnings** - In horses, diazepam may cause muscle fasiculations, weakness and ataxia at doses sufficient to cause sedation. Doses greater than 0.2 mg/kg may induce recumbency as a result of its muscle relaxant properties and general CNS depressant effects.

Cats may exhibit changes in behavior (irritability, depression, aberrant demeanor) after receiving diazepam. There have been recent reports of cats developing hepatic failure after receiving oral diazepam for several days; until this potential adverse effect is confirmed or refuted, use with caution in cats.

Dogs may exhibit a contradictory response (CNS excitement) following administration of diazepam. The effects with regard to sedation and tranquilization are extremely variable with each dog. Because of this individual variation, diazepam is not an ideal sedating agent for this species.

**Overdosage** - When administered alone, diazepam overdoses are generally limited to significant CNS depression (confusion, coma, decreased reflexes, etc). Hypotension, respiratory depression, and cardiac arrest have been reported in human patients, but apparently are quite rare.

Treatment of acute toxicity consists of standard protocols for removing and/or binding the drug in the gut if taken orally, and supportive systemic measures. The use of analeptic agents (CNS stimulants such as caffeine) are generally not recommended.

**Drug Interactions** - Metabolism of diazepam may be decreased and excessive sedation may occur if given with the following drugs: **cimetidine, erythromycin, isoniazid, ketoconazole, propranolol, & valproic acid**. If administered with other **CNS depressant agents (barbiturates, narcotics, anesthetics**, etc.) additive effects may occur. **Antacids** may slow the rate, but not the extent of oral absorption; administer 2 hours apart to avoid this potential interaction. The pharmacologic effects of **digoxin** may be increased; monitor serum digoxin levels or symptoms of toxicity. **Rifampin** may induce hepatic microsomal enzymes and decrease the pharmacologic effects of benzodiazepines.

**Laboratory Interactions**: Patients receiving diazepam, may show false negative **urine glucose** results if using *Diastix*® or *Clinistix*® tests.

**Doses** -
**Horses**:

For seizures:

a) Foals: 0.05 - 0.4 mg/kg IV; repeat in 30 minutes if necessary;
Adults: 25 - 50 mg IV; repeat in 30 minutes if necessary. (Sweeney and Hansen 1987)

Treatment of seizures secondary to intraarterial injection of xylazine or other similar agents:

To Drug Monograph Index To Ophthalmic Product Index

a) 0.10 - 0.15 mg/kg IV (Thurmon and Benson 1987)

As an appetite stimulant:

a) 0.02 mg/kg IV; immediately after dosing offer animal food. Keep loud noises and distractions to a minimum. If effective, usually only 2-3 treatments in a 24-48 hour period is required. (Ralston 1987)

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

To control musth:
a) A 20 year-old African bull (weight not specified) was placed on the following regimen to reduce signs of musth: 400 mg diazepam in the a.m and 200 mg diazepam in the p.m for 5 days; concentrate feeds reduced by ½; a calming effect was noted; dose was tapered to 400 mg / day over a 5 day period; concentrates gradually increased; dose reduced to 100 mg / day for 10 days; concentrates increased; diazepam discontinued on day 20 and normal diet resumed. Thakuria,D.B. and Barthakur,T. 1996. Management of musth in a male African elephant by chemical sedatives in the Assam state zoo, Guwahati. Indian Veterinary Journal 73:(3):339-340 Note: This article also discusses a successful regimen using lorazepam.

b) To treat extrapyramidal signs associated with overdose of long-acting neuroleptics. Elephant-specific dose not listed. Ebedes,H. 1995. **The use of long term neuroleptics in the confinement and transport of wild animals**. Joint Conf AAZV/WDA/AAWV. Pages: 173-176

c) As an anti-convulsant in Asian elephants, 400 - 800 mg diazepam / animal IM. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants** . In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

**Monitoring Parameters** - Horses should be observed carefully after receiving this drug.

**Client Information** - Keep out of reach of children and in tightly closed containers.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Diazepam oral tablets 2 mg, 5 mg, 10 mg; *Valium*® (Roche); Generic; (Rx)

Diazepam timed-release oral capsules 15 mg; *Valrelease*® (Roche); (Rx)

Diazepam oral solution 1 mg/ml in 500 ml containers and unit-dose (5 & 10 mg) 5 mg/ml in 30 ml dropper bottle; *Diazepam Intensol*® (Roxane); *Generic* (Rx)

Diazepam Injection 5 mg/ml in 2 ml amps & syringes & 1, 2, 10 ml vials, 2 ml Tel-E-Ject; Emulsified Injection: 5 mg/ml in 3 ml vials; *Valium*® (Roche); *Zetran*® (Hauck);*Dizac*® (Ohmeda); Generic; (Rx)

Diazepam is a **Class-IV controlled substance**.

To Drug Monograph Index To Ophthalmic Product Index

## DICHLORVOS

**Chemistry** - An organophosphate insecticide, dichlorvos is also known as 2,2,-dichlorovinyl dimethyl phosphate or DDVP.

**Storage/Stability/Compatibility** - Dichlorvos tablets and capsules should be kept refrigerated (2-8°C). Dichlorvos feed additives should not be stored at temperatures below freezing. Dichlorvos is sensitive to hydrolysis if exposed to moisture and to oxidizing agents.

**Pharmacology** - Like other organophosphate agents, dichlorvos inhibits acetylcholinesterase interfering with neuromuscular transmission in susceptible parasites.

**Uses/Indications** - Dichlorvos is indicated for use internally in dogs and cats for the treatment of roundworms (*Toxocara canis, Toxocara cati, Toxacaris leonina*) and hookworms (*Ancylostoma caninum, Ancylostoma tubaeforme, Uncinaria stenocephala*). It is effective in swine against *Ascaris, Trichuris, Ascarops strongylina* and *Oesophagostomum spp*.. In horses, dichlorvos is labeled as being effective for the treatment and control of bots, pinworms, large and small bloodworms and large roundworms. It is also used as a premise spray to keep fly populations controlled and as a flea and tick collar for dogs and cats.

**Pharmacokinetics** - Specific information was not located for this agent.

**Contraindications/Precautions/Reproductive Safety** - Do not administer to horses suffering from heaves, colic, diarrhea, constipation, or infectious diseases until these conditions have been corrected. In dogs and cats, dichlorvos is contraindicated in animals exhibiting symptoms of severe constipation, intestinal impaction, liver dysfunction, circulatory failure, or to animals exposed to, or showing signs of infection. Dogs infected with D. immitis should not receive dichlorvos. Dichlorvos should not be used in conjunction with any other anthelmintics, taeniacides, filaricides (DEC exempted) or within a few days of other medications that inhibit cholinesterase (see drug interactions below). Studies performed in target species have demonstrated no teratogenic effects at usual doses.

**Adverse Effects/Warnings** - Adverse effects are generally dose-related and may include those listed below in the Overdosage/Acute Toxicity section. Cats, young animals, or debilitated animals may be more susceptible to toxic effects. Use in young kittens, cats with any other concurrent diseases or debilitated or animals otherwise stressed, should probably be avoided.

**Overdosage/Acute Toxicity** - If overdoses occur, vomiting, tremors, bradycardia, respiratory distress, hyperexcitability, salivation and diarrhea may occur. Atropine (see atropine and pralidoxime monographs for more information) may be antidotal. Use of succinylcholine, theophylline, aminophylline, reserpine, or respiratory depressant drugs (*e.g.,* narcotics, phenothiazines) should be avoided in patients with organophosphate toxicity. If an ingestion occurs by a human, contact a poison control center, physician or hospital emergency room.

**Drug Interactions** - **Acepromazine or other phenothiazines** should not be given within one month of worming with an organophosphate agent as their effects may be potentiated. Because of its anticholinesterase activity, avoid the use of organophosphates with **DMSO**. Cythioate could theoretically enhance the toxic effects of **levamisole**. **Pyrantel Pamoate (or tartrate)** adverse effects could be intensified if used concomitantly with an organophosphate. Patients receiving organophosphate anthelmintics should not receive **succinylcholine** or other depolarizing muscle relaxants for at least 48 hours. Drugs such as **morphine, neostigmine, physostigmine** and **pyridostigmine** should be avoided when using organophosphates as they can inhibit cholinesterase.

To Drug Monograph Index To Ophthalmic Product Index

**Doses -**
**Large Animals:**
Read and follow label directions, including any withdrawal times stated.

**Monitoring Parameters** - 1) Efficacy; 2) Adverse Effects

**Client Information** - Keep out of reach of children. Handling of dichlorvos liquid preparations (*e.g.*, premise spray) must be done with extreme care; follow all label directions! Oral pellets are non-digestible and may be seen in the animals feces.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Dichlorvos Oral: Tablets 10 mg, 20 mg; Capsules 68 mg, 136 mg, 204 mg; Pellets (in packets) 136 mg, 204 mg, 544 mg; *Task*® & *Task*® *Tabs* (Fermenta); (Rx). Approved for use in dogs (Capsules, Pellets and Tabs) and cats (Tabs Only).

Dichlorvos Oral Equine Wormer 78 g/pkt; *Cutter Dichlorvos Horse Wormer*® (Miles); (OTC)

Dichlorvos Feed Additives: *Atgard*® *C* (Fermenta); (OTC); *Atgard*® *Swine Wormer* (Fermenta); (OTC)

Also available in a 9.6% flea and tick collar for dogs and cats: *Pet Insecticide Collar* (Fermenta); (OTC) and a 40.2% concentrate for premise spraying in 5 gallon containers: *Vapona*® *Concentrate* (Fermenta); (OTC).

**Human-Approved Products:** None

## DIGITOXIN

**Chemistry** - A cardiac glycoside, digitoxin occurs as a bitter tasting, odorless, white to pale buff colored, microcrystalline powder. It is practically insoluble in water and one gram is soluble in approximately 150 ml of alcohol.

**Storage/Stability/Compatibility** - Digitoxin tablets should be stored at room temperature (15-30°C) and kept in well-closed containers. Digitoxin injection is hydrolyzed at pH's less than 3. It is said to be compatible with most available IV solutions and it is not compatible with acids or alkalies.

**Uses/Indications** - Like digoxin, digitoxin is indicated for heart failure or atrial arrhythmias, but because it is metabolized by the liver to a greater extent, some clinicians feel that it should be used instead of digoxin in patients with diminished renal function. Others believe that digoxin may be used in these patients if adequate serum level monitoring is performed and dosage adjustments are made as necessary. Digitoxin is not routinely used in cats and some clinicians state it is contraindicated in this species.

**Pharmacokinetics** - Digitoxin has only one steroidal hydroxyl group (versus two for digoxin) and therefore is much less polar. It is rapidly and nearly completely absorbed in the small intestine after oral administration. It is unknown if the presence of food alters either the rate or extent of absorption.

Digitoxin is highly protein bound (97% in humans, 70-90% in dogs) and values generally are the same in uremic patients. It is unknown if digitoxin enters the milk.

Digitoxin is extensively metabolized and the elimination half-life usually remains unchanged in renal failure patients. The elimination half-life in dogs has been reported range from 8-49 hours. Like digoxin, this

apparent interpatient variability suggests that digitoxin serum levels msut be monitored to optimize therapy and reduce the chance for toxicity. Digitoxin is usually not recommended for use in cats because of its "very long" half-life, but one study reported a $t_{1/2}$ of only 32 hours, although other values have been reported to be longer than 100 hours.

**Pharmacology, Contraindications/Precautions, Adverse Effects/Warnings, Overdosage, Drug Interactions** -
See the information listed for digoxin.

**Doses** -
**Horses**:

a) 0.03 - 0.06 mg/kg PO for digitalization; 0.01 mg/kg PO for maintenance (Robinson 1987)

**Monitoring Parameters** -

1) Serum levels
   Because of this drug's narrow therapeutic index, and interpatient variability, it is strongly recommended to monitor serum levels to help guide therapy. Unless the patient (dog) received an initial loading dose, at least 36 hours should pass after starting therapy to monitor serum levels to allow levels to approach steady-state. Suggested therapeutic serum levels in the dog are 15-35 ng/ml (Neff-Davis 1985). Toxicity is usually associated with levels greater than 40 ng/ml. Levels at the higher end of the suggested range may be necessary to treat some atrial arrhythmias, but may also result in higher incidences of adverse effects. Usually a trough level (just before next dose or at least 4-10 hours after the last dose) is recommended.
2) Appetite/weight
3) Cardiac rate, ECG changes
4) Serum electrolytes
5) Clinical efficacy for CHF (improved perfusion, decreased edema, increased venous (or arterial) $O_2$ levels).

**Client Information** - Contact veterinarian if animal displays changes in behavior, vomits, has diarrhea, lack of appetite, symptoms of colic (horses), becomes lethargic or depressed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Digitoxin Tablets 0.05 mg, 0.1 mg; *Crystodigin*® (Lilly); (Rx)

## DIGOXIN

**Chemistry** - A cardiac glycoside, digoxin occurs as bitter tasting, clear to white crystals or as white, crystalline powder. It is practically insoluble in water, slightly soluble in diluted alcohol, and very slightly soluble in 40% propylene glycol solution. Above 235°C it melts with decomposition.

The commercial injection consists of a 40% propylene glycol, 10% alcohol solution having a pH of 6.6-7.4.

**Storage/Stability/Compatibility** - Digoxin tablets, capsules, elixir and injection should be stored at room temperature (15-30°C) and protected from light.

To Drug Monograph Index To Ophthalmic Product Index

At pH's from 5-8, digoxin is stable, but in solutions with a pH of less than 3, it is hydrolyzed.
The injectable product is compatible with most commercially available IV solutions, including lactated Ringer's, $D_5W$, and normal saline. To prevent the possibility of precipitation occurring, one manufacturer (Glaxo Wellcome) recommends that the injection be diluted by a volume at least 4 times with either sterile water, $D_5W$, or normal saline. Digoxin injection has been demonstrated to be **compatible** with bretylium tosylate, cimetidine HCl, lidocaine HCl, and verapamil HCl.

Digoxin is **incompatible** with dobutamine HCl, acids and alkalies. The manufacturer does not recommend mixing digoxin injection with other medications. Compatibility is dependent upon factors such as pH, concentration, temperature, diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** - The pharmacology of the digitalis glycosides have been extensively studied, but a thorough discussion is beyond the scope of this reference. Suffice it to say that digitalis glycosides cause the following effects in patients with a failing heart: increased myocardial contractility (inotropism) with increased cardiac output; increased diuresis with reduction of edema secondary to a decrease in sympathetic tone; reduction in heart size, heart rate, blood volume, and pulmonary and venous pressures; and (usually) no net change in myocardial oxygen demand.

The digitalis glycosides also have several electrocardiac effects, including: decreased conduction velocity through the AV node, and prolonged effective refractory period (ERP). They may also increase the PR interval, decrease the QT interval and cause ST segment depression.
The exact mechanism of action of these agents have not been fully described, but their ability to increase the availability of $Ca^{++}$ to myocardial fibers and to inhibit $Na^{+}$-$K^{+}$-ATPase with resultant increased intracellular $Na^{+}$ and reduced $K^{+}$ probably largely explain their actions.
For additional information, it is suggested to refer to a pharmacology text.

**Uses/Indications** - The veterinary indications for digitalis glycosides include treatment of congestive heart failure, atrial fibrillation or flutter, and supraventricular tachycardias.

**Pharmacokinetics** - Absorption following oral administration occurs in the small intestine and is variable dependent upon the oral dosage form used (see Dosage Forms below). Food may delay, but does not alter the extent of absorption. Peak serum levels generally occur within 45-60 minutes after oral elixir, and at about 90 minutes after oral tablet administration. In patients receiving an initial oral dose of digoxin, peak effects may occur in 6-8 hours after the dose.

The drug is distributed widely throughout the body with highest levels found in kidneys, heart, intestine, stomach, liver and skeletal muscle. Lowest concentrations are found in the brain and the plasma. At therapeutic levels, approximately 20-30% of the drug is bound to plasma proteins. Because only small amounts are found in fat, obese patients may receive too high dosages if dosing is based on total body weight versus lean body weight.

Digoxin is metabolized slightly, but the primary method of elimination is renal excretion both by glomerular filtration and tubular secretion. As a result, dosage adjustments must be made in patients with significant renal disease. Values reported for the elimination half-life of digoxin in dogs have been highly variable, with values reported from 14.4-56 hours. Elimination half-lives reported in other species include: Cats≈33.3±9.5 hrs; Sheep≈7.15 hrs.; Horses≈16.9 - 23.2 hrs.; and Cattle≈7.8 hrs.

**Contraindications/Precautions** - Digitalis cardioglycosides are contraindicated in patients with ventricular fibrillation or in digitalis intoxication. They should be used with extreme caution in patients with glomerulonephritis and heart failure or with idiopathic hypertrophic subaortic stenosis (IHSS). They should be used with caution in patients with severe pulmonary disease, hypoxia, acute myocarditis, myxedema, or

acute myocardial infarction, frequent ventricular premature contractions, ventricular tachycardias, chronic constrictive pericarditis or incomplete AV block. They may be used in patients with stable, complete AV block or severe bradycardia with heart failure if the block was not caused by the cardiac glycoside.

When used to treat atrial fibrillation or flutter prior to administration with an antiarrhythmic agent that has anticholinergic activity (*e.g.,* quinidine, procainamide, disopyramide), digitalis glycosides will reduce, but not eliminate the increased ventricular rates that may be produced by those agents. Since digitalis glycosides may cause increased vagal tone, they should be used with caution in patients with increased carotid sinus sensitivity.

Elective cardioversion of patients with atrial fibrillation should be postponed until digitalis glycosides have been withheld for 1-2 days, and should not be attempted in patients with signs of digitalis toxicity.

Because digoxin is principally eliminated by the kidneys, it should be used with caution and serum levels monitored in patients with renal disease. Animals that are hypernatremic, hypokalemic, hypercalcemic, hyper- or hypothyroid may require smaller dosages; monitor carefully.

The veterinary elixir is available in two separate concentrations, do not confuse the two.

**Adverse Effects/Warnings** - Adverse effects of digoxin are usually associated with high or toxic serum levels and are categorized into cardiac and extracardiac signs and symptoms. There are species differences with regard to the sensitivity to digoxin's toxic effects also. Cats are relatively sensitive to digoxin while dogs tend to be more tolerant of high serum levels.

Cardiac effects may be seen before other extra-cardiac symptoms and may include almost every type of cardiac arrhythmia described with a resultant worsening of heart failure symptoms. More common arrhythmias or ECG changes seen, include complete or incomplete heart block, bigeminy, ST segment changes, paroxysmal ventricular or atrial tachycardias with block, and multifocal premature ventricular contractions. Because these effects can also be caused by worsening heart disease, it may be difficult to determine if they are a result of the disease process or of digitalis intoxication. If in doubt, monitor serum levels or stop digoxin therapy temporarily.

Extracardiac symptoms most commonly seen in veterinary medicine include mild GI upset, anorexia, weight loss and diarrhea. Vomiting has been associated with IV injections and should not cause anxiety nor alarm. Ocular and neurologic effects are routinely seen in humans, but are not prevalent in animals or are not detected.

**Overdosage** - Symptoms of chronic toxicity are discussed above. In dogs the acute toxic dose after IV administration has been reported to be 0.177 mg/kg.

Treatment of chronic digoxin toxicity is dictated by the severity of the signs and symptoms associated with it. Many patients will do well after temporarily stopping the drug and reevaluating the dosage regimen.

If an acute ingestion has recently occurred and no present cardiotoxic or neurologic signs (coma, seizures, etc.) have been manifested, emptying the stomach may be indicated followed with activated charcoal administration. Because digoxin can be slowly absorbed and there is some enterohepatic recirculation of the drug, repeated charcoal administration may be beneficial even if the ingestion occurred well before treatment. Anion-exchange resins such as colestipol or cholestyramine have also been suggested to reduce the absorption and enterohepatic circulation of digoxin and digitoxin, but are not readily available in most veterinary practices. These agents may be of more benefit to adsorb less polar compounds such as digitoxin.

To Drug Monograph Index To Ophthalmic Product Index

Dependent on the type of cardiotoxicity, supportive and symptomatic therapy should be implemented. Serum electrolyte concentrations, drug level if available on a “stat” basis, arterial blood gases if available, and continuous ECG monitoring should be instituted. Acid-base, hypoxia, and fluid and electrolyte imbalances should be corrected. The use of potassium in normokalemic patients is very controversial and should only be attempted with constant monitoring and clinical expertise.

The use of specific antiarrhythmic agents in treating life-threatening digitalis-induced arrhythmias may be necessary. Phenytoin, lidocaine, and propranolol are most commonly employed for these arrhythmias. Atropine may be used to treat sinus bradycardia, SA arrest, or 2nd or 3rd degree AV block.

Digoxin immune Fab is a promising treatment for digoxin or digitoxin life-threatening toxicity. It is produced from specific digoxin antibodies from sheep and will bind directly to the drug, inactivating it. It is extremely expensive however and veterinary experience with it is extremely limited.

**Drug Interactions** - Many digoxin interactions are listed in human medicine, the following may be of importance in veterinary medicine: **Antacids, cimetidine, metoclopramide, neomycin (oral), chemotherapy agents (***e.g.,* **cyclophosphamide, doxorubicin, vinca alkaloids, cytarabine**) may decrease the amount of digoxin absorbed from the GI tract. The following agents may either increase the serum level, decrease the elimination rate, or enhance the toxic effects of digoxin: **diazepam, quinidine, anticholinergics, succinylcholine, verapamil, tetracycline and erythromycin.** Patients on digoxin that receive **thyroid replacement therapy** may need their digoxin dosage adjusted. **Penicillamine** may decrease serum levels of digoxin independent of route of digoxin dosing. Drugs that can affect electrolyte balance can alter the efficacy or enhance the toxic effects of digoxin. **Diuretics (furosemide, thiazides)** may predispose the patient to digitalis toxicity. Other drugs which can deplete body potassium **(amphotericin B, glucocorticoids, ACTH, laxatives, sodium polystyrene sulfonate**) or decrease extracellular potassium **(glucagon, high dose IV dextrose, dextrose/insulin infusions)** may also predispose patients to toxic effects of digitalis drugs. **Spironolactone** may enhance or decrease the toxic effects of digoxin. Refer to specialized references for more information.

**Doses** -
**Horses**:

a) 0.022 mg/kg daily orally (maintenance) (McConnell and Hughey 1987)
b) 0.06 - 0.08 mg/kg PO q8h for 5-6 doses to digitalize, then 0.01 - 0.02 mg/kg PO maintenance. (Hilwig 1987)

Note: a case report of serious digoxin toxicity in a horse has been reported following 0.035 - 0.07 mg/kg/day for 5 days; digitalize with caution.

**Monitoring Parameters** -

1) Serum levels
   Because of the significant interpatient pharmacokinetic variation seen with this drug and its narrow therapeutic index, it is strongly recommended to monitor serum levels to help guide therapy. Unless the patient received an initial loading dose, at least 6 days should pass after beginning therapy to monitor serum levels as to allow levels to approach steady-state. Suggested therapeutic serum levels in the dog are 0.9 - 3.0 ng/ml and 0.9 - 2.0 ng/ml in cat (Neff-Davis 1985). For other species, values from 0.5 - 2.0 ng/ml can be used as guidelines. Levels at the higher end of the suggested range may be necessary to treat some atrial arrhythmias, but may also result in higher incidences of adverse effects. Usually a trough level (just before next dose or at least 8 hours after last dose) is recommended.
2) Appetite/weight
3) Cardiac rate, ECG changes
4) Serum electrolytes

To Drug Monograph Index  To Ophthalmic Product Index

5) Clinical efficacy for CHF (improved perfusion, decreased edema, increased venous (or arterial) $O_2$ levels).

**Client Information** - Contact veterinarian if animal displays changes in behavior, vomits, has diarrhea, lack of appetite, symptoms of colic (horses), becomes lethargic or depressed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -
There are bioavailability differences between dosage forms and in tablets produced by different manufacturers. It is recommended that tablets be used from a manufacturer that the clinician has confidence in and that brands not be routinely interchanged. Should a change in dosage forms be desired, the following bioavailability differences can be used as guidelines in altering the dose: Intravenous = 100%, IM ≈ 80%, Oral tablets ≈ 60%, Oral elixir ≈ 75%, Oral capsules ≈ 90-100%. The bioavailability of digoxin in veterinary species has only been studied in a limited manner. One study in dogs yielded similar values as those above for oral tablets and elixir, but in horses only about 20% of an intragastric dose was bioavailable.

**Veterinary-Approved Products**:

Digoxin Elixir 0.05 mg/ml 60 ml dropper bottle; *Cardoxin® LS* (Evsco); (Rx)

Digoxin Elixir 0.15 mg/ml in 60 ml dropper bottle; *Cardoxin®* (Evsco); (Rx)

Digoxin tablets and elixir have been approved for veterinary use, but no species are listed in the indications. There are no drug residue data for meat or milk published and no meat or milk withdrawal times are available.

**Human-Approved Products**:

Digoxin for Injection 0.1 mg/ ml in 1 ml amps & 0.25 mg/ml in 2 ml amps, & 1 & 2 ml Tubex; *Lanoxin®* (Glaxo Wellcome), *Digoxin®* (Elkins-Sinn) and (Wyeth-Ayerst) (Rx)

Digoxin tablets 0.125 mg, 0.25 mg and 0.5 mg; *Lanoxin®* (Glaxo Wellcome), generic; (Rx)

Digoxin capsules 0.05 mg, 0.1 mg, 0.2 mg; *Lanoxicaps®* (Glaxo Wellcome); (Rx)

Digoxin Elixir Pediatric 0.05 mg/ml in 60 ml dropper bottle, 50 ml and UD 2.5 & 5 ml; *Lanoxin®* (Glaxo Wellcome); (Rx); generic (Rx)

## DIMERCAPROL

**Chemistry** - A dithiol chelating agent, dimercaprol occurs as a colorless or nearly colorless, viscous liquid that is soluble in alcohol, vegetable oils, and water, but is unstable in aqueous solutions. It has a very disagreeable mercaptan-like odor. The commercially available injection is a peanut oil and benzyl benzoate solution. Although the solution may be turbid or contain small amounts of flocculent material or sediment, this does not mean the solution is deteriorating.

Dimercaprol may also be known as BAL, British Anti-Lewisite, dimercaptopropanol, or dithioglycerol.

**Storage/Stability/Compatibility** - Dimercaprol injection should be stored below 40°C; preferably at room temperature (15-30°C).

**Pharmacology** - The sulfhydryl groups found on dimercaprol form heterocyclic ring complexes with heavy metals, principally arsenic, lead, mercury and gold. This binding helps prevent or reduce heavy metal binding to sulfhydryl-dependent enzymes. Different metals have differing affinities for both dimercaprol and sulfhydryl-dependent enzymes and the drug is relatively ineffective in chelating some metals (*e.g.,*

selenium). Chelation to dimercaprol is not irreversible and metals can dissociate from the complex as dimercaprol concentrations decrease, in an acidic environment, or if oxidized. The dimercaprol-metal complex is excreted via renal and fecal routes.

**Uses/Indications** - The principal use of dimercaprol in veterinary medicine is in treating intoxications caused by arsenical compounds. It is occasionally used for lead, mercury and gold intoxication.

**Pharmacokinetics** - After IM injection, peak blood levels occur in 30-60 minutes. The drug is slowly absorbed through the skin after topical administration.
Dimercaprol is distributed throughout the body, including the brain. Highest tissue levels are found in the liver and kidneys.

Non-metal bound drug is rapidly metabolized to inactive compounds and excreted in the urine, bile and feces. In humans, the duration of action is thought to be about 4 hours, with the drug completely eliminated within 6-24 hours.

**Contraindications/Precautions/Reproductive Safety** - Dimercaprol is contraindicated in patients with impaired hepatic function, unless secondary to acute arsenic toxicity. The drug is also contraindicated in iron, cadmium, and selenium poisoning as the chelated complex can be more toxic than the metal alone.

Because dimercaprol is potentially nephrotoxic, it should be used cautiously in patients with impaired renal function. In order to protect the kidneys, the urine should be alkalinized to prevent the chelated drug from dissociating in the urine. Animals with diminished renal function or who develop renal dysfunction while on therapy should either have the dosage adjusted or discontinue therapy dependent on the clinical situation.

**Adverse Effects/Warnings** - IM injections are necessary with this compound but can be very painful, particularly if the drug is not administered deeply. Vomiting and seizures can occur with higher dosages. Transient increases in blood pressure with concomitant tachycardia has been reported. Most adverse effects are transient in nature as the drug is eliminated rapidly.
Dimercaprol is potentially nephrotoxic.

**Overdosage/Acute Toxicity** - Symptoms of dimercaprol overdosage in animals include vomiting, seizures, tremors, coma and death. No specific doses were located to correspond with these symptoms, however.

**Drug Interactions** - Because dimercaprol can form a toxic complex with certain metals (cadmium, selenium, uranium and iron). Do not administer with **iron or selenium salts**. At least 24 hours should pass after the last dimercaprol dose, before iron or selenium therapy is begun.

**Drug/Laboratory Interactions** - **Iodine $I^{131}$ thyroidal uptake values** may be decreased during or immediately following dimercaprol therapy as it interferes with normal iodine accumulation by the thyroid.

**Doses** -
**Horses**:

For arsenic toxicity:

a) Dimercaprol therapy in horses is difficult because it must be used acutely and any substantial delays in treatment significantly decrease its effectiveness, as well as the amounts of dimercaprol that are required and the necessity to inject the drug IM. If available, the dose is: 5 mg/kg IM initially, followed by 3 mg/kg IM q6h for the remainder of the first day, then 1 mg/kg IM q6h for two or more additional days, as needed. (Oehme 1987a) (Note: Refer to this reference for additional information on the use of sodium thiosulfate and protective laxative therapy.)

**Monitoring Parameters** -

To Drug Monograph Index To Ophthalmic Product Index

1) Liver function
2) Renal function
3) Hemogram
4) Hydration and perfusion status
5) Electrolytes and acid/base status
6) Urinary pH

**Client Information** - Because of the potential toxicity of this agent and the seriousness of most heavy metal intoxications, this drug should be used with close professional supervision only. Dimercaprol can impart a strong, unpleasant mercaptan-like odor to the animal's breath.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Dimercaprol Injection 100 mg/ml (for IM use only) in 3 ml amps; *BAL in Oil*® (Becton Dickinson); (Rx)

## DIMETHYL SULFOXIDE

**Chemistry** - DMSO is a clear, colorless to straw-yellow liquid. It is dipolar, aprotic (acts as a Lewis base) and extremely hygroscopic. It has a melting/freezing point of 18.5°C, boiling point of 189°C, and a molecular weight of 78.1. It is miscible with water (heat is produced), alcohol, acetone, chloroform, ether and many organic solvents. A 2.15% solution in water is isotonic with serum.

**Storage/Stability/Compatibility** - Must be stored in airtight containers and away from light. As DMSO may react with some plastics, it should be stored in glass or in the container provided by the manufacturer. If DMSO is allowed to contact room air it will self-dilute to a concentration of 66-67%. DMSO is apparently compatible with many compounds, but because of the chances for accidental percutaneous absorption of potentially toxic compounds, the admixing of DMSO with other compounds is not to be done casually.

**Pharmacology** - The pharmacologic effects of DMSO are diverse. DMSO traps free radical hydroxide and its metabolite, dimethyl sulfide (DMS) traps free radical oxygen. It appears that these actions help to explain some of the anti-inflammatory, cryopreservative, antiischemic, and radioprotective qualities of DMSO.

DMSO will easily penetrate the skin. It also serves as a carrier agent in promoting the percutaneous absorption of other compounds (including drugs and toxins) that normally would not penetrate. Drugs such as insulin, heparin, phenylbutazone, and sulfonamides may all be absorbed systemically when mixed with DMSO and applied to the skin.

DMSO has weak antibacterial activity when used clinically and possible clinical efficacy when used topically as an antifungal. The mechanism for these antimicrobial effects have not been elucidated.

The anti-inflammatory/analgesic properties of DMSO have been thoroughly investigated. DMSO appears to be more effective an anti-inflammatory agent when used for acute inflammation versus chronic inflammatory conditions. The analgesic effects of DMSO has been compared to that produced by narcotic analgesics and is efficacious for both acute and chronic musculoskeletal pain.

DMSO decreases platelet aggregation, but reports on its effects on coagulability have been conflicting, as has its effect on the myocardium. DMSO has diuretic activity independent of the method of administration. It

also provokes histamine release from mast cells, which probably contributes to the local vasodilatory effects seen after topical administration.

DMSO also apparently has some anticholinesterase activity and enhances prostaglandin E, but blocks the synthesis of prostaglandins $E_2$, $F_{2\text{-alpha}}$, $H_2$, and $G_2$. It inhibits the enzyme alcohol dehydrogenase, which not only is responsible for the metabolism of alcohol, but also the metabolism of ethylene glycol into toxic metabolites.

**Uses/Indications** - Purported uses for DMSO are rampant, but the only FDA-approved veterinary indication for DMSO is: "...as a topical application to reduce acute swelling due to trauma" (Package Insert - *Domoso*® — Syntex). Other possible indications for DMSO include: adjunctive treatment in transient ischemic conditions, CNS trauma and cerebral edema, skin ulcers/wounds/burns, adjunctive therapy in intestinal surgeries, and analgesia for post-operative or intractable pain, amyloidosis in dogs, reduction of mammary engorgement in the nursing bitch, enhancement of antibiotic penetration in mastitis in cattle, and limitation of tissue damage following extravasation injuries secondary to chemotherapeutic agents.

DMSO's effect on alcohol dehydrogenase, may make it useful in the treatment of ethylene glycol poisoning, but this has not been sufficiently studied as of yet. DMSO's attributes as a potential carrier of therapeutic agents across the skin and into the systemic circulation and its synergistic effects with other agents are potentially exciting, but require much more study before they can be routinely recommended.

While the potential indications for DMSO are many, unfortunately, the lack of well-controlled studies leave many more questions than answers regarding this drug.

**Pharmacokinetics** - DMSO is well absorbed after topical administration, especially at concentrations between 80-100%. It is extensively and rapidly distributed to virtually every area of the body. After IV administration to horses, the serum half-life was approximately 9 hours. DMSO is metabolized to dimethyl sulfide (DMS) and is primarily excreted by the kidneys, although biliary and respiratory excretion also takes place.
In cattle, the drug is eliminated quite rapidly and after 20 days no detectable drug or metabolites are found in milk, urine, blood, or tissues.

**Contraindications/Precautions** - Wear rubber gloves when applying topically, and apply with clean or sterile cotton to minimize the chances for contaminating with potentially harmful substances. Apply only to clean, dry areas to avoid carrying other chemicals into the systemic circulation.

DMSO may mask existing pathology with its anti-inflammatory and analgesic activity.
At high doses DMSO has been shown to be teratogenic in hamsters and chicks, but not in mice, rats or rabbits; weigh the risks versus benefits when using in pregnant animals.

Because DMSO may degranulate mast cells, animals with mastocytomas should only receive DMSO with extreme caution. DMSO should be used cautiously in animals suffering from dehydration or shock as its diuretic and peripheral vasodilatory effects may exacerbate these conditions.

**Adverse Effects/Warnings** - When used as labeled, DMSO appears to be an extremely safe drug. Local effects ("burning", erythema, vesiculation, dry skin, local allergic reactions) and garlic or oyster-like breath odor are the most likely adverse effects. They are transient and quickly resolve when therapy is discontinued. Lenticular changes, which may result in myopia, have been noted primarily in dogs and rabbits when DMSO is used chronically and at high doses. These effects are slowly reversible after the drug is discontinued.

To Drug Monograph Index  To Ophthalmic Product Index

When DMSO is administered intravenously to horses it may cause hemolysis and hemoglobinuria. These effects can be minimized by using concentrations of 20% or less (not less than 2% in water) and slowly administering.

Reports of hepatotoxicity and renal toxicity have also been reported for various species and dosages. These occur fairly rarely and some clinicians actually believe DMSO has a protective effect on ischemically insulted renal tissue.

**Overdosage** - The reported $LD_{50}$'s following IV dosage in dogs and cats are: Cats ≈ 4 g/kg, and Dogs ≈ 2.5 g/kg. Signs of toxicity include: sedation and hematuria at non-lethal doses; coma, seizures, opisthotonus, dyspnea and pulmonary edema at higher dosages. Should an acute overdosage be encountered, treat supportively.

**Drug Interactions** - Because of its anticholinesterase activity, avoid the use of **organophosphates** or **other cholinesterase inhibitors** with DMSO. A fatality secondary to mercury intoxication was reported when DMSO was mixed with a **mercury salt** "red blister" and applied topically to the leg of a horse. Because it inhibits alcohol dehydrogenase, DMSO may prolong the effects of **alcohol**. **Insulin**, **corticosteroids** (including endogenous steroids), and **atropine** may be potentiated by DMSO.

**Doses** -
**Horses**:

a) Liberal application should be administered topically to the skin over the affected area 2-3 times daily. Total daily dosage should not exceed 100 grams (or mls of liquid) and therapy should not exceed 30 days. (Package Insert - *Domoso*®; Syntex Animal Health)
b) For treatment of cerebral edema secondary to eastern equine encephalitis (EEE): 1 g/kg as a 20% solution in $D_5W$ IV over 30 minutes once daily for up to 3 days. (Wilson 1987)
c) Adjunctive treatment of equine protozoal myeloencephalitis (EPM): 1 g/kg as a 20% solution in $D_5W$ IV over 30 minutes once to twice daily. (Brewer 1987)
d) For spinal cord injury: 1 gm/kg IV as a 20% solution in saline once daily for 3 days, then every other day for 6 days (Robinson 1987)
e) For cantharidin poisoning: 0.9 gm/kg IV as a 10% solution in polyionic fluids (Schmitz and Reagor 1987)
f) 0.25 - 1.0 grams/kg diluted in normal saline or $D_5W$ at a concentration of not more than 20%. Concentrations greater than 10% should be given slowly IV. Generally felt that the higher dosages are necessary to treat increased intracranial pressure and cerebral edema with twice daily dosing. At U of Minn. usual dose is 110 ml in 1 liter of saline (10%) given daily to an average sized horse. (Plumb 1988)

**Monitoring Parameters** -

1) Efficacy
2) Hemoglobinuria/hematocrit if indicated
3) Ophthalmic exams with high doses or chronic use in the dog

**Client Information/FDA Approval Status** - Do not use non-medical grades of DMSO as they may contain harmful impurities. Wear rubber gloves when applying topically. DMSO should be applied with clean or sterile cotton to minimize the chances for contaminating with potentially harmful substances. Apply only to clean, dry skin. Use in well ventilated area; avoid inhalation and contact with eyes. May damage some fabrics. Keep lid tightly on container when not in use. Keep out of reach of children. Do not mix with any other substance without veterinarian's approval.

Selected DMSO products are approved for use in dogs and in horses not intended for food purposes. It is a veterinary prescription (Rx) drug.

To Drug Monograph Index To Ophthalmic Product Index

**Dosage Forms/Preparations** -

**Veterinary Approved Products:**

Dimethyl Sulfoxide Veterinary Gel 90%; Domoso® (Fort Dodge) Gel 90% (medical grade) in 60 g., and 120 g. tubes, and 425 g. jars.

Dimethyl Sulfoxide Veterinary Solution 90%; Domoso® (Fort Dodge) 90% (medical grade) in 4 oz spray bottle, 16 oz., and 1 gallon bottles

**Human Approved Products:**

Dimethylsulfoxide Solution 50 % aqueous solution in 50 mls and 70% solution in 250 mls; *Rimso-50*® (Research Industries) (Rx);*Rimso-50*® (Roberts);*Kemsol*® (Horner); (Rx)

Note: A topical otic product, *Synotic*® (Fort Dodge) which contains: DMSO 60% and fluocinolone acetonide 0.01% is also available for veterinary use. Supplied in 8 ml and 60 ml dropper bottles.

For more information, refer to the excellent article reviewing DMSO by Brayton. (Brayton, CF. Dimethyl Sulfoxide (DMSO): A Review, Cornell Vet., 1986, 76; 61-90)

## DINOPROST TROMETHAMINE

**Chemistry** - The tromethamine (THAM) salt of the naturally occurring prostaglandin $F_{2\ alpha}$, dinoprost tromethamine occurs as a white to off-white, very hygroscopic, crystalline powder with a melting point of about 100°C. One gram is soluble in about 5 ml of water. 1.3 micrograms of dinoprost tromethamine is equivalent to 1 micrograms of dinoprost. Dinoprost tromethamine may also be known as dinoprost trometamol, $PGF_{2\ alpha}$ THAM, or prostaglandin $F_{2\ alpha}$ tromethamine.

**Storage/Stability/Compatibility** - Dinoprost for injection should be stored at room temperature (15-30°C) in airtight containers. The human-approved product is recommended to be stored under refrigeration. Dinoprost is considered to be relatively insensitive to heat, light, and alkalis.

**Pharmacology** - Prostaglandin $F_{2alpha}$ has several pharmacologic effects on the female reproductive system, including stimulation of myometrial activity, relaxation of the cervix, inhibition of steroidogenesis by corpora lutea, and can potentially lyse corpora lutea.

**Uses/Indications -** *Lutalyse*® (Upjohn) is labeled for use in cattle as a luteolytic agent for estrous synchronization, unobserved (silent) estrous in lactating dairy cattle, pyometra, and as an abortifacient in feedlot and non-lactating dairy cattle. It is labeled in swine to act as a parturitient inducing agent. The product is labeled for use in mares as a luteolytic agent to control the time of estrus in cycling mares and to assist in inducing estrus in “difficult to breed mares.”

Unlabeled uses of dinoprost include its use in small animals as an abortifacient agent and as adjunctive medical therapy in pyometra. Although not approved, dinoprost is used also in sheep and goat reproductive medicine.

**Pharmacokinetics** - In studies done in rodents, dinoprost was demonstrated to distribute very rapidly to tissues after injection. In cattle, the serum half-life of dinoprost has been stated to be only “minutes” long.

**Contraindications/Precautions** - Unless being used as an abortifacient or parturition inducer, dinoprost should not be used during pregnancy in all species. Dinoprost is contraindicated in animals with

To Drug Monograph Index To Ophthalmic Product Index

bronchoconstrictive respiratory disease (*e.g.,* asthma, “heavey” horses). It should not be administered intravenously.

In swine, dinoprost should not be administered prior to 3 days of normal predicted farrowing as increased neonatal mortality may result.

According to the manufacturer, dinoprost is contraindicated in mares with acute or subacute disorders of the vascular system, GI tract, respiratory system or reproductive tract.
Dinoprost should be used with extreme caution, if at all, in dogs or cats greater than 8 years old, or with preexisting cardiopulmonary or other serious disease (liver, kidney, etc.). Some clinicians regard closed-cervix pyometra as a relative contraindication to the use of dinoprost.

**Adverse Effects/Warnings** - In cattle, increased temperature has been reported when administered in overdose (5-10X recommended doses) quantities. Limited salivation and bacterial infections at the injection site have been reported. If administered intravenously, increased heart rates have been noted.

In mares, transient decreased body (rectal) temperature and sweating have been reported most often. Less frequently, increased respiratory and heart rates, ataxia, abdominal pain and lying down have also been noted. These effects are generally seen within 15 minutes of administration and resolve within an hour.

In swine, dinoprost has caused erythema and pruritis, urination, defecation, slight ataxia, hyperpnea, dyspnea, nesting behavior, abdominal muscle spasms, tail movements, increased vocalization and salivation. These effects may last up to 3 hours. At doses of 10 times recommended, vomiting may be seen in swine.

In dogs and cats, dinoprost can cause abdominal pain, emesis, defecation, urination, pupillary dilation followed by constriction, tachycardias, restlessness and anxiety, fever, hypersalivation, dyspnea and panting. Cats may also exhibit increased vocalization and intense grooming behavior. Severity of effects is generally dose dependent. Defecation can be seen even with very low dosages. Reactions generally appear in 5-120 minutes after administration and may persist for 20-30 minutes. Fatalities have occurred (especially in dogs) after use. Dogs and cats should be monitored for cardiorespiratory effects, especially after receiving higher dosages.
When used as an abortifacient in humans, dinoprost causes nausea, vomiting or diarrhea in about 50% of patients.

**Overdosage** - Dogs are apparently more sensitive to the toxic effects of dinoprost than other species. The $LD_{50}$ in the bitch has been reported to be 5.13 mg/kg after SQ injection which may be only 5X greater than the recommended dose by some clinicians. In cattle, swine, and horses, dinoprost’s effects when administered in overdose quantities are outlined above in the Adverse effects section. If symptoms are severe in any species and require treatment; supportive therapy is recommended.

**Drug Interactions** - Other **oxytocic agents**’ activity may be enhanced by dinoprost. Reduced effect of dinoprost would be expected with concomitant administration of a **progestin**.

**Doses** -
**Horses**:

To induce cyclic activity in animals who are acyclic due to persistent corpus lutea:

a) 5 mg IM; most effective in mares with corpora lutea older than 5 days and who have progesterone levels >1 ng/ml (4 ng/ml even better). (Rossdale 1987)

For difficult to breed mares secondary to progesterone levels consistent with the presence of a functional corpus luteum:

a) 1 mg per 45 kg body weight IM (Package Insert; *Lutalyse*®—Upjohn)

To Drug Monograph Index To Ophthalmic Product Index

For controlling time of estrus of estrous cycling mares:

a) 1 mg per 45 kg body weight IM. When treated during diestrus, most mares return to estrus in 2-4 days and ovulate 8-12 days after treatment. (Package Insert; *Lutalyse*®—Upjohn)

As an abortifacient:

a) Prior to the 12th day of pregnancy: 5 mg IM

After the 4th month of pregnancy: 1 mg per 45 kg body weight (1 mg per 100 pounds) daily until abortion takes place. (Lofstedt 1986)

b) From day 80-300: 2.5 mg q12h; approximately 4 injections required on average to induce abortion (Roberts 1986a)

For estrus synchronization in normally cycling mares:

a) Three methods:

1) Two injection method— On day 1 give 5 mg dinoprost and again on day 16. Most (60%) mares will begin estrus 4 days after the second injection and about 90% will show estrous behavior by the 6th day after the second injection. Breed using AI every second day during estrus or inseminate at predetermined times without estrus detection. Alternatively, an IM injection of HCG (2500-3300 Units) can be added on the first or second day (usually day 21) of estrus to hasten ovulation. Breed using AI on days 20, 22, 24, and 26. This may be of more benefit when used early in the breeding season.

2) Progestagen/Prostaglandin method— Give altrenogest (0.44 mg/kg) for 8-12 days PO. On last day of altrenogest therapy (usually day 10) give dinoprost *(dose not noted, but suggest using same dose as "1" above)*. Majority of mares will show estrus 2-5 days after last treatment. Inseminante every 2 days after detection of estrus. Synchronization may be improved by giving 2500 IU of HCG IM on first or second day of estrus or 5-7 days after altrenogest is withdrawn.

3) On day 1, inject 150 mg progesterone and 10 mg estradiol-17beta daily for 10 days. On last day, also give dinoprost *(dose not noted, but suggest using same dose as "1" above)*. Perform AI on alternate days after estrus detection or on days 19, 21, and 23. (Bristol 1987)

**Monitoring Parameters** - Depending on use, see above. Monitoring for adverse effects is especially important in small animals.

**Client Information** - Dinoprost should be used by individuals familiar with its use and precautions. Pregnant women, asthmatics or other persons with bronchial diseases should handle this product with extreme caution. Any accidental exposure to skin should be washed off immediately.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Dinoprost Tromethamine for injection, equivalent to 5 mg/ml of dinoprost in 10 ml and 30 ml vials;

*Lutalyse*® (Upjohn); (Rx) Approved for use in beef and non-lactating dairy cattle, swine and mares. No preslaughter withdrawal or milk withdrawal is required when used as labeled; no specific tolerance for dinoprost residues have been published. It is not for use in horses intended for food

**Human-Approved Products**: None

## DIPHENHYDRAMINE HCL

**Chemistry** - An ethanolamine-derivative antihistamine, diphenhydramine HCl occurs as an odorless, white, crystalline powder which will slowly darken upon exposure to light. It has a melting range of 167 - 172° C.

To Drug Monograph Index To Ophthalmic Product Index

One gram is soluble in about 1 ml of water or 2 ml of alcohol. Diphenhydramine HCl has a $pK_a$ of about 9, and the commercially available injection has its pH adjusted to 5-6.

**Storage/Stability/Compatibility** - Preparations containing diphenhydramine should be stored at room temperature (15-30°C) and solutions should be protected from freezing. Tablets and oral solutions should be kept in well-closed containers. Capsules and the elixir should be stored in tight containers.

Diphenhydramine for injection is reportedly **compatible** with all commonly used IV solutions and the following drugs: amikacin sulfate, aminophylline, ascorbic acid injection, atropine sulfate, bleomycin sulfate, butorphanol tartrate, cephapirin sodium, chlorpromazine HCl, colistimethate sodium, diatrizoate meglumine/sodium, dimenhydrinate, droperidol, erythromycin lactobionate, fentanyl citrate, glycopyrrolate, hydromorphone HCl, hydroxyzine HCl, iothalamate meglumine/sodium, lidocaine HCl, meperidine HCl, methicillin sodium, metoclopramide, methyldopate HCl, morphine sulfate, nafcillin sodium, netilmicin sulfate, penicillin G potassium/sodium, pentazocine lactate, perphenazine, polymyxin B sulfate, prochlorperazine edisylate, promazine HCl, promethazine HCl, scopolamine HBr, tetracycline HCl and vitamin B complex w/C. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

Diphenhydramine is reportedly **incompatible** with the following drugs: amobarbital sodium, amphotericin B, cephalothin sodium, hydrocortisone sodium succinate, iodipamide meglumine, pentobarbital sodium, secobarbital sodium, and thiopental sodium.

**Pharmacology** - Like other antihistamines, diphenhydramine competitively inhibits histamine at $H_1$ receptors. In addition; it also has substantial sedative, anticholinergic, antitussive, and antiemetic effects.

**Uses/Indications** - In veterinary medicine, diphenhydramine is used principally for its antihistaminic effects, but also for its other pharmacologic actions as well. Its sedative effects can be of benefit in treating the agitation (pruritis, etc.) associated with allergic responses. It has also been used for treatment and prevention of motion sickness and as an antiemetic in small animals. It has also been suggested for use as adjunctive treatment of aseptic laminitis in cattle. For other suggested uses, refer to the Dosage section below.

**Pharmacokinetics** - The pharmacokinetics of this agent have apparently not been studied in domestic animals. In humans, diphenhydramine is well absorbed after oral administration, but because of a relatively high first-pass effect, only about 40-60% reaches the systemic circulation.

Following IV administration in rats, diphenhydramine reaches its highest levels in the spleen, lungs and brain. The drug is distributed into milk, but has not been measured quantitatively. In humans, diphenhydramine crosses the placenta and is approximately 80% bound to plasma proteins.

Diphenhydramine is metabolized in the liver and the majority of the drug is excreted as metabolites into the urine. The terminal elimination half-life in adult humans ranges from 2.4-9.3 hours.

**Contraindications/Precautions** - Diphenhydramine is contraindicated in patients who are hypersensitive to it or other antihistamines in its class. Because of their anticholinergic activity, antihistamines should be used with caution in patients with angle closure glaucoma, prostatic hypertrophy, pyloroduodenal or bladder neck obstruction, and COPD if mucosal secretions are a problem. Additionally, they should be used with caution in patients with hyperthyroidism, cardiovascular disease or hypertension.

**Adverse Effects/Warnings** - The most commonly seen adverse effects are CNS depression (lethargy, somnolence), and anticholinergic effects (dry mouth, urinary retention). The sedative effects of

antihistamines may diminish with time. GI effects (diarrhea, vomiting, anorexia), are a possibility. The sedative effects of antihistamines may adversely affect the performance of working dogs.

**Overdosage** - Overdosage can cause CNS stimulation (excitement to seizures) or depression (lethargy to coma), anticholinergic effects, respiratory depression and death. Treatment consists of emptying the gut if the ingestion was oral using standard protocols. Induce emesis if the patient is alert and CNS status is stable. Administration of a saline cathartic and/or activated charcoal may be given after emesis or gastric lavage. Treatment of other symptoms should be performed using symptomatic and supportive therapies. Phenytoin (IV) is recommended in the treatment of seizures caused by antihistamine overdose in humans; barbiturates and diazepam should be avoided.

**Drug Interactions** - Increased sedation can occur if diphenhydramine is combined with **other CNS depressant drugs**. Antihistamines may partially counteract the anticoagulation effects of **heparin** or **warfarin**. Diphenhydramine may enhance the effects of **epinephrine**.

**Laboratory Interactions** - Antihistamines can decrease the wheal and flare response to **antigen skin testing**. In humans, it is suggested that antihistamines be discontinued at least 4 days before testing.

**Doses** -
**Horses**:
For adjunctive therapy of anaphylaxis:
a) 0.25 - 1 mg/kg IV or IM (Evans 1996)

**Monitoring Parameters** -
1) Clinical efficacy and adverse effects

**Client Information/FDA Approval Status** - Diphenhydramine is approved for use in humans. The oral dosage forms are either prescription or non-prescription agents, depending on the product's labeling. The injectable products are prescription only.

**Dosage Forms/Preparations** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:
Diphenhydramine HCl Capsules 25 mg, 50 mg; 12.5 mg chewable) & 50 mg Tablets
Diphenhydramine HCl Oral Elixir or Syrup 12.5 mg/5 ml (2.5 mg/ml) in 4 oz, pint and gallon bottles
Diphenhydramine Injection 10 mg/ml in 10 ml or 30 ml vials; 50 mg/ml in 1 ml amps and 10 ml vials

Diphenhydramine is available under several trade names; a commonly known product is *Benadryl*® (Parke-Davis).

## DIPRENORPHINE HYDROCHLORIDE

**Elephants:** The references listed below include information about diprenorphine. Refer to the etorphine and carfentanil monographs for abstracts and dose information.

**Elephant References:**
a) du Toit,J.G., 2001. **Veterinary Care of African Elephants**. Novartis, Pretoria, Republic of South Africa, 1-59 pp. www.wildlifedecisionsupport.com

To Drug Monograph Index To Ophthalmic Product Index

b) Raath,J.P., 1999. **Relocation of African elephants**. In: Fowler,M.E. and Miller,R.E. (Editors), Zoo and Wild Animal Medicine: Current Therapy 4. W.B. Saunders, Philadelphia, PA, USA pp. 525-533

c) Stegmann,G.F. 1999. **Etorphine-halothane anaesthesia in two five-year-old African elephants (Loxodonta africana)**. Journal of the South African Veterinary Medical Association

d) Elkan,P.W., Planton,H.P., Powell,J.A., Haigh,J.A., and Karesh,W.B. 1998. **Chemical immobilization of African elephant in lowland forest, southwestern Cameroon**. Pachyderm 25:(Jan-July):32-37

e) Osofsky,S.A. 1997. **A practical anesthesia monitoring protocol for free-ranging adult African elephants (Loxodonta africana)**. Journal of Wildlife Diseases 33:(1):72-77

f) Singh,L.A.K., Nayak,B.N., and Acharjya,S.K. 1996. **Chemical capture of a problem-elephant in Bolangir, Orissa**. Indian Forester. Special issue: wildlife management. 122:(10):955-960

g) Still,J., Raath,J.P., and Matzner,L. 1996. **Respiratory and circulatory parameters of African elephants (Loxodonta africana) anesthetized with etorphine and azaperone**. Journal of the South African Veterinary Medical Association 67:(3):123-127

h) Fowler,M.E., 1995. **Elephants**. In: Restraint and handling of wild and domestic animals. Iowa State University Press, Ames, Iowa, USA pp. 265-269

i) Osofsky,S.A. 1995. **Pulse oximetry monitoring of free-ranging African elephants (*Loxodonta africana*) immobilized with an etorphine/hyaluronidase combination antagonized with diprenorphine.** Joint Conference AAZV/WDA/AAWV. Pages: 237-277

j) Schumacher,J., Heard,D.J., Caligiuri,R., Norton,T., and Jacobson,E.R. 1995. **Comparative effects of etorphine and carfentanil on cardiopulmonary parameters in juvenile African elephants (*Loxodonta africana*).** Journal of Zoo and Wildlife Medicine 26:(4):503-507

k) Hattingh,J., Knox,C.M., and Raath,J.P. 1994. **Arterial blood pressure of the African elephant (Loxodonta africana) under etorphine anaesthesia and after remobilisation with diprenorphine**. Veterinary Record 135:(19):458-459

l) Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants**. In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441

m) Raath,J.P., 1993. **Chemical capture of the African elephant**. In: The Capture and care manual : capture, care, accommodation and transportation of wild African animals. Pretoria : Wildlife Decision Support Services : South African Veterinary Foundation, Pretoria pp. 484-511

n) Lance,W.R. 1991. **New pharmaceutical tools for the 1990's**. Proceedings of the American Association of Zoo Veterinarians 354-359

o) Jacobson,E.R., Kollias,G.V., Heard,D.J., and Caligiuri,R. 1988. **Immobilization of African elephants with carfentanil and antagonism with nalmefene and diprenorphine**. Journal of Zoo Animal Medicine 19:1-7

p) Lateur,N. and Stolk,P. 1986. **Repeated general anesthesia in a male Indian elephant**. Proc.Am.Assoc.Zoo Vet. Pages: 128-131

To Drug Monograph Index  To Ophthalmic Product Index

q) Kock,N., Kock,M., Arif,A., and Wahid,M.N.S.A. 1984. **Immobilization techniques and complications associated with a bull Indian elephant (*Elephas maximus indicus*) during musth**. Proc.Am.Assoc.Zoo Vet. Pages: 68-74

r) Ebedes,H. 1975. **The immobilization of adult male and female elephant, *Loxodonta africana*, with etorphine and observation on the action of diprenorphine**. Madogua 9:19-24

s) Alford,B.T., Burkhart,R.L., and Johnson,W.P. 1974. **Etorphine and diprenorphine as immobilizing and reversing agents in captive and free-ranging mammals**. Journal of the American Veterinary Medical Association 164:(7):702-705

## DOBUTAMINE HCL

**Chemistry** - Dobutamine HCl is a synthetic inotropic agent related structurally to dopamine. It occurs as a white, to off-white, crystalline powder with a $pK_a$ of 9.4. Dobutamine is sparingly soluble in water and alcohol.

**Storage/Stability/Compatibility** - Dobutamine injection should be stored at room temperature (15-30°C). It must be further diluted before administration (see Preparation of Solution below); diluted solutions should be used within 24 hours.

Dobutamine is compatible with the usually used IV solutions ($D_5W$, sodium chloride 0.45% & 0.9%, dextrose-saline combinations, lactated Ringer's) and is reported to be **compatible** with the following drugs: amiodarone HCl, atropine sulfate, dopamine HCl, epinephrine HCl, hydralazine HCl, isoproterenol HCl, lidocaine HCl, meperidine HCl, metaraminol bitartrate, morphine sulfate, nitroglycerin, norepinephrine (levarterenol) bitartrate, phentolamine mesylate, phenylephrine HCl, procainamide HCl, propranolol HCl, and verapamil HCl.

Dobutamine may be **incompatible** with the following agents: aminophylline, bretylium tosylate, bumetamide, calcium chloride or gluconate, diazepam, digoxin, furosemide, heparin (inconsistent results), regular insulin, magnesium sulfate, phenytoin sodium, potassium chloride (at high concentrations only - 160 mEq/l), potassium phosphate, and sodium bicarbonate.

**Pharmacology** - Dobutamine is considered a direct $beta_1$-adrenergic agonist. It also has mild $beta_2$- and $alpha_1$-adrenergic effects at therapeutic doses. These effects tend to balance one another and cause little direct effect on the systemic vasculature. In contrast to dopamine, dobutamine does not cause the release of norepinephrine. It has relatively mild chronotropic, arrhythmogenic, and vasodilative effects.

Increased myocardial contractility and stroke volumes result in increased cardiac output. Decreases in left ventricular filling pressures (wedge pressures) and total peripheral resistance occur in patients with a failing heart. Blood pressure and cardiac rate generally are unaltered or slightly increased because of increased cardiac output. Increased myocardial contractility may increase myocardial oxygen demand and coronary blood flow.

**Uses/Indications** - Dobutamine is used as a rapid-acting injectable positive inotropic agent for short term treatment of heart failure.

**Pharmacokinetics** - Because it is rapidly metabolized in the GI tract and is not available after oral administration, dobutamine is only administered intravenously (as a constant infusion). After intravenous administration, the onset of action generally occurs within 2 minutes and peaks after 10 minutes.

To Drug Monograph Index  To Ophthalmic Product Index

Dobutamine is metabolized rapidly in the liver and other tissues and has a plasma half-life of approximately 2 minutes in humans. The drug's effects diminish rapidly after cessation of therapy.

Pharmacokinetic data for domestic animals is apparently unavailable. It is unknown if dobutamine crosses the placenta or into milk.

**Contraindications/Precautions** - Dobutamine is contraindicated in patients with known hypersensitivity to the drug or with idiopathic hypertropic subaortic stenosis (IHSS). The injectable formulation contains sodium bisulfite as a preservative which has been documented to cause allergic-type reactions in some human patients. Hypovolemic states must be corrected before administering dobutamine. Because it may increase myocardial oxygen demand and increase infarct size, dobutamine should be used very cautiously after myocardial infarction. Dobutamine can enhance atrioventricular conduction, animals with atrial fibrillation should be digitalized prior to receiving dobutamine.

**Adverse Effects/Warnings** - The most commonly reported adverse effects in humans are: ectopic beats, increased heart rate, increased blood pressure, chest pain, and palpitations. Similar adverse effects could be expected for veterinary patients. At usual doses these effects are generally mild and will not necessitate halting therapy, but dosage reductions should be performed. Other, more rare adverse effects reported include: nausea, headache, vomiting, leg cramps, paresthesias, and dyspnea.

**Overdosage** - Symptoms reported with excessive dosage include tachycardias, increased blood pressure, nervousness, and fatigue. Because of the drug's short duration of action, temporarily halting therapy is usually all that is required to reverse these effects.

**Drug Interactions** - beta**-Blockers (***e.g.,* **propranolol)** may antagonize the cardiac effects of dobutamine, and result in a preponderance of alpha adrenergic effects and increased total peripheral resistance. Use of **halothane or cyclopropane** with dobutamine may result in increased incidences of ventricular arrhythmias. Synergistic effects (increased cardiac output and reduced wedge pressure) may result if dobutamine is used with **nitroprusside**.
**Insulin** requirements may increase in diabetic patients receiving dobutamine.
**Oxytocic drugs** may induce severe hypertension when used with dobutamine in obstetric patients.

**Doses** - Dobutamine is administered as a constant rate intravenous infusion only.
**Horses**:

a) 1 - 5 micrograms/kg/minute (Muir and McGuirk 1987b)
b) 2 - 10 micrograms/kg/minute IV infusion (Robinson 1987)

**Elephants:**
**a)** In an African elephant under general anesthesia, low mean blood pressure (54 mm of Hg) responded to reduction in halothane (vaporizer setting 1 to 0.75%) and slow infusion of dobutamine HCl ((250 mg/1,000 ml) given to effect. The systolic blood pressure increased to 90 mm of Hg and remained high with a continuous infusion of dobutamine (5 µg/kg/min). Heard,D.J., Kollias,G.V., Webb,A.I., Jacobson,E.R., and Brock,K.A. 1988. **Use of halothane to maintain anesthesia induced with etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 193:254-256 **Excerpts:** Sixteen 3- to 5-year-old African elephants were anesthetized one or more times for a total of 27 diagnostic and surgical procedures. Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing juvenile elephants during a 45-minute transport period before administration of general anesthesia. After IM or IV administration of etorphine (1.9 ± 0.56 micrograms/kg), the mean time to lateral recumbency was 20 ± 6.6 and 3 ± 0.0 minutes, respectively. The mean heart rate, systolic blood pressure, and respiration rate during all procedures was 50 ± 12 beats/min, 106 ± 19 mm of Hg, and 10 ± 3 breaths/min, respectively.

To Drug Monograph Index To Ophthalmic Product Index

Cardiac arrhythmias were detected during 2 procedures. In one elephant paroxysmal ventricular tachycardia was detected and the procedure terminated when the arrhythmia failed to stabilize after multiple doses of lidocaine (1 mg/kg, IV). In another elephant, second degree atrioventricular block returned to normal sinus rhythm after IV administration of atropine (0.04 mg/kg).

In one elephant, low mean blood pressure (54 mm of Hg) responded to reduction in halothane (vaporizer setting 1 to 0.75%) and slow infusion of dobutamine HCl ((250 mg/1,000 ml) given to effect. The systolic blood pressure increased to 90 mm of Hg and remained high with a continuous infusion of dobutamine (5 µg/kg/min).

Immediately after induction in another elephant, profound respiratory depression (< 1breath/minute) and palpably weak arterial pulse were identified. Intravenous administration of diprenorphine at half the recommended reversal dose resulted in improvement of respiration and palpable arterial pulse, without the elephant developing signs of complete anesthetic reversal.

Alterations in systolic blood pressure, ear flapping, and trunk muscle tone were useful for monitoring depth of anesthesia. Results indicated that halothane in oxygen was effective for maintenance of surgical anesthesia in juvenile African elephants after induction with etorphine. Note: A correction appeared in a later volume 193(6): p.721.

**Monitoring Parameters** -

1) Heart rate and rhythm, blood pressure if possible
2) Urine flow
3) Ideally, measurement of central venous or pulmonary wedge pressures and cardiac output

**Client Information** - This drug should only be used by professionals familiar with its use and in a setting where adequate patient monitoring can be performed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Dobutamine HCl Injection 12.5 mg/ml in 20 ml vial; *Dobutrex*® (Lilly); Generic (Rx)

**Preparation of Solution** - The solution for injection must be further diluted to a concentration no greater than 5 mg/ml (total of at least 50 ml of diluent) before administering.
Generally, it is added to $D_5W$, normal saline (if not severely sodium restricted) or other compatible IV solution. The following approximate concentrations will result if 1 vial (250 mg) is added either 250, 500, or 1000 ml IV solutions:
1 vial (250 mg) in: 250 ml ≈ 1000micrograms/ml
"
500 ml ≈ 500micrograms/ml
"
1000 ml ≈ 250micrograms/ml
A mechanical fluid administration control device should be used, if available, to administer dobutamine. When using a mini-drip IV administration set (60 drops ≈ 1 ml), 1 drop contains approximately 8.3 micrograms at the 500 micrograms/ml concentration.

**DOCUSATE**
**DOCUSATE CALCIUM**
**DOCUSATE POTASSIUM**

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - Docusate is available in sodium, potassium, and calcium salts. They are anionic, surface-active agents and possess wetting and emulsifying properties.

Docusate sodium (also known as dioctyl sodium succinate, DSS, or DOSS) occurs as a white, wax-like plastic solid with a characteristic odor. One gram is soluble in approximately 70 ml of water and it is freely soluble in alcohol and glycerin. Solutions are clear and have a bitter taste.
Docusate calcium (also known as dioctyl calcium succinate) occurs as a white, amorphous solid with a characteristic odor (octyl alcohol). It is very slightly soluble in water, but freely soluble in alcohol.

Docusate potassium (also known as dioctyl potassium succinate) occurs as a white, amorphous solid with a characteristic odor (octyl alcohol). It is sparingly soluble in water and soluble in alcohol.

**Storage/Stability/Compatibility** - Capsules of salts of docusate should be stored in tight containers at room temperature. Temperatures above 86°F can soften or melt soft gelatin capsules. Docusate sodium solutions should be stored in tight containers and the syrup should be stored in tight, light-resistant containers.

**Pharmacology** - Docusate salts reduce surface tension and allow water and fat to penetrate the ingesta and formed feces, thereby softening the stool. Recent *in vivo* studies have also demonstrated that docusate also increases cAMP concentrations in colonic mucosal cells which may increase both ion secretion and fluid permeability from these cells into the colon lumen.

**Uses/Indications -** Docusate is used in small animals when feces are hard or dry, or in anorectal conditions when passing firm feces would be painful or detrimental. Docusate is used alone and in combination with mineral oil in treating fecal impactions in horses.

**Pharmacokinetics** - It is unknown how much docusate is absorbed after oral administration, but it is believed that some is absorbed from the small intestine and is then excreted into the bile.

**Contraindications/Precautions** - Use with caution in patients with pre-existing fluid or electrolyte abnormalities; monitor.

**Adverse Effects/Warnings** - At usual doses, clinically significant adverse effects should be very rare. Cramping, diarrhea and intestinal mucosal damage are possible. The liquid preparations may cause throat irritation if administered by mouth.

**Overdosage** - In horses, single doses of 0.65 - 1 gm/kg have caused dehydration, intestinal mucosal damage, and death. Because of the secretory effects that high dose docusate can produce, hydration and electrolyte status should be monitored and treated if necessary.

**Drug Interactions** - Theoretically, **mineral oil** should not be given with docusate (DSS) as enhanced absorption of the mineral oil could occur. However, this interaction does not appear to be of significant clinical concern with large animals. It is less clear whether there is a significant problem in using this combination in small animals and the concurrent use of these agents together in dogs or cats cannot be recommended. If it is deemed necessary to use both docusate and mineral oil in small animals, separate doses by at least two hours.

**Doses** -
**Horses**:

a) 10 - 20 mg/kg diluted in 2 L of warm water PO; may repeat in 48 hours. (Clark and Becht 1987)
b) 7.5 - 30 grams (150 - 600 mls of a 5% solution) PO; or 3 - 5 grams (60 - 100 mls of 5% solution) if used with mineral oil. (Sellers and Lowe 1987)

To Drug Monograph Index To Ophthalmic Product Index

**Monitoring Parameters** -1 ) Clinical efficacy; hydration and electrolyte status if indicated

**Client Information** - Unless otherwise directed, give this medication on an empty stomach. Do not give with other laxative agents without the approval of the veterinarian.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** - There are several docusate products marketed for veterinary use; their approval status is unknown. Docusate products are available without prescription (OTC).

Docusate Sodium 100 mg Tablets & Docusate Sodium Capsules 50 mg, 100 mg, 240 mg, 250 mg, 300 mg; Softgel 100 mg

Docusate Sodium Syrup 20 mg/4 ml in 473 ml; 50 mg/15 ml in UD 15 & 30 ml, 60 mg/15 ml in 240 ml, pt and gal.; 150 mg/15 ml in pt and gal.

Docusate Sodium Liquid/Solution 50 mg/ml and 100 mg/ml in 60 ml and gal.; Veterinary products for use in large animals are generally available in gallons in concentrations of either 5% (50 mg/ml) or 10% (100 mg/ml). There are many trade names for docusate sodium, perhaps the best known is *Colace*® (Bristol-Meyers Squibb). It is also available generically.

Docusate Calcium 50 mg and 240 mg capsules (human-labeled); There are many trade names for docusate calcium, perhaps the best known is *Surfak*® (Hoechst). It is also available generically.

Docusate Potassium Tablets 100 mg & Docusate Potassium Capsules 240 mg; *Kasof*® (Stuart), *Dialose*® (Stuart), Generic

## DORAMECTIN

**Chemistry/Storage/Stability/Compatibility** - An avermectin antiparasitic compound, doramectin is isolated from fermentations from the soil organism *Streptomyces avermitilis*. The commercially available injectable solution is a colorless to pale yellow, sterile solution. The injectable solution should be stored below 86°F (30°C).

**Pharmacology** - The primary mode of action of avermectins like doramectin is to affect chloride ion channel activity in the nervous system of nematodes and arthropods. Doramectin binds to receptors that increase membrane permeability to chloride ions. This inhibits the electrical activity of nerve cells in nematodes and muscle cells in arthropods and causes paralysis and death of the parasites. Avermectins also enhance the release of gamma amino butyric acid (GABA) at presynaptic neurons. GABA acts as an inhibitory neurotransmitter and blocks the post-synaptic stimulation of the adjacent neuron in nematodes or the muscle fiber in arthropods. Avermectins are generally not toxic to mammals as they do not have glutamate-gated chloride channels and these compounds do not readily cross the blood-brain barrier where mammalian GABA receptors occur.

**Uses/Indications** - Doramectin injection is indicated for the treatment and control of the following endo- and ectoparasites in cattle: roundworms (adults and some fourth stage larvae)—*Ostertagia ostertagi* (including inhibited larvae), *O. lyrata*, *Haemonchus placei*, *Trichostrongylus axei*, *T. colubriformis*, *T. longispicularis*, *Cooperia oncophora*, *C. pectinata, C. punctata*, *C. surnabada (syn. mcmasteri)*, *Bunostomum phlebotomum*, *Strongyloides papillosus*, *Oesophagostomum radiatum*, *Trichuris spp.*,; lungworms (adults and fourth stage larvae)—*Dictyocaulus viviparus*; eyeworms (adults)—*Thelazia spp*.; grubs (parasitic stages)—*Hypoderma bovis, H. lineatum* ; lice—*Haematopinus eurysternus, Linognathus vituli, Solenopotes capillatus*; and mange mites—*Psoroptes bovis, Sarcoptes scabiei*.

To Drug Monograph Index To Ophthalmic Product Index

The manufacturer states the doramectin protects cattle against infection or reinfection with *Ostertagia ostertagi* for up to 21 days.

**Pharmacokinetics** - After subcutaneous injection, the time to peak plasma concentration in cattle is about 5 days. Bioavailability is for practical purposes, equal with subQ and IM injections.

**Contraindications/Precautions/Reproductive Safety -** The manufacturer warns to not use in other animal species as severe adverse reactions, including fatalities in dogs, may result.
Studies performed in breeding animals (bulls, and cows in early and late pregnancy), at a dose of 3X recommended had no effect on breeding performance.

**Adverse Effects/Warnings** - No listed adverse effects. Intramuscular injections may have a higher incidence of injection site blemishes at slaughter than do subcutaneous injections.

**Overdosage** - In field trials, no toxic signs were seen in cattle given up to 25X the recommended dose. In breeding animals (bulls, and cows in early and late pregnancy), a dose 3 times the recommended dose had no effect on breeding performance.

**Drug Interactions** - None noted.

**Doses** -
**Cattle**:

For labeled indications: 200 mcg/kg (1 ml per 110 lb. body weight)) SubQ or IM. Injections should be made using 16 to 18 gauge needles. Subcutaneous injections should be administered under the loose skin in front of or behind the shoulder. Intramuscular injections should be administered into the muscular region of the neck. Beef Quality Assurance guidelines recommend subcutaneous administration as the preferred route. (Label Directions; *Dectomax*®—Pfizer)

**Monitoring Parameters** - Efficacy

**Client Information/Withdrawal Times -** Cattle must not be slaughtered for human consumption within 35 days of treatment. Not for use in female dairy cattle 20 months of age or older. A withdrawal period has not been established for this product in pre-ruminating calves. Should not be used in calves to be processed for veal.

**Dosage Forms/Preparations/FDA Approval Status -**

**Human-Approved Products:** None

**Veterinary-Approved Products:**

Doramectin 10 mg/ml Injectable Solution in 100 ml, 250 ml, and 500 ml multi-dose vials; *Dectomax*® (Pfizer); (OTC). Approved for use in cattle (see limitations in Client Information above).

## DOXAPRAM HCL

**Chemistry** - Doxapram HCl is a white to off-white, odorless, crystalline powder that is stable in light and air. It is soluble in water, sparingly soluble in alcohol and practically insoluble in ether. Injectable products have a pH from 3.5-5. Benzyl alcohol or chlorobutanol is added as a preservative agent in the commercially available injections.

To Drug Monograph Index  To Ophthalmic Product Index

**Storage/Stability/Compatibility** - Store at room temperature and avoid freezing solution. Do not mix with alkaline solutions (*e.g.,* thiopental, aminophylline, sodium bicarbonate). Doxapram is **compatible** with $D_5W$ or normal saline.

**Pharmacology** - Doxapram is a general CNS stimulant, with all levels of the CNS affected. The effects of respiratory stimulation are a result of direct stimulation of the medullary respiratory centers and possibly through the reflex activation of carotid and aortic chemoreceptors. Transient increases in respiratory rate and volume occur, but increases in arterial oxygenation usually do not ensue. This is because doxapram usually increases the work associated with respirations with resultant increased oxygen consumption and carbon dioxide production.

**Pharmacokinetics** - Little pharmacokinetic data appears to be published for domestic animals. Onset of effect in humans and animals after IV injection usually occurs within 2 minutes. The drug is well distributed into tissues. In dogs, doxopram is rapidly metabolized and most is excreted as metabolites in the urine within 24-48 hours after administration. Small quantities of metabolites may be excreted up to 120 hours after dosing.

**Uses/Indications** - The manufacturer of *Dopram®-V* lists the following indications:
For Dogs, Cats, and Horses: To stimulate respiration during and after general anesthesia and/or to speed awakening and reflexes after anesthesia. For Neonatal Dogs and Cats: Initiate or stimulate respirations following dystocia or cesarean section.

Doxopram also has been used for treatment of CNS depression in food animals (not approved) and has been suggested as a treatment of respiratory depression in small animals caused by reactions to radiopaque contrast media or for barbiturate overdosage (see precautions below).

**Contraindications/Precautions** - Doxapram should not be used as a substitute for aggressive artificial (mechanical) respiratory support in instances of severe respiratory depression.

Contraindications from the human literature include: seizure disorders, head trauma, uncompensated heart failure, severe hypertension, cardiovascular accidents, respiratory failure secondary to neuromuscular disorders, airway obstruction, pulmonary embolism, pneumothorax, acute asthma, dyspnea, or whenever hypoxia is not associated with hypercapnea. Doxapram should be used with caution in patients with history of asthma, arrhythmias, or tachycardias. It should be used with extreme caution in patients with cerebral edema or increased CSF pressure, pheochromocytoma or hyperthyroidism. Patients who have a history of hypersensitivity to the drug or are receiving mechanical ventilation should not receive doxapram. The above contraindications/precautions are not listed in the veterinary product literature provided by the manufacturer.

Avoid the use of a single injection site for a prolonged period of time or extravasation when administering intravenously. However, subcutaneous injection has been recommended for use in neonatal feline and canine patients.

**Adverse Effects/Warnings** - Hypertension, arrhythmias, seizures, and hyperventilation leading to respiratory alkalosis has been reported. These effects are most probable with repeated or high doses. The drug reportedly has a narrow margin of safety when used in humans. Safety of doxopram has not been established in pregnant animals. The potential risks versus benefits should be weighed before using.

**Overdosage** - Symptoms of overdosage include: hypertension, skeletal muscle hyperactivity, tachycardia, and generalized CNS excitation including seizures. Treatment is supportive. Drugs such as short acting IV barbiturates may be used to help decrease CNS hyperactivity. Oxygen therapy may be necessary.

To Drug Monograph Index  To Ophthalmic Product Index

**Drug Interactions** - Additive pressor effects may occur with **sympathomimetic** agents
Doxapram may mask the effects of **muscle relaxant** drugs. Doxapram may increase epinephrine release; therefore use should be delayed for approximately 10 minutes after discontinuation of anesthetic agents (*e.g.,* **halothane, enflurane**) that have been demonstrated to sensitize the myocardium to catecholamines.

**Doses** -
**Horses**:

a) 0.5 - 1 mg/kg IV at 5 minute intervals (do not exceed 2 mg/kg in foals); For foal resuscitation: 0.02 - 0.05 mg/kg/min IV (Robinson 1987)

**Elephants:**

a) To stimulate respirations in a new born calf, calculate dose at 0.5 mg/kg. Give under the tongue or IV. Can repeat the dose or double the dose one time if necessary.
200 lb (90 kg) calf = 45 mg (2.25 ml)
250 lb (113 kg) calf = 56 mg (2.8 ml)
300 lb (136 kg) calf = 68 mg (3.4 ml) Schmitt,D.L. 2001. **Riddle's Elephant and Wildlife Sanctuary Elephant Birth Protocol**.

b) 100 mg/ton IM or IV; authors' personal experience. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants** . In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

c) One African elephant immobilized with carfentanil and maintained on halothane experienced respiratory depression and was given two IV doses of doxapram at a dosage of 0.22 mg/kg. Jacobson,E.R., Kollias,G.V., Heard,D.J., and Caligiuri,R. 1988. **Immobilization of African elephants with carfentanil and antagonism with nalmefene and diprenorphine**. Journal of Zoo Animal Medicine 19:1-7

**Monitoring Parameters** -

1) Respiratory rate
2) Cardiac rate and rhythm
3) Blood gases if available and indicated
4) CNS level of excitation
5) Blood pressure if possible and indicated

**Client Information**- This agent should be used in an inpatient setting or with direct professional supervision.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Doxapram HCl for Injection: 20 mg/ml; 20 ml multi-dose vial; *Dopram-V*® (Fort Dodge); (Rx) Approved for use in dogs, cats & horses

**Human-Approved Products**:-

Doxapram HCl for Injection: 20 mg/ml in 20 ml vial; *Dopram*® (Robins); (Rx) ; generic, (Rx)

To Drug Monograph Index To Ophthalmic Product Index

**DOXYCYCLINE**
**DOXYCYCLINE HYCLATE**
**DOXYCYCLINE MONOHYDRATE**

**Chemistry** - A semi-synthetic tetracycline that is derived from oxytetracycline, doxycycline is available as hyclate, calcium and monohydrate salts. The hyclate salt is used in the injectable dosage form and in oral tablets and capsules. It occurs as a yellow, crystalline powder that is soluble in water and slightly soluble in alcohol. After reconstitution with sterile water, the hyclate injection has a pH of 1.8-3.3. Doxycycline hyclate may also be known as doxycycline hydrochloride.

The monohydrate salt is found in the oral powder for reconstitution. It occurs as a yellow, crystalline powder that is very slightly soluble in water and sparingly soluble in alcohol. The calcium salt is formed *in situ* during manufacturing. It is found in the commercially available oral syrup.

**Storage/Stability/Compatibility** - Doxycycline hyclate tablets and capsules should be stored in tight, light resistant containers at temperatures less than 30°C, and preferably at room temperature (15-30°C). After reconstituting with water, the monohydrate oral suspension is stable for 14 days when stored at room temperature.

The hyclate injection when reconstituted with a suitable diluent (*e.g.,* $D_5W$, Ringer's injection, Sodium Chloride 0.9%, or Plasma-Lyte 56 in $D_5W$) to a concentration of 0.1 to 1 mg/ml may be stored for 72 hours if refrigerated. Frozen reconstituted solutions (10 mg/ml in sterile water) are stable for at least 8 weeks if kept at -20°C, but should not be refrozen once thawed. If solutions are stored at room temperature, different manufacturers give different recommendations regarding stability, ranging from 12-48 hours. Infusions should generally be completed within 12 hours of administration.

Doxycycline hyclate for injection is reportedly **compatible** with the following IV infusion solutions and drugs: $D_5W$, Ringer's injection, sodium chloride 0.9%, or Plasma-Lyte 56 in $D_5W$, Plasma-Lyte 148 in $D_5W$, Normosol M in $D_5W$, Normosol R in $D_5W$, invert sugar 10%, acyclovir sodium, hydromorphone HCl, magnesium sulfate, meperidine HCl, morphine sulfate, perphenazine and ranitidine HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Tetracyclines generally act as bacteriostatic antibiotics and inhibit protein synthesis by reversibly binding to 30S ribosomal subunits of susceptible organisms, thereby preventing binding to those ribosomes of aminoacyl transfer-RNA. Tetracyclines also are believed to reversibly bind to 50S ribosomes and additionally alter cytoplasmic membrane permeability in susceptible organisms. In high concentrations, tetracyclines can also inhibit protein synthesis by mammalian cells.

As a class, the tetracyclines have activity against most *mycoplasma*, spirochetes (including the Lyme disease organism), *Chlamydia* and *Rickettsia*. Against gram positive bacteria, the tetracyclines have activity against some strains of *staphylococcus* and *streptococci*, but resistance of these organisms is increasing. Gram positive bacteria that are usually covered by tetracyclines, include *Actinomyces sp., Bacillus anthracis*, *Clostridium perfringens* and *tetani*, *Listeria monocytogenes* and *Nocardia*. Among gram negative bacteria that tetracyclines usually have *in vitro* and *in vivo* activity against, include *Bordetella sp., Brucella, Bartonella, Haemophilus sp., Pasturella multocida, Shigella,* and *Yersinia pestis*. Many or most strains of *E. coli, Klebsiella, Bacteroides, Enterobacter, Proteus* and *Pseudomonas aeruginosa* are resistant to the tetracyclines.

To Drug Monograph Index To Ophthalmic Product Index

Doxycycline generally has very similar activity as other tetracyclines against susceptible organisms, but some strains of bacteria may be more susceptible to doxycycline or minocycline and additional *in vitro* testing may be required.

**Uses/Indications** - Although there are no veterinary-approved doxycycline products available, its favorable pharmacokinetic parameters (longer half-life, higher CNS penetration) when compared to either tetracycline HCl or oxytetracycline HCl make it a reasonable choice to use in small animals when a tetracycline is indicated, particularly when a tetracycline is indicated in an azotemic patient. Because there is apparently less clinical experience with this agent in small animals than with either tetracycline or oxytetracycline, some caution should be employed before routinely using.

In avian species, some clinicians feel that doxycycline is the drug of choice in the oral treatment of psittacosis, particularly when treating only a few birds.

**Pharmacokinetics** - Doxycycline is well absorbed after oral administration. Bioavailability is 90-100% in humans. No bioavailability data was located for veterinary species, but it is thought that the drug is also readily absorbed in monogastric animals. Unlike tetracycline HCl or oxytetracycline, doxycycline absorption may only be reduced by 20% by either food or dairy products in the gut. This is not considered to be clinically important.

Tetracyclines as a class, are widely distributed to the heart, kidney, lungs, muscle, pleural fluid, bronchial secretions, sputum, bile, saliva, synovial fluid, ascitic fluid, and aqueous and vitreous humor. Doxycycline is more lipid soluble and penetrates body tissues and fluids better than tetracycline HCl or oxytetracycline, including to the CSF, prostate and eye. While CSF levels are generally insufficient to treat most bacterial infections, doxycycline has been shown to be efficacious in the treatment of the CNS effects associated with Lyme disease in humans. The volume of distribution at steady-state in dogs is approximately 1.5 L/kg. Doxycycline is bound to plasma proteins in varying amounts dependent upon species. The drug is approximately 25-93% bound to plasma proteins in humans, 75-86% in dogs, and about 93% in cattle and pigs.

Doxycycline's elimination from the body is relatively unique. The drug is primarily excreted into the feces via non-biliary routes in an inactive form. It is thought that the drug is partially inactivated in the intestine by chelate formation and then excreted into the intestinal lumen. In dogs, about 75% of a given dose is handled in this manner. Renal excretion of doxycycline can only account for about 25% of a dose in dogs, and biliary excretion less than 5%. The serum half-life of doxycycline in dogs is approximately 10-12 hours and a clearance of about 1.7 ml/kg/min. In calves, the drug has similar pharmacokinetic values. Doxycycline does not accumulate in patients with renal dysfunction.

**Contraindications/Precautions/Reproductive Safety** - Doxycycline is contraindicated in patients hypersensitive to it. Because tetracyclines can retard fetal skeletal development and discolor deciduous teeth, they should only be used in the last half of pregnancy when the benefits outweigh the fetal risks. Doxycycline is considered to be less likely to cause these abnormalities than other more water soluble tetracyclines (*e.g.,* tetracycline, oxytetracycline). Unlike either oxytetracycline or tetracycline, doxycycline can be used in patients with renal insufficiency.

Until further studies documenting the safety of intravenous doxycycline in horses are done, the parenteral route of administering this drug in horses should be considered contraindicated.

**Adverse Effects/Warnings** - The most commonly reported sided effects of oral doxycycline therapy in dogs and cats are nausea and vomiting. To alleviate these effects, the drug could be given with food without clinically significant reductions in drug absorption.

To Drug Monograph Index  To Ophthalmic Product Index

Tetracycline therapy (especially long-term) may result in overgrowth (superinfections) of non-susceptible bacteria or fungi.

In humans, doxycycline (or other tetracyclines) has also been associated with photosensitivity reactions and, rarely, hepatotoxicity or blood dyscrasias.

Intravenous injection of even relatively low doses of doxycycline has been associated with cardiac arrhythmias, collapse and death in horses.

**Overdosage/Acute Toxicity** - With the exception of intravenous dosing in horses (see above), doxycycline is apparently quite safe in most mild overdose situations. Oral overdoses would most likely be associated with GI disturbances (vomiting, anorexia, and/or diarrhea). Although doxycycline is less vulnerable to chelation with cations than other tetracyclines, oral administration of divalent or trivalent cation antacids may bind some of the drug and reduce GI distress. Should the patient develop severe emesis or diarrhea, fluids and electrolytes should be monitored and replaced if necessary.

Rapid intravenous injection of doxycycline has induced transient collapse and cardiac arrhythmias in several species, presumably due to chelation with intravascular calcium ions. If overdose quantities are inadvertently administered, these effects may be more pronounced.

**Drug Interactions** - When orally administered, tetracyclines can chelate **divalent or trivalent cations** which can decrease the absorption of the tetracycline or the other drug if it contains these cations. Oral antacids, saline cathartics or other GI products containing aluminum, calcium, magnesium, zinc or bismuth cations are most commonly associated with this interaction. Doxycycline has a relatively low affinity for calcium ions, but it is recommended that all oral tetracyclines be given at least 1-2 hours before or after the cation-containing product.
**Oral iron products** are also associated with decreased tetracycline absorption, and administration of iron salts should preferably be given 3 hours before or 2 hours after the tetracycline dose. **Oral sodium bicarbonate, kaolin, pectin, or bismuth subsalicylate** may impair tetracycline absorption when given together orally. Bacteriostatic drugs like the tetracyclines, may interfere with bactericidal activity of the **penicillins, cephalosporins,** and **aminoglycosides**. There is some amount of controversy regarding the actual clinical significance of this interaction, however. Tetracyclines may increase the bioavailability of **digoxin** in a small percentage of patients (human) and lead to digoxin toxicity. These effects may persist for months after discontinuation of the tetracycline. Tetracyclines may depress plasma prothrombin activity and patients on **anticoagulant (***e.g.,* **warfarin)** therapy may need dosage adjustment. Tetracyclines have been reported to increase the nephrotoxic effects of **methoxyflurane** and tetracycline HCl or Oxytetracycline are not recommended to used with methoxyflurane. GI side effects may be increased if tetracyclines are administered concurrently with **theophylline** products. Tetracyclines have reportedly reduced **insulin** requirements in diabetic patients, but this interaction is yet to be confirmed with controlled studies.

**Drug/Laboratory Interactions** - Tetracyclines (not minocycline) may cause falsely elevated values of **urine catecholamines** when using fluorometric methods of determination.
Tetracyclines reportedly can cause false-positive **urine glucose** results if using the cupric sulfate method of determination (Benedict's reagent, *Clinitest*®), but this may be the result of ascorbic acid which is found in some parenteral formulations of tetracyclines. Tetracyclines have also reportedly caused false-negative results in determining urine glucose when using the glucose oxidase method (*Clinistix*®*, Tes-Tape*®).

**Doses** -
**Horses**:

**Warning**: Doxycycline intravenously in horses has been associated with fatalities. Until further work is done demonstrating the safety of this drug, it cannot be recommended for parenteral use in this species.

To Drug Monograph Index To Ophthalmic Product Index

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects

**Client Information** - Oral doxycycline products may be administered without regard to feeding. Milk or other dairy products do not significantly alter the amount of doxycycline absorbed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products:** None

**Human-Approved Products**:

Doxycycline (as the hyclate) Tablets and Capsules 50 mg, 100 mg; *Vibramycin*®(Pfizer); *Doxychel*® *Hyclate* (Rachelle), *Doxy Caps*® (Edwards); *Bio-Tab*® (Inter. Ethical Labs); *Vibra-Tabs*® (Pfizer); generic; (Rx)

Doxycycline (as monohydrate) Tablets and Capsules 50 mg, 100 mg; *Monodox*® (Oclassen) (Rx)

Doxycycline coated pellets (as hyclate) 100 mg; *Doryx*® (Parke-Davis) (Rx)

Doxycycline (as the monohydrate) Powder for Oral Suspension 5 mg/ml 25 mg/5 ml after reconstitution in 60 ml bottles

*Vibramycin*® (Pfizer); (Rx)

Doxycycline (as the calcium salt) Oral Syrup 10 mg/ml in 50 ml bottles. *Vibramycin*® (Pfizer); (Rx)

Doxycycline (as the hyclate) Powder for Injection 100 mg and 200 mg vials

*Vibramycin*® *IV* (Roerig); *Doxychel*® *Hyclate* (Rachelle); *Doxy 100 & 200* (Lyphomed); generic; (Rx)

## DOXYLAMINE SUCCINATE

**Chemistry** - An ethanolamine-derivative antihistamine, doxylamine succinate occurs as a white to creamy-white powder with a characteristic odor. It has a melting range of 103-108°C and $pK_a$ values of 5.8 and 9.3. Doxylamine succinate has solubilities of 0.5 g/ml in alcohol and 1 g/ml in water. The commercially available injection has an approximate pH of 4.8 - 5.2.

**Storage/Stability/Compatibility** - Tablets should be stored in well-closed, light-resistant packaging at room temperature. No information on the storage, stability, or compatibility was found regarding the injectable product.

**Pharmacology** - Like other antihistamines, doxylamine competitively inhibits histamine at $H_1$ receptors. It also has substantial sedative and anticholinergic effects.

**Uses/Indications** - This drug is recommended (by the manufacturer) “for use in conditions in which antihistaminic therapy may be expected to alleviate some signs of disease in dogs, cats, and horses.”

**Pharmacokinetics** - Pharmacokinetic parameters are apparently unavailable for domestic animals. Doxylamine has a serum half-life of approximately 10 hours in human adults.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions** - The manufacturer recommends that the injectable product should not be administered by the IV route in dogs or cats, and that IM and SQ injection sites be divided. Inject slowly IV in horses. Do not use in horses intended for food purposes.

Doxylamine is also contraindicated in patients who are hypersensitive to it or other antihistamines in its class. Because of their anticholinergic activity, antihistamines should be used with caution in patients with angle closure glaucoma, prostatic hypertrophy, pyloroduodenal or bladder neck obstruction, and COPD if mucosal secretions are a problem. Additionally, they should be used with caution in patients with hyperthyroidism, cardiovascular disease or hypertension.

**Adverse Effects/Warnings** - The manufacturer lists CNS depression, incoordination and GI disturbances as adverse effects at therapeutic dosages.

**Overdosage** - The manufacturer includes CNS stimulation (excitement, seizures) and ataxia as symptoms associated with overdosage. Treatment should be supportive, as outlined in the previous antihistamine monographs.

**Drug Interactions** - Potential drug interactions for doxylamine include, increased sedation if doxylamine is combined with **other CNS depressant drugs**.
Antihistamines may partially counteract the anticoagulation effects of **heparin** or **warfarin**.
Doxylamine may enhance the effects of **epinephrine**.

**Laboratory Interactions** - Antihistamines can decrease the wheal and flare response to **antigen skin testing**. In humans, it is suggested that antihistamines be discontinued at least 4 days before testing.

**Doses** -
**Horses**:

a) 0.55 mg/kg IV(slowly), IM or SQ q8-12h *prn*. For maintenance therapy: 2.2 - 4.4 mg/kg/day PO divided into 3 or 4 daily doses. (Package Insert; *A-H® Injection* - Coopers Animal Health)
b) 0.55 mg/kg q8-12h IM or SQ (Schultz 1986)

**Monitoring Parameters** -

1) Efficacy/Adverse effects

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**:

Doxylamine Succinate for Injection 11.36 mg/ml; 250 ml vials; *A-H® Injection* (Schering); (Rx) Approved for use in dogs, cats, and horses (not intended for food purposes).

Doxylamine Succinate Tablets 25 mg, 100 mg; bottles of 50; *A-H® Tablets* (Schering); (Rx) Approved for use in dogs, cats, and horses (not intended for food purposes).

**Human-Approved Products**: None

## EDETATE CALCIUM DISODIUM

**Chemistry** - A heavy metal chelating agent, edetate calcium disodium (CaEDTA) occurs as an odorless, white, crystalline powder or granules and is a mixture of dihydrate and trihydrate forms. It has a slight saline taste and is slightly hygroscopic. CaEDTA is freely soluble in water and very slightly soluble in alcohol. The

commercially available injection (human) has a pH of 6.5-8 and has approximately 5.3 mEq of sodium per gram of CaEDTA.

Edetate calcium disodium has several synonyms including: calcium disodium edathamil, Calcium EDTA (CaEDTA), calcium disodium edetate, calcium edetate, calcium disodium ethylenediaminetetra-acetate and sodium calcium edetate.

**Storage/Stability/Compatibility** - CaEDTA should be stored at temperatures less than 40°, and preferably at room temperature (15-30°C). The injection can be diluted with either normal saline or 5% dextrose.

**Pharmacology** - The calcium in CaEDTA can be displaced by divalent or trivalent metals to form a stable water soluble complex that can be excreted in the urine. One gram of CaEDTA can theoretically bind 620 mg of lead, but in reality only about 5 mg per gram is actually excreted into the urine in lead poisoned patients. In addition to chelating lead, CaEDTA also chelates and eliminates zinc from the body. CaEDTA also binds cadmium, copper, iron and manganese, but to a much lesser extent than either lead or zinc. CaEDTA is relatively ineffective for use in treating mercury, gold or arsenic poisoning.

**Uses/Indications** - CaEDTA is used as a chelating agent in the treatment of lead poisoning.

**Pharmacokinetics** - CaEDTA is well absorbed after either IM or SQ administration. It is distributed primarily in the extracellular fluid. Unlike dimercaprol, CaEDTA does not penetrate erythrocytes or enter the CNS in appreciable amounts. The drug is rapidly excreted renally, either as unchanged drug or chelated with metals. Changes in urine pH or urine flow do not significantly alter the rate of excretion. Decreased renal function can cause accumulation of the drug and can increase its nephrotoxic potential. In humans with normal renal function, the average elimination half-life of CaEDTA is 20-60 minutes after IV administration, and 1.5 hours after IM administration.

**Contraindications/Precautions/Reproductive Safety** - CaEDTA is contraindicated in patients with anuria. It should be used with extreme caution and with dosage adjustment in patients with diminished renal function.

Most small animal clinicians recommend using the SQ route when treating small animals as IV administration of CaEDTA has been associated with abrupt increases in CSF pressure and death in children with lead-induced cerebral edema.

**Adverse Effects/Warnings** - The most serious of adverse effect associated with this compound is renal toxicity (renal tubular necrosis), but in dogs CaEDTA also can cause depression and GI symptoms. GI symptoms (vomiting, diarrhea) in dogs may be alleviated by zinc supplementation.

Do not administer CaEDTA orally as it may increase the amount of lead absorbed from the GI tract.

Animals with symptoms of cerebral edema should not be overhydrated.
Chronic therapy may lead to zinc deficiency; zinc supplementation should be considered in these animals.

**Overdosage/Acute Toxicity** - Doses greater than 12 g/kg are lethal in dogs; refer to Adverse Effects for more information.

**Drug Interactions** - Concurrent administration of CaEDTA with **zinc insulin preparations (NPH, PZI)** will decrease the sustained action of the insulin preparation.
The renal toxicity of CaEDTA may be enhanced by the concomitant administration of **glucocorticoids**. Use with caution with **other nephrotoxic compounds** (*e.g.,* aminoglycosides, amphotericin B).

To Drug Monograph Index  To Ophthalmic Product Index

**Drug/Laboratory Interactions** - CaEDTA may cause increased **urine glucose** values and/or cause inverted T-waves on **ECG**.

**Doses** -
The manufacturer of the injectable (human) product recommends diluting the injection to a concentration of 2 - 4 mg/ml with either normal saline or 5% dextrose when used for intravenous use. Because the injection is painful when given IM, 1 ml of procaine HCl 1% is recommended to be added to each ml of injection before administering IM.

**Horses**:

For lead poisoning:

a) Remove animal from source of lead. If severely affected give CaEDTA at 75 mg/kg IV slowly in $D_5W$ or saline daily for 4-5 days (may divide daily dose into 2-3 administrations per day). Stop therapy for 2 days and repeat for another 4-5 days. Give adequate supportive and nutritional therapy. (Oehme 1987d)

**Monitoring Parameters** -

1) Blood lead or zinc (serial), and/or urine *d*-ALA
2) Renal function tests, urinalyses, hydration status
3) Serum phosphorus and calcium values
4) Periodic cardiac rate/rhythm monitoring may be warranted during administration

**Client Information** - Because of the potential toxicity of this agent and the seriousness of most heavy metal intoxications, this drug should be used with close professional supervision only.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

Note: Do not confuse with Edetate Disodium which should not be used for lead poisoning as it may cause severe hypocalcemia.

**Veterinary-Approved Products**:

Edetate Calcium Disodium Injection 50 mg/ml in 500 ml single dose vials. *Meta-Dote*® (Anthony) (Rx). Approved for use in cattle, horses, goats, sheep and swine. Not intended for use on animals to be used as food.

**Human-Approved Products**:

Edetate Calcium Disodium Injection 200 mg/ml in 5 ml amps (1 gram/amp); *Calcium Disodium Versenate*® (3M Pharm.) (Rx)

## ENROFLOXACIN

**Chemistry** - A fluoroquinolone antibiotic, enrofloxacin occurs as a pale yellow, crystalline powder. It is slightly soluble in water. Enrofloxacin is related structurally to the human-approved drug ciprofloxacin (enrofloxacin has an additional ethyl group on the piperazinyl ring).

**Storage/Stability/Compatibility** - Unless otherwise directed by the manufacturer, enrofloxacin tablets should be stored in tight containers at temperatures less than 30°C. Protect from strong UV light.

**Pharmacology** - Enrofloxacin is a bactericidal agent. The bactericidal activity of enrofloxacin is concentration dependent, with susceptible bacteria cell death occuring within 20-30 minutes of exposure. Enrofloxacin has demonstrated a significant post-antibiotic effect for both gram - and + bacteria and is active in both stationary and growth phases of bacterial replication.

To Drug Monograph Index To Ophthalmic Product Index

Its mechanism of action is not thoroughly understood, but it is believed to act by inhibiting bacterial DNA-gyrase (a type-II topoisomerase), thereby preventing DNA supercoiling and DNA synthesis.

Both enrofloxacin and ciprofloxacin have similar spectrums of activity. These agents have good activity against many gram negative bacilli and cocci, including most species and strains of *Pseudomonas aeruginosa, Klebsiella sp., E. coli, Enterobacter, Campylobacter, Shigella, Salmonella, Aeromonas, Haemophilus, Proteus, Yersinia, Serratia*, and *Vibrio* species. Of the currently commercially available quinolones, ciprofloxacin and enrofloxacin have the lowest MIC values for the majority of these pathogens treated. Other organisms that are generally susceptible include *Brucella sp, Chlamydia trachomatis, Staphylococci* (including penicillinase-producing and methicillin-resistant strains), Mycoplasma, and *Mycobacterium sp*. (not the etiologic agent for Johne's Disease).

The fluoroquinolones have variable activity against most *Streptococci* and are not usually recommended to be used for these infections. These drugs have weak activity against most anaerobes and are ineffective in treating anaerobic infections.

Resistance does occur by mutation, particularly with *Pseudomonas aeruginosa, Klebsiella pneumonia*, *Acinetobacter* and enterococci, but plasmid-mediated resistance is not thought to occur.

**Uses/Indications** - Enrofloxacin is approved for use in dogs and cats (oral only) for the management of of diseases assicaited with bacteria susceptible to enrofloxacin. It is also been approved for use in cattle (not dairy cattle or veal calves) and for chickens and turkeys.

**Pharmacokinetics** - Both enrofloxacin and ciprofloxacin are well absorbed after oral administration in most species. But in dogs, enrofloxacin's bioavailability (approximately 80%) is about twice that of ciprofloxacin after oral dosing. 50% of Cmax is reportedly attained within 15 minutes of dosing and peak levels (Cmax) occur within one hour of dosing. The presence of food in the stomach may delay the rate, but not the extent of absorption.

Enrofloxacin/ciprofloxacin are distributed throughout the body. Volume of distribution in dogs is at least 2.8 L/kg. Only about 27% is bound to canine plasma proteins. Highest concentrations are found in the bile, kidney, liver, lungs, and reproductive system (including prostatic fluid and tissue). Therapeutic levels are also attained in bone, synovial fluid, skin, muscle, aqueous humor and pleural fluid. Low concentrations are found in the CSF, and levels may only reach 6-10% of those found in the serum.

Enrofloxacin/ciprofloxacin is eliminated via both renal and non-renal mechanisms. Approximately 15-50% of the drugs are eliminated unchanged into the urine, by both tubular secretion and glomerular filtration. Enrofloxacin/ciprofloxacin are metabolized to various metabolites that are less active than the parent compounds. Approximately 30-40% of circulating enrofloxacin is metabolized to ciprofloxacin. These metabolites are eliminated both in the urine and feces. Because of the dual (renal and hepatic) means of elimination, patients with severely impaired renal function may have slightly prolonged half-lives and higher serum levels which may not require dosage adjustment. The elimination half-lives in dogs are approximately 4-5 hours and in cats, 6 hours.

**Contraindications/Precautions/Reproductive Safety** - Enrofloxacin is contraindicated in small and medium breed dogs from 2 months to 8 months of age. Bubble-like changes in articular cartilage have been noted when the drug was given at 2-5 times recommend doses for 30 days, although clinical symptoms have only been seen at the 5X dose. Large and giant breed dogs may be in the rapid-growth phase for periods longer than 8 months of age, so longer than 8 months may be necessary to avoid cartilage damage. Quinolones are also contraindicated in patients hypersensitive to them.

To Drug Monograph Index To Ophthalmic Product Index

Because ciprofloxacin has occasionally been reported to cause crystalluria, animals should not be allowed to become dehydrated during therapy with either ciprofloxacin or enrofloxacin. In humans, ciprofloxacin has been associated with CNS stimulation and should be used with caution in patients with seizure disorders. Patients with severe renal or hepatic impairment may require dosage adjustments to prevent drug accumulation.

The safety of enrofloxacin in pregnant dogs has been investigated. Breeding, pregnant and lactating dogs receiving up to 15 mg/kg day demonstrated no treatement related effects. However, because of the risks of cartilage abnormalities in young animals, the fluoroquinolones are not generally recommended to be used during pregnancy unless the benefits of therapy clearly outweigh the risks. Limited studies in male dogs at various dosages have indicated no effects on male breeding performance. Safety in breeding, pregnant, or lactating cats has not been established.

**Adverse Effects/Warnings** - With the exception of potential cartilage abnormalities in young animals (see Contraindications above), the adverse effect profile of these drugs appears to be minimal. GI distress (vomiting, anorexia) is the most common, yet infrequently reported adverse effect. Although not reported thus far in animals, hypersensitivity reactions, crystalluria and CNS effects (dizziness, stimulation) could potentially occur.

**Overdosage/Acute Toxicity** - It is unlikely an acute overdose of either compound would result in symptoms more serious than either anorexia and vomiting. Dogs receiving 10 times the labeled dosage rate of enrofloxacin for at least 14 days developed only vomiting and anorexia. Death did occur in some dogs when fed 25 times the labeled rate for 11 days, however.

**Drug Interactions** - **Antacids** containing cations ($Mg^{++}$, $Al^{+++}$, $Ca^{++}$) may bind to enrofloxacin/ciprofloxacin and prevent its absorption. **Sucralfate** may inhibit absorption of enrofloxacin/ciprofloxacin, separate doses of these drugs by at least 2 hours. Enrofloxacin/ciprofloxacin administered with **theophylline** may increase theophylline blood levels. **Probenecid** blocks tubular secretion of enrofloxacin/ciprofloxacin and may increase its blood level and half-life. Synergism may occur, but is not predictable, against some bacteria (particularly *Pseudomonas aeruginosa* or other Enterobacteriaceae) with these compounds and **aminoglycosides, 3rd generation cephalosporins agents, and extended-spectrum penicillins**. Although enrofloxacin/ciprofloxacin has minimal activity against anaerobes, *in vitro* synergy has been reported when used with **clindamycin** against strains of *Peptostreptococcus*, *Lactobacillus* and *Bacteroids fragilis*. **Nitrofurantoin** may antagonize the antimicrobial activity of the fluoroquinolones and their concomitant use is not recommended. Fluoroquinolones may exacerbate the nephrotoxicity of **cyclosporine** (used systemically). Because the fluoroquinolones are relatively new additions to the therapeutic armamentarium, more interactions may be forthcoming.

**Drug/Laboratory Interactions** - In some human patients, the fluoroquinolones have caused increases in **liver enzymes, BUN,** and **creatinine** and decreases in **hematocrit**. The clinical relevance of these mild changes is not known at this time.

**Doses** -

**Horses:**

Note: Usage of enrofloxacin in horses is controversial. While there has been much discussion regarding the potential for cartilage abnormalities or other arthropathies in horses, objective data are lacking. At the present time however, it probably should only be used in adult horses when other antibiotics are inappropriate with the client informed of, and agrees to accept the risks for any potential adverse effects.

a) 2.5 mg/kg q12h (Whittem 1993)

To Drug Monograph Index To Ophthalmic Product Index

**Elephants:**

a) 1.07 – 1.25 mg/kg orally BID. No adverse effects noted after 2 weeks. Schmidt, M.J: Senior Research Veterinarian, Washington Park Zoo, Portland, Oregon, personal communication, 1986. In: Olsen,J.H., 1999. **Antibiotic therapy in elephants**. In: Fowler,M.E. and Miller R.E. (Editors), **Zoo and Wild Animal Medicine: Current Therapy 4.** W.B. Saunders, Philadelphia, PA,USA p. 538

b) 1.5 – 2.8 mg/kg orally once daily. Blood levels evaluated on one elephant found that once daily dosing maintained blood levels. Houck, R: Senior Veterinarian, Ringling Brothers and Barnum and Bailey Circus, 8607 Westwood Center Drive, Vienna, Virginia, 22182, personal communication, 1986. In: Olsen,J.H., 1999. **Antibiotic therapy in elephants**. In: Fowler,M.E. and Miller R.E. (Editors), **Zoo and Wild Animal Medicine: Current Therapy 4.** W.B. Saunders, Philadelphia, PA,USA p.538

c) **Pharmacokinetics of a single dose of enrofloxacin administered orally to captive Asian elephants(Elephas maximus). 2005.** C. R. Sanchez, S. Z. Murray, R. Isaza and M. G. Papich. Am J Vet Res 2005 Vol. 66 Issue 11 Pages 1948-1953.

OBJECTIVE: To determine the pharmacokinetics of enrofloxacin after oral administration to captive elephants. ANIMALS: 6 clinically normal adult Asian elephants (Elephas maximus). PROCEDURE: Each elephant received a single dose of enrofloxacin (2.5 mg/kg, PO). Three elephants received their complete diet (pellets and grain) within 2 hours after enrofloxacin administration, whereas the other 3 elephants received only hay within 6 hours after enrofloxacin administration. Serum concentrations of enrofloxacin and ciprofloxacin were measured by use of high-performance liquid chromatography. RESULTS: Harmonic mean half-life after oral administration was 18.4 hours for all elephants. Mean +/- SD peak serum concentration of enrofloxacin was 1.31 +/- 0.40 microg/mL at 5.0 +/- 4.2 hours after administration. Mean area under the curve was 20.72 +/- 4.25 (microg x h)/mL. CONCLUSIONS AND CLINICAL RELEVANCE: Oral administration of enrofloxacin to Asian elephants has a prolonged elimination half-life, compared with the elimination half-life for adult horses. In addition, potentially therapeutic concentrations in elephants were obtained when enrofloxacin was administered orally at a dosage of 2.5 mg/kg. Analysis of these results suggests that enrofloxacin administered with feed in the manner described in this study could be a potentially useful antimicrobial for use in treatment of captive Asian elephants with infections attributable to organisms, such as Bordetella spp, Escherichia coli, Mycoplasma spp, Pasteurella spp, Haemophilus spp, Salmonella spp, and Staphylococcus spp.

d) Pharmacokinetics of enrofloxacin in African elephants (Loxodonta africana) after a single rectal dose J. Miller and M. McClean. 2008. Proc American Associaton of Zoo Veterinarians and Assoc of Reptile and Amphibian Veterinarians Pages: 224-225.

Captive African elephants (*Loxodonta Africana*) are susceptible to many types of gram negative bacterial infections such as *Escherichia coli, Mycoplasma* spp., *Salmonella* spp., *Klebsiella* spp., *Pseudomonas* spp., and *Proteus* spp. Enrofloxacin (Baytril®, Bayer Health Care, Animal Health Division, P.O. Box 390, Shawnee Mission, KS 66201) is a potentially effective antibiotic for treatment of these bacterial infections in elephants. Very limited data exists on the pharmacokinetics of enrofloxacin in elephants2 and most of the dosage regimes for gastrointestinal absorption are based on horse dosages since they share a similar gastrointestinal tract. Three African elephants from Wildlife Safari in Winston, Oregon, two females both 37-yr-old and one male 26-yr-old, were used to determine whether therapeutic levels of enrofloxacin could be achieved thru rectal administration of liquid injectable enrofloxacin (Baytril 100®, 100 mg/ml, Bayer Health Care, Animal Health Division, P.O. Box 390, Shawnee Mission, KS 66201) at a dosage of 2.5 mg/kg. A pretreatment baseline blood sample was collected. Following administration, blood samples were collected at 45 min, 1.5hr, 2.5hr, 5hr, 9hr, 23hr, 36hr to determine plasma enrofloxacin levels. Plasma enrofloxacin levels were measured at North Carolina State University, College of Veterinary Medicine using high performance liquid chromatography (HPLC) analysis. Plasma ciprofloxacin levels were measured

To Drug Monograph Index To Ophthalmic Product Index

concurrently. Results indicate plasma concentrations of enrofloxacin did not reach adequate bacteriocidal levels for any of the the following common bacterial isolates in captive elephants: *Mycoplasma* spp., *Escherichia coli, Salmonella* spp., *Klebsiella* spp., *Pseudomonas* spp., and *Proteus* spp. The study determined that a rectally administered dosage of 2.5 mg/kg of liquid injectable enrofloxacin was insufficient to obtain therapeutic levels in African elephants. The low plasma levels of enrofloxacin in all three elephants may be a result of poor absorption in the distal large intestine. A future study will determine if oral administration will provide a more efficient mode of drug delivery and absorption in African elephants. It is also possible that the current dosage of 2.5 mg/kg is too low to achieve adequate therapeutic levels. ACKNOWLEDGMENTS I would like to thank the elephant and veterinary staff at Wildlife Safari for their participation in conducting this study. Thanks to Doctors: Modesto McClean, Jason Bennett, Andi Chariffe, Tessa Lohe, Benji Alacantar. Also thanks to Dinah Wilson, Carol Matthews, Anthony Karels, Mary Iida, Shawn Finnell, Patches Stroud, Katie Alayan. LITERATURE CITED: 1. Haines, G.R., et. al. 2000. Serum concentrations and pharmacokinetics of enrofloxacin after intravenous and intragastric administration to mares. Can. J.Vet. Res. 64(3):171-177. 2. Sanchez, C.R., et. al. 2005. Pharmacokinetics of a single dose of enrofloxacin administered orally to captive Asian elephants (*Elephas maximus*). Am. J. Vet. Res. 66:1948-1953.

**Serum concentrations of antimycobacterial drugs in Asian Elephants (Elephas maximus).** 2016. L. Young, S. Scott, M. Salfinger and E. Ramsay. Proc. AAZV / EAZWV / IZW Joint Conference 2016

Mycobacterium tuberculosis is an important disease of captive Asian elephants (Elephas maximus.) In this study six adult Asian elephants which had Mycobacterium tuberculosis cultured from trunk wash samples or had reactive DPP/MAPIA serologic responses were treated, concurrently, with one to three antimycobacterial drugs. Enrofloxacin hydrochloride, 2.5 mg/kg p.o., s.i.d., was administered to all animals in various foodstuffs for 9-15 mo. Serum enrofloxacin concentrations ranged from 230-2380 µg/ml (targeted concentrations = 125-1000 µg/ml).1 Pyrazinamide (PZA), 30 mg/kg p.o., s.i.d., was administered to five elephants in various foodstuffs for 9-12 mo. Serum PZA concentrations ranged from 26-57 µg/ml (targeted concentrations = 20- 60 µg/ml).2 Ethambutol (EMB), 30 mg/kg p.o., s.i.d., was administered to one elephant for 12 mo. A serum EMB concentration of 4.07 µg/ml was achieved (targeted concentration = 2-6 µg/ml).2 Rifampin (RIF), 10 mg/kg p.o., s.i.d., was administered to one elephant for 9 mo. A serum RIF concentration of 16 µg/ml was achieved (targeted concentration = 8-24 µg/ml). All elephants were monitored for adverse clinical effects throughout treatments. Notable side effects were limited to excess, foamy lacrimation, believed to have occurred secondary to PZA administration. Clinical chemistries and complete blood counts were monitored in all animals and values remained within reference intervals throughout treatments. This study shows antimycobacterial drug dosages may require individuation, but concurrent, long-term, multidrug regimens for the treatment of Mycobacterium tuberculosis in Asian elephants can achieve appropriate therapeutic levels with minimal detrimental side effects.

**Monitoring Parameters** -1) Clinical efficacy; 2) Adverse effects

**Client Information** - Do not crush tablets as drug is very bitter tasting.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: (Note: See additional dosage forms in the dosage section for cattle and birds)

Enrofloxacin Oral Tablets 22.7 mg, 68 mg; *Baytril*® (Miles); (Rx) Approved for use in dogs and cats.

Enrofloxacin Injection 22.7 mg/ml in 20 ml vials; *Baytril*® (Miles); (Rx) Approved for use in dogs. A non-approved method for diluting the IM injectable product for IV administration has been described: Dilute 1 part of *Baytril*® injection with 2 parts of sterile water for injection and administer IV over 20 minutes or so.

To Drug Monograph Index To Ophthalmic Product Index

**Human-Approved Products**: None. Note: Use of enrofloxacin by humans cannot be recommmended due to a high degree of CNS effects.

## EPINEPHRINE

**Chemistry** - An endogenous catecholamine, epinephrine occurs as white to nearly white, microcrystalline powder or granules. It is only very slightly soluble in water, but it readily forms water soluble salts (*e.g.,* HCl) when combined with acids. Both the commercial products and endogenous epinephrine are in the levo form, which is about 15 times more active than the dextro-isomer. The pH of commercial injections are from 2.5 - 5. Epinephrine is sometimes known as Adrenalin.

**Storage/Stability/Compatibility** - Epinephrine HCl for injection should be stored in tight containers and protected from light. Epinephrine will darken (oxidation) upon exposure to light and air. Do not use the injection if it is pink, brown or contains a precipitate. The stability of the injection is dependent on the form and the preservatives present, and may vary from one manufacturer to another. Epinephrine is rapidly destroyed by alkalies, or oxidizing agents.

Epinephrine HCl is reported to be **compatible** with the following intravenous solutions: Dextran 6% in dextrose 5%, Dextran 6% in normal saline, dextrose-Ringer's combinations, dextrose-lactated Ringer's combinations, dextrose-saline combinations, dextrose 2.5%, dextrose 5% (becomes unstable at a pH > 5.5), dextrose 10%, Ringer's injection, lactated Ringer's injection, normal saline, and sodium lactate 1/6 M. Epinephrine HCl is reportedly **compatible** with the following drugs: amikacin sulfate, cimetidine HCl, dobutamine HCl, metaraminol bitartrate, and verapamil HCl.

Epinephrine HCl is reported to be **incompatible** with the following intravenous solutions: Ionosol-D-CM, Ionosol-PSL (Darrow's), Ionosol-T w/ dextrose 5% (Note: other Ionosol product are compatible), sodium chloride 5%, and sodium bicarbonate 5%. Epinephrine HCl is reportedly **incompatible** with the following drugs: aminophylline, cephapirin sodium, hyaluronidase, mephentermine sulfate, sodium bicarbonate, and warfarin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** - Epinephrine is an endogenous adrenergic agent that has both alpha and beta activity. It relaxes smooth muscle in the bronchi and the iris, antagonizes the effects of histamine, increases glycogenolysis, and raises blood sugar. If given by rapid IV injection it causes direct stimulation of the heart (increased heart rate and contractility), and increases systolic blood pressure. If given slowly IV, it usually produces a modest rise in systolic pressure and a decrease in diastolic blood pressure. Total peripheral resistance is decreased because of beta effects.

**Uses/Indications** - Epinephrine is employed primarily in veterinary medicine as a treatment for anaphylaxis and in cardiac resuscitation. Because of its vasocontrictive properties, epinephrine is also added to local anesthetics to retard systemic absorption and prolong effect.

**Pharmacokinetics** - Epinephrine is well absorbed following IM or SQ administration. IM injections are slightly faster absorbed than SQ administration; absorption can be expedited by massaging the injection site. Epinephrine is rapidly metabolized in the GI tract and liver after oral administration and is not effective via this route. Following SQ injection, the onset of action is generally within 5-10 minutes. The onset of action following IV administration is immediate and intensified.

Epinephrine does not cross the blood-brain barrier, but does cross the placenta and is distributed into milk.

To Drug Monograph Index  To Ophthalmic Product Index

Epinephrine's actions are ended primarily by the uptake and metabolism of the drug into sympathetic nerve endings. Metabolism takes place in both the liver and other tissues by monoamine oxidase (MAO) and catechol-*O*-methyltransferase (COMT) to inactive metabolites.

**Contraindications/Precautions** - Epinephrine is contraindicated in patients with narrow-angle glaucoma, hypersensitivity to epinephrine, shock due to non-anaphylactoid causes, during general anesthesia with halogenated hydrocarbons or cyclopropane, during labor (may delay the second stage) and in cardiac dilatation or coronary insufficiency. Epinephrine should also not be used in cases where vasopressor drugs are contraindicated (*e.g.,* thyrotoxicosis, diabetes, hypertension, toxemia of pregnancy). It should not be injected with local anesthetics into small appendages of the body (*e.g.,* toes, ears, etc.) because of the chance of necrosis and sloughing.

Use epinephrine with caution in cases of hypovolemia; it is not a substitute for adequate fluid replacement therapy. It should be used with extreme caution in patients with a prefibrillatory cardiac rhythm, because of its excitatory effects on the heart. While epinephrine's usefulness in asystole is well documented, it also can cause ventricular fibrillation; use cautiously in cases of ventricular fibrillation.

**Adverse Effects/Warnings** - Epinephrine can induce a feeling of fear or anxiety, tremor, excitability, vomiting, hypertension (overdosage), arrhythmias (especially if patient has organic heart disease or has received another drug that sensitizes the heart to arrhythmias), hyperuricemia, and lactic acidosis (prolonged use or overdosage). Repeated injections can cause necrosis at the injection site.

**Overdosage** - Symptoms seen with overdosage or inadvertent IV administration of SQ or IM dosages can include: sharp rises in systolic, diastolic, and venous blood pressures, cardiac arrhythmias, pulmonary edema and dyspnea, vomiting, headache, and chest pain. Cerebral hemorrhages may result because of the increased blood pressures. Renal failure, metabolic acidosis and cold skin may also result.

Because epinephrine has a relatively short duration of effect, treatment is mainly supportive. If necessary, the use an alpha-adrenergic blocker (*e.g.,* phentolamine) or a beta-adrenergic blocker (*e.g.,* propranolol) can be considered to treat severe hypertension and cardiac arrhythmias. Prolonged periods of hypotension may follow, which may require treatment with norepinephrine.

**Drug Interactions** - Do not use with other **sympathomimetic amines (***e.g.,* **isoproterenol)** because of additive effects and toxicity. Certain **antihistamines (diphenhydramine, chlorpheniramine, etc.) and l-thyroxine** may potentiate the effects of epinephrine.
**Propranolol** (or other beta-blockers) may potentiate hypertension, and antagonize epinephrine's cardiac and bronchodilating effects by blocking the beta effects of epinephrine.
**Nitrates, alpha-blocking agents, or diuretics** may negate or diminish the pressor effects of epinephrine. When epinephrine is used with drugs that sensitize the myocardium **(halothane, high doses of digoxin**) monitor for signs of arrhythmias. Hypertension may result if epinephrine is used with **oxytocic agents**.

**Doses** -
Note: Be certain when preparing injection that you do not confuse 1:1000 (1 mg/ml) with 1:10,000 (0.1 mg/ml) concentrations. To convert a 1:1000 solution to a 1:10,000 solution for IV or intratracheal use, dilute each ml with 9 ml of normal saline for injection. Epinephrine is only one aspect of treating cardiac arrest, refer to specialized references or protocols for more information.
**Horses**:

For anaphylaxis:

a) 3 - 5 ml of 1:1,000 per 450 kg of body weight either IM or SQ. For foal resuscitation: 0.1 ml/kg of 1:1,000 IV (preferably diluted with saline) (Robinson 1987)

**Elephants:**

To Drug Monograph Index To Ophthalmic Product Index

a) For emergency treatment of a newborn calf, calculate the dose at 0.1 ml/kg of a 1:1000 solution. Have prepared and labeled in a syringe. Give inter-cardiac, intra-tracheal, or IV if there is no heatrbeat:
200 lb (90 kg) calf = 9 ml
250 lb (113 kg) calf = 11.3 ml
300 lb (136 kg ) calf = 13.6 ml (Schmitt, 2001).

Schmitt,D.L. 2001. **Riddle's Elephant and Wildlife Sanctuary Elephant Birth Protocol**.

**Monitoring Parameters** -

1) Cardiac rate/rhythm
2) Respiratory rate/auscultation during anaphylaxis
3) Urine flow if possible
4) Blood pressure, and blood gases if indicated and if possible

**Client Information** - Pre-loaded syringes containing an appropriate amount of epinephrine may be dispensed to clients for treatment of anaphylaxis in animals with known hypersensitivity. Anaphylactic symptoms (depending on species) should be discussed. Clients should be instructed in proper injection technique (IM or SQ) and storage conditions for epinephrine. Do not use epinephrine if it is outdated , discolored or contains a precipitate.
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved and Human-Approved Products**: Epinephrine is approved for use in dogs, cats, horses, cattle, sheep, and swine.

Epinephrine HCl for Injection 0.1 mg/ml (1:10,000) in 10 ml syringes (human-label); (Rx)

Epinephrine HCl for Injection 1 mg/ml (1:1,000) in 1 ml amps & syringes and 10 ml, 30 ml and 100 ml vials; *Adrenalin Chloride*® (P-D); Veterinary-labeled generic; (Rx)

It is also available in products labeled for human use as a powder form (aerosol) for inhalation, and a sterile suspension for injection. Epinephrine bitartrate is available as a powder form (aerosol) for inhalation. Epinephrine HCl is also available as a solution for nebulization and in automatically injecting syringes for treatment of hypersensitivity reactions.

## ERYTHROMYCIN
## ERYTHROMYCIN ESTOLATE
## ERYTHROMYCIN ETHYLSUCCINATE
## ERYTHROMYCIN LACTOBIONATE
## ERYTHROMYCIN GLUCEPTATE

**Chemistry** - A macrolide antibiotic produced from *Streptomyces erythreus*, erythromycin is a weak base that is available commercially in several salts and esters. It has a $pK_a$ of 8.9.
Erythromycin base occurs as a bitter-tasting, odorless or practically odorless, white to slight yellow, crystalline powder. Approximately 1 mg is soluble in 1 ml of water; it is soluble in alcohol.

Erythromycin estolate occurs as a practically tasteless and odorless, white, crystalline powder. It is practically insoluble in water and approximately 50 mg are soluble in 1 ml of alcohol. Erythromycin estolate may also be known as erythromycin propionate lauryl sulfate.

Erythromycin ethylsuccinate occurs as a practically tasteless and odorless, white to slight yellow, crystalline powder. It is very slightly soluble in water and freely soluble in alcohol.

To Drug Monograph Index  To Ophthalmic Product Index

Erythromycin lactobionate occurs as white to slightly yellow crystals or powder. It may have a faint odor and is freely soluble in water and alcohol. Erythromycin gluceptate occurs as a practically odorless, white, slightly hygroscopic powder that is freely soluble in water and alcohol. It may also be known as erythromycin glucoheptonate.

**Storage/Stability/Compatibility** - Erythromycin (base) capsules and tablets should be stored in tight containers at room temperature (15-30°C). Erythromycin estolate preparations should be protected from light. To retain palatability, the oral suspensions should be refrigerated.
Erythromycin ethylsuccinate tablets and powder for oral suspension should be stored in tight containers at room temperature. The commercially available oral suspension should be stored in the refrigerator to preserve palatability. After dispensing, the oral suspensions are stable for at least 14 days at room temperature, but individual products may have longer labeled stabilities.

Erythromycin lactobionate powder for injection should be stored at room temperature. For initial reconstitution (vials), only sterile water for injection should be used. After reconstitution, the drug is stable for 24 hours at room temperature and 2 weeks if refrigerated. To prepare for administration via continuous or intermittent infusion, the drug is further diluted in 0.9% sodium chloride, Lactated Ringer's, or *Normosol-R*. Other infusion solutions may be used, but first must be buffered with 4% sodium bicarbonate injection (1 ml per 100 ml of solution). At pH's of <5.5, the drug is unstable and loses potency rapidly. Many drugs are physically incompatible with erythromycin lactobionate; refer to an appropriate reference (*e.g.,* Trissell—see bibliography) for more information.

Erythromycin gluceptate powder for injection should be stored at room temperature. For initial reconstitution (vials), only sterile water for injection (without preservatives) should be used. After reconstitution, the drug is stable for 7 days if refrigerated. Many drugs are physically incompatible with erythromycin gluceptate; refer to an appropriate reference (*e.g.,* Trissell—see bibliography) for more information.

**Pharmacology** - Erythromycin is usually a bacteriostatic agent, but in high concentrations or against highly susceptible organisms it may be bactericidal. The macrolides (erythromycin and tylosin) are believed to act by binding to the 50S ribosomal subunit of susceptible bacteria, thereby inhibiting peptide bond formation.

Erythromycin has *in vitro* activity against gram positive cocci (staphylococci, streptococci), gram positive bacilli (*Bacillus anthracis*, *Corynebacterium*, *Clostridium sp.*, (not *C. difficile*), *Listeria*, *Erysipelothrix*), some strains of gram negative bacilli, including *Haemophilus*, *Pasturella*, and *Brucella*. Some strains of *Actinomyces*, *Mycoplasma*, *Chlamydia*, *Ureaplasma*, and Rickettsia are also inhibited by erythromycin. Most strains of the family Enterobacteriaceae (*Pseudomonas, E. coli, Klebsiella*, etc.) are resistant to erythromycin.

Erythromycin is less active at low pH's and many clinicians suggest alkalinizing the urine if using the drug to treat UTI's.

**Uses/Indications** - Erythromycin is approved for use to treat infections caused by susceptible organisms in dogs, cats, swine, sheep, and cattle. It is often employed when an animal is hypersensitive to penicillins or if other antibiotics are ineffective against a certain organism.
Erythromycin is at the present time considered to be the treatment of choice (with rifampin) for the treatment of *C. (Rhodococcus) equi* infections in foals.

**Pharmacokinetics** - Erythromycin is absorbed after oral administration in the upper small intestine. Several factors can influence the bioavailability of erythromycin, including salt form, dosage form, GI acidity, food in the stomach, and stomach emptying time. Both erythromycin base and stearate are susceptible to acid degradation, and enteric coatings are often used to alleviate this. Both the ethylsuccinate and estolate forms are dissociated in the upper small intestine and then absorbed. After IM or SQ injection of the polyethylene-

To Drug Monograph Index To Ophthalmic Product Index

based veterinary product (*Erythro®-200*; *Gallimycin®-200*) in cattle, absorption is very slow. Bioavailabilities are only about 40% after SQ injection, and 65% after IM injection.

Erythromycin is distributed throughout the body into most fluids and tissues including the prostate, macrophages, and leukocytes. CSF levels are poor. Erythromycin may be 73-81% bound to serum proteins and the estolate salt, 96% bound. Erythromycin will cross the placenta and levels of 5-20% of those in the mother's serum can be found in the fetal circulation. Erythromycin levels of about 50% of those found in the serum can be detected in milk. The volume of distribution for erythromycin in dogs is reportedly 2 L/kg, 3.7 - 7.2 L/kg in foals, 2.3 L/kg in mares, and 0.8 L/kg in cattle.

Erythromycin is primarily excreted unchanged in the bile, but is also partly metabolized by the liver via *N*-demethylation to inactive metabolites. Some of the drug is reabsorbed after biliary excretion. Only about 2-5% of a dose is excreted unchanged in the urine. The reported elimination half-life of erythromycin in various species are: 60-90 minutes in dogs and cats, 60-70 minutes in foals and mares, and 190 minutes in cattle.

**Contraindications/Precautions/Reproductive Safety** - Erythromycin is contraindicated in patients hypersensitive to it. In humans, the estolate form has been associated rarely with the development of cholestatic hepatitis. This effect has not apparently been reported in veterinary species, but the estolate should probably be avoided in patients with preexisting liver dysfunction.

Many clinicians believe that erythromycin is contraindicated in adult horses (see Adverse Effects below), and oral erythromycin should not be used in ruminants as severe diarrheas may result.

While erythromycin has not demonstrated teratogenic effects in rats and the drug is not thought to posses serious teratogenic potential, it should only be used during pregnancy when the benefits outweigh the risks.

**Adverse Effects/Warnings** - Adverse effects are relatively infrequent with erythromycin when used in small animals, swine, sheep, or cattle. When injected IM, local reactions and pain at the injection site may occur. Oral erythromycin may cause GI disturbances with diarrhea, anorexia, and vomiting occasionally seen. Rectal edema and partial anal prolapse have been associated with erythromycin in swine. Intravenous injections must be given very slowly, as the intravenous forms can readily cause thrombophlebitis. Allergic reactions can occur, but are thought to be very rare.

Oral erythromycin should not be used in ruminants as severe diarrheas may result. In foals treated with erythromycin, a mild, self-limiting diarrhea may occasionally occur. Adult horses may develop severe, sometimes fatal diarrheas from erythromycin and the use of the drug in adults is very controversial.

Erythromycin may alter temperature homeostasis in foals. Foals between the ages of 2 and 4 months old have been reported to develop hyperthermia with associated respiratory distress and tachypnea. Physically cooling off these animals is reported to be successful in controlling this effect.

**Overdosage/Acute Toxicity** - With the exception of the adverse effects outlined above, erythromycin is apparently quite non-toxic. However, shock reactions have been reported in baby pigs receiving erythromycin overdosages.

**Drug Interactions** - Because erythromycin, the **lincosamides** (**clindamycin**, **lincomycin**), and **chloramphenicol** all bind to the 50S ribosomal subunit, competition for binding can occur and some clinicians state these drugs should not be used concurrently. *In vitro* synergy with other antimicrobials (*e.g.,* sulfonamides, rifampin) has been reported with erythromycin. The concomitant use of erythromycin with bactericidal antibiotics (*e.g.,* penicillin) is controversial, but documentation of either clinical synergy, additive activity, or antagonism is apparently lacking.

To Drug Monograph Index To Ophthalmic Product Index

Decreased clearance of **theophylline** may occur with resultant toxicity in patients receiving erythromycin (particularly high dosages). Patients should be monitored for symptoms of theophylline toxicity and serum theophylline levels monitored if necessary.
Patients stabilized on **warfarin** anticoagulant therapy may develop prolonged prothrombin times and bleeding when erythromycin is added. Enhanced monitoring is recommended.
The metabolism of **methylprednisolone** may be inhibited by concurrent administration of erythromycin. The clinical significance of this interaction is unknown. Erythromycin may increase the bioavailability of **digoxin** in a small percentage of human patients and can lead to digoxin toxicity. Veterinary significance of this interaction is questionable. Interactions have also been reported with erythromycin and the following human drugs (rarely used in veterinary species—refer to other references if necessary): **carbamazepine**, **cyclosporine** (systemic), and **triazolam**.

**Drug/Laboratory Interactions** - Erythromycin may cause falsely elevated values of **AST** (SGOT), and **ALT** (SGPT) when using colorimetric assays. Fluorometric determinations of **urinary catecholamines** can be altered by concomitant erythromycin administration.

**Doses** –
**Horses**:

For treatment of *C. (Rhodococcus) equi* infections in foals:

a) Erythromycin estolate or ethylsuccinate: 25 mg/kg PO *tid* with rifampin: 5 mg/kg PO *tid*. (Hillidge and Zertuche 1987)
b) Erythromycin estolate: 25 mg/kg PO q6h
Erythromycin gluceptate: 5 mg/kg IV q4-6h (Caprile and Short 1987)
c) Erythromycin estolate: 25 mg/kg PO *qid*
Erythromycin gluceptate: 5 mg/kg IV 4-6 times daily
Erythromycin base (veterinary) injectable: 10 mg/kg IM *bid* (Prescott, Hoover, and Dohoo 1983)

For susceptible infections:

a) Erythromycin estolate: 25 mg/kg PO q6h
Erythromycin ethylsuccinate: 25 mg/kg PO q8h
Erythromycin gluceptate: 5 mg/kg IV q4-6h
Erythromycin lactobionate: 3 - 5 mg/kg IV q6-8h (Brumbaugh 1987)

**Elephants:**
There are no published pharmacokinetic studies on erythromycin (or other macrolides and lincosamides) in elephants.
a) Severe gastrointestinal pain and upset may result after only 1-2 days. Schmidt, M.J: Senior Research Veterinarian, Washington Park Zoo, Portland, Oregon, personal communication, 1986. In: Olsen,J.H., 1999. **Antibiotic therapy in elephants**. In: Fowler,M.E. and Miller R.E. (Editors), **Zoo and Wild Animal Medicine: Current Therapy 4.** W.B. Saunders, Philadelphia, PA,USA p. 538

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects (periodic liver function tests if patient receiving erythromycin estolate long-term; may not be necessary for foals receiving erythromycin and rifampin for *Rhodococcus* infections)

**Client Information** - The intramuscular 100 mg/ml (*Erythro-100*®) & 200 mg/ml products (*Erythro-200*®) have quite specific instructions on where and how to inject the drug. Refer to the label directions or package insert for more information before using.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Erythromycin 100 mg/ml for IM Injection (with 2% butyl aminobenzoate as a local anesthetic) in 100 ml vials

*Erythro-100*® (Rhone Merieux); (OTC) Approved for use in dogs, cats, cattle, sheep, and swine. Milk withdrawal = 72 hours. Slaughter withdrawal for cattle, sheep, swine = 48 hours.

Erythromycin 200 mg/ml for IM Injection in 100 ml, 250 ml, and 500 ml vials

*Erythro-200*® (Rhone Merieux); (OTC) Approved for use in cattle, sheep, and swine. Milk withdrawal = 72 hours. Slaughter withdrawal for cattle =14 days (21 days to avoid excessive trimming). Slaughter withdrawal for sheep = 3 days (10 days to avoid excessive trimming). Slaughter withdrawal for swine = 7 days (10 days to avoid excessive trimming).

Erythromycin Mastitis Infusion Tube for Dry Cows; 600 mg erythromycin per 12 ml tube

*Erythro*®*-Dry* (Rhone Merieux); (OTC) Approved for use in dry dairy cattle. Milk withdrawal = 36 hours. Slaughter withdrawal = 14 days nor within 96 hours of calving. Calves born to treated cows may not be slaughtered for food at less than 10 days of age.

Erythromycin Mastitis Infusion Tube for Lactating Cows; 50 mg/ml of erythromycin per 6 ml tube

*Erythro*®*-36* (Rhone Merieux); (OTC) Approved for use in dry dairy cattle. Milk withdrawal = 36 hours. Slaughter withdrawal = 14 days.

There are also several erythromycin premixes alone and in combination with other drugs for use in swine and/or poultry.

**Human-Approved Products**:

Erythromycin Base Oral Tablets enteric-coated 250 mg, 500 mg; *Ery-Tab*® (Abbott); *E-Mycin*® (Boots), *Robimycin*® *Robitabs*® (Robins);*E-Base*® (Barr); (Rx)

Erythromycin Base Oral Tablets film-coated 250 mg, 500 mg

*Erythromycin Film-Tabs*® (Abbott); (Rx)

Erythromycin Base Oral Capsules delayed release enteric-coated pellets 250 mg; *Eryc*® (Parke-Davis); (Rx)

Erythromycin Base Delayed Relased Tablets 333 mg, generic, (Rx)

Erythromycin Base Tablets with polymer coated particles 500 mg; *PCE Dispertab* ® (Abbott) (Rx)

Erythromycin Base Oral Capsules delayed release 250 mg; generic (Rx)

Erythromycin Estolate Tablets 500 mg (as estolate) *Ilosone*® (Dista) (Rx)

Erythromycin Estolate Capsules 250 mg (as estolate); *Ilosone Pulvules*® (Dista) (Rx); generic, (Rx)

Erythromycin Estolate Suspension: 125 mg (as estolate) per 5 ml in 480 mls and 250 mg (as estolate) per 5 ml in 100 & 480 mls; *Ilosone*® (Dista); generic, (Rx)

Erythromycin Stearate Film-coated tablets 250 mg, 500 mg; generic; (Rx)

Erythromycin Ethylsuccinate Chewable Tablets: 200 mg (as ethylsuccinate; equiv. to 125 mg of base); *EryPed*® (Abbott) (Rx)

Erythromycin Ethylsuccinate Tablets: 400 mg (as ethylsuccinate); *E.E.S. 400;* generic, (Rx)

Oral Suspension: 40 mg/ml (equiv. to 25 mg/ml base), 80 mg/ml (equiv. to 50 mg/ml base) in 100, 200, 480, and 500 ml bottles; 100 mg per 2.5 ml in 50 mls, 200 & 400 mg (as ethylsuccinate) per 5 ml in 60, 100, 200 and 480 ml and UD 5 ml (100's); *EryPed Drops*® (Abbott); *EryPed 400*® (Abbott); *E.E.S. 400*; generic (Rx)

Powder for Oral Suspension: 200 mg (as ethylsuccinate) per 5 ml when reconstituted in 100 & 200 mls ; *E.E.S. Granules*® (Abbott) (Rx)

Granules for Oral Suspension: 400 mg (as ethylsuccinate) per 5 ml when reconstituted; *EryPed Drops* ® (Abbott)

To Drug Monograph Index To Ophthalmic Product Index

Erythromycin Lactobionate Powder for Injection: 500 mg & 1 g (as lactobionate); generic (Rx)
Erythromycin Lactobionate Injection: 1 g erythromycin (as gluceptate) per vial in 30 mls; *Ilotycin Gluceptate*® (Dista) (Rx)

## ESTRADIOL CYPIONATE

**Chemistry** - Estradiol is a naturally occurring steroidal estrogen. Estradiol cypionate is produced by esterifying estradiol with cyclopentanepropionic acid, and occurs as a white to practically white, crystalline powder. It is either odorless or may have a slight odor and has a melting range of 149-153°C. Less than 0.1 mg/ml is soluble in water and 25 mg/ml is soluble in alcohol. Estradiol cypionate is sparingly soluble in vegetable oils.

**Storage/Stability/Compatibility** - Estradiol cypionate should be stored in light-resistant containers at temperatures of less than 40°C, preferably at room temperature (15-30°C); avoid freezing.

Commercially available injectable solutions of estradiol cypionate are sterile solutions in a vegetable oil (usually cottonseed oil); they may contain chlorobutanol as a preservative.
It is not recommended to mix estradiol cypionate with other medications.

**Pharmacology** - The most active endogenous estrogen, estradiol possesses the pharmacologic profile expected of the estrogen class. Estrogens are necessary for the normal growth and development of the female sex organs and in some species contribute to the development and maintenance of secondary female sex characteristics. Estrogens cause increased cell height and secretions of the cervical mucosa, thickening of the vaginal mucosa, endometrial proliferation and increased uterine tone.

Estrogens have effects on the skeletal system. They increase calcium deposition, accelerate epiphyseal closure and increase bone formation. Estrogens have a slight anabolic effect and can increase sodium and water retention.

Estrogens affect the release of gonadotropins from the pituitary gland. This can cause inhibition of lactation, inhibition of ovulation and inhibition of androgen secretion.

**Uses/Indications -** For mares, indications for the use of estradiol include, induction of estrus during the non-breeding or breeding seasons and to enhance the mare's uterine defense mechanism. Estradiol cypionate has also been used as an abortifacient agent (see warnings below) in cattle, cats and dogs.

One product (*ECP*® — Upjohn) approved for use in breeding cattle, indications listed in its package insert for use in bovine medicine include:
To correct anestrus (absence of heat period) in the absence of follicular cysts in some cases.
To treat cattle having persistent corpus luteum due to certain causes.
To expel purulent material from the uterus in pyometra of cows.
To stimulate uterine expulsion of retained placentas and mummified fetuses.

**Pharmacokinetics** - No specific information was located regarding the pharmacokinetics of estradiol in veterinary species. In humans, estrogen in oil solutions after IM administration are absorbed promptly and absorption continues over several days. Esterified estrogens (*e.g.,* estradiol cypionate) have delayed absorption after IM administration. Estrogens are distributed throughout the body and accumulate in adipose tissue. Elimination of the steroidal estrogens occurs principally by hepatic metabolism. Estrogens and their metabolites are primarily excreted in the urine, but are also excreted into the bile, where most is reabsorbed from the GI.

To Drug Monograph Index  To Ophthalmic Product Index

**Contraindications/Precautions** - Estradiol is contraindicated during pregnancy. It has been demonstrated to cause fetal malformations of the genitourinary system and to induce bone marrow depression in the fetus.

In cases of prolonged corpus luteum in cows, thorough uterine exam should be completed to determine if endometritis or a fetus is present

**Adverse Effects/Warnings** - Estrogens have been associated with severe adverse reactions in small animals; see the Adverse Effects section in the DES monograph (prior to this one) for more information.

In cattle, prolonged estrus, genital irritation, decreased milk flow, precocious development and follicular cysts may develop after estrogen therapy. These effects may be secondary to overdosage and dosage adjustment may reduce or eliminate them.

**Overdosage** - No reports of inadvertent acute overdosage in veterinary patients was located; see Adverse Effects above.

**Drug Interactions** - **Rifampin** may decrease estrogen activity if administered concomitantly. This is presumably due to microsmal enzyme induction with resultant increase in estrogen metabolism. Other known enzyme inducers (*e.g.,* **phenobarbital, phenylbutazone**, etc.), may have a similar effect, but clinical significance is unclear. Enhanced glucocorticoid effects may result if estrogens are used concomitantly with **corticosteroid agents**. It has been postulated that estrogens may either alter the protein binding of corticosteroids and/or decrease their metabolism. Corticosteroid dosage adjustment may be necessary when estrogen therapy is either started or discontinued. **Oral anticoagulant** activity may be decreased if estrogens are administered concurrently. Increases in anticoagulant dosage may be necessary if adding estrogens.

**Drug/Laboratory Interactions -** Estrogens in combination with progestins (*e.g.,* oral contraceptives) have been demonstrated in humans to increase **thyroxine-binding globulin** (TBG) with resultant increases in total circulating thyroid hormone. Decrease **$T_3$ resin uptake** also occurs, but free $T_4$ levels are unaltered. It is unclear if estradiol affects these laboratory tests.

**Doses** -
**Horses**:

For induction of estrus during the non-breeding season:

a) 10 mg estradiol cypionate will result in estrus 2-3 days after treatment (Squires and McKinnon 1987)

For induction of estrus in mares with “silent heat” during breeding season:

a) 1 mg estradiol (Squires and McKinnon 1987)

To enhance the mare’s uterine defense mechanism:

a) 1 - 2 mg estradiol daily for 3-5 days (Squires and McKinnon 1987)

**Elephants:**

a) The administration of 10 mg estradiol cypionate IM followed by the 200 IU oxytocin IV on day 15 postpartum and an additional 10 IU oxytocin the following day facilitated the removal of a retained placenta in an Asian cow. **a)** Murray,S., Bush,M., and Tell,L.A. 1996. **Medical management of postpartum problems in an Asian elephant (*Elephas maximus*) cow and calf.** Journal of Zoo and Wildlife Medicine 27:(2):255-258 **Abstract:** An 18-yr old female Asian elephant (*Elephas maximus*) gave birth to a 120-kg female calf following 22 mo of gestation. Immediately after parturition, the cow became agitated and aggressive towards the calf. Before the keepers were able to safely intervene

To Drug Monograph Index To Ophthalmic Product Index

and remove the calf, the cow stepped on the calf's head and right front leg. Within 30 min, the cow calmed down, allowing the calf's safe reintroduction under close keeper supervision and control. The cow had a retained placenta, poor mammary development, and low milk production. The calf's injuries, in combination with the cow's low milk production, impeded the calf's ability to nurse and gain weight. Within 10 days, the calf lost 10% of its weight. Serum protein electrophoresis indicated failure of passive transfer of maternal immunoglobulin. On day 10, the calf received a transfusion of concentrated immunoglobulin extracted and concentrated from the cow's previously banked plasma. On day 13, the calf developed a urinary tract infection, as diagnosed by white blood cells and bacteria in the urine. Following immunoglobulin administration and antibiotic therapy, clinical signs slowly resolved and the calf gained weight. The cow passed the fetal membranes during parturition, but the placenta was retained. Despite prophylactic systemic antibiotics and vaginal flushing, the cow became depressed and developed a leukocytosis and anemia. A mucopurulent vaginal discharge and ventral edema were noted on day 3, and milk production was minimal. Because decreased milk production has been reported as a common sequel to retained placenta, efforts were focused on removing the placenta. Intermittent oxytocin therapy on days 2-14 did not result in expulsion of the placenta and produced only transient abdominal contractions and minimal increases in milk letdown. On day 15, 10 mg estradiol cypionate was administered i.m. followed by 200 IU oxytocin i.v. (in 2 L of saline over 75 minutes). An additional 100 IU oxytocin (in 1 L of saline over 30 minutes) was administered i.v. on day 16. The friable placenta was palpable within the vaginal vault on day 17. The remaining placenta was removed by gentle traction applied by a modified weighted pressure cuff. Once the placenta was removed, the cow's clinical problems slowly resolved and the calf continued to gain weight.

**Monitoring Parameters** - When therapy is either at high dosages or chronic; see adverse effects for more information.

Done at least monthly:

1) Packed Cell Volumes (PCV)
2) White blood cell counts (CBC)
3) Platelet counts

Baseline, one month after therapy, and repeated 2 months after cessation of therapy if abnormal:

1) Liver function tests

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Estradiol Cypionate in Oil for Injection 2 mg/ml in 50 ml vials

*ECP*® (Upjohn), Generic; (Rx) Approved for use in cattle. No slaughter withdrawal times were located for these products.

**Human-Approved Products**:

Estradiol Cypionate in Oil for Injection 5 mg/ml in 5 & 10 ml vials )

Generic; Many trade names; (Rx)

## ETHAMBUTOL

The following section was authored by **Joel Maslow MD PhD MBA**

**Chemistry** – Ethambutol is a synthetic compound that occurs a white crystalline powder and is soluble in water and alcohol with pKa of 6.1 and 9.2.

To Drug Monograph Index To Ophthalmic Product Index

**Storage/Stability/Compatibility** – Ethambutol is stable at room temperature in tablet and powder form. It should be protected from light, moisture, and excessive heat.

**Mechanism of action** – The mechanism of action of ethambutol is unknown although it is considered to inhibit the biosynthesis of the mycobacterial cell wall and is bacteriostatic.

**Uses/Indications** – Ethambutol is indicated for the treatment of *M. tuberculosis* complex (*M. tuberculosis* and *M. bovis*) and *M. avium* complex (*M. avium* and *M. intracellulare*) infection. It also has activity against *M. marinum*, *M. kansasii*, and *M. fortuitum*. Ethambutol should only be used in conjunction with other anti-mycobacterial agents to avoid the development of bacterial resistance.

**Pharmacokinetics** – Ethambutol is only available for oral administration. It is absorbed well from the gastrointestinal tract with 75-80% absorption in humans. Ethambutol is distributed throughout the body. CSF distribution is minimal with non-inflamed meninges but achieves CSF concentrations 10-50% of serum levels with inflamed meninges. Ethambutol has excellent intracellular penetration.

Ethambutol is well absorbed rectally in elephants via enema dosing, however, the drug causes rectal irritation and rapid expulsion of drug and is therefore poorly tolerated by this route especially after the first dose. Ethambutol was more rapidly absorbed than oral dosing for humans (1 versus 2.5 hr, respectively) with similar peak concentrations (Cmax of 4.24 at a dose of 30 mg/kg versus 4.5 at a dose of 25 mg /kg) (Maslow JN, unpublished observations and (Peloquin, 1999)). However, for the elimination half-life was shorter for elephants than for humans (2.65 versus 12.1 hr) with a resultant lower AUC∞ (10.1 versus 28.9, respectively) (Maslow JN, unpublished observations and (Peloquin, 1999)).

Ethambutol has been successfully administered subcutaneously to bongo antelope (Auclair, 2002). A single s.c. dose of 25 mg/kg yielded a Cmax of 1.6 mcg/ml with a Tmax of 2.5 hrs, a serum half life of 2.4 hrs, and a volume of distribution of 7.3 L/kg. The pharmacokinetics in bongo was similar to rabbits, although the volume of distribution was significantly greater than for rabbits as well as humans. **Population pharmacokinetics of antituberculous drugs and treatment of *Mycobacterium bovis* infection in Bongo Antelope (*Tragelaphus eurycrus isaaci* ).** B. Auclair, S. Mikota, C. A. Peloquin, R. Aguilar and J. N. Maslow. Journal of Zoo and Wildlife Medicine 2002 Vol. 33 Issue 3 Pages 193-203.

Approximately 25% of ethambutol is metabolized to inactive metabolite, 80% of ethambutol and the inactive metabolite are excreted in the urine necessitating adjustment of dosage in renal insufficiency. Unabsorbed drug is excreted unchanged in the stool.

**Contraindications/Precautions/Reproductive Safety** – Ethambutol should be used with caution in patients with renal dysfunction.

**Ethambutol in pregnancy** – Although ethambutol has caused teratogenic effects when given in high doses to animals, the drug has been used successfully to treat active TB in humans. To date, no adverse effects related to the fetus have been reported for use in pregnancy.

**Ethambutol in children** – Ethambutol has been used to treat pediatric TB, although this is only when such treatment is carefully monitored with visual screening.

**Adverse Effects/Warnings** – The major toxicity of ethambutol is neuropathy. Retrobulbar neuropathy is the most common side effect resulting in visual field constriction and loss of color vision or loss of visual acuity. This has been observed more frequently with higher doses in humans (that should correlate with higher serum levels in animals) and is slowly reversible. Less frequent adverse effects in humans include gastrointestinal symptoms, hyperuricemia, and dermatitis, arthralgias, and fever.

To Drug Monograph Index To Ophthalmic Product Index

In elephants, ethambutol has been observed to cause rectal irritation when administered via enema causing rapid expulsion of the drug on subsequent dosing.

**Drug Interactions** –

**Doses** –
**Human dosing**:
The initial human dose of ethambutol is 25 mg/kg per day given as a single daily dose. After 2 months of treatment, this dose is decreased to 15 mg/kg day. Higher doses (50 mg/kg/day) are avoided due to retrobulbar neuritis.

**Monitoring –** The efficacy of antituberculosis drug administration should be monitored by measurement of serum concentrations. Ideally, serum concentrations should be ascertained over a range of times to determine both the pharmacokinetics (as a means to monitor total area under the curve (AUC)) and the time (Tmax) of occurrence individual peak serum concentration (Cmax). For elephants administered rectal ethambutol, peak serum concentrations occur at 1 hr. For bongo antelope levels should be determined a 2.5 hrs after subcutaneous administration. Based on studies in humans, a serum concentration of 2-6 mcg/ml is associated with therapeutic success (Peloquin, 1997).

**Elephants:**

**Pharmacokinetics of ethambutol (EMB) in elephants.** J. N. Maslow, S. K. Mikota, M. Zhu, H. Riddle and C. A. Peloquin. J Vet Pharmacol Ther 2005 Vol. 28 Issue 3 Pages 321-323

Link to full article:
https://d1wqtxts1xzle7.cloudfront.net/32372276/Maslow_PK__EMB_in_eleph_2005-libre.pdf?1391551143=&response-content-disposition=inline%3B+filename%3DPharmacokinetics_of_ethambutol_EMB_in_el.pdf&Expires=1693238376&Signature=aLk8Mk4B7gRLkpOXtURzZ-3xZIvriBX1zH8RSEw1q0ZsaOQwWnHHx7mA3jNUfA6EEwKpU954I~-kt99~MoQ0klpMmvGPxqZqwx6AIL1ZHsXwtANBAgWfLqOZ5WJcnbeAGe~MXttLU4L6z7WXigwf4JUatWnqKXJz2d0lAZARAS6Uux2Fi1WGFEBkUfAJ~kkmu0aGwlUO6dAxtDWIDXU8a18Hbli4aaC1oIRn6PTrMhnct1pY1-3-ZaZqd6zLE-4lS8jiD4FumBDF5VmKwTD0fsDrJEHDRlKnqnoPCdyJT8q28cxN~xHhAEAPK4GepjzqEOOeYi59196IaeChYPfeMQ__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA

**The pharmacokinetics of a single oral or rectal dose of concurrently administered isoniazid, rifampin, pyrazinamide, and ethambutol in Asian elephants (Elephas maximus).**
2014. A. P. Brock, R. Isaza, E. F. Egelund, R. P. Hunter and C. A. Peloquin. Journal of Veterinary Pharmacology and Therapeutics Vol. 37 Issue 5 Pages 472-479.
Accession Number: WOS:000342801400007 DOI: 10.1111/jvp.12119

Tuberculosis, caused by Mycobacterium tuberculosis, is a disease of concern in captive Asian elephants (Elephas maximus). Treatment for tuberculosis in elephants utilizes multidrug protocols combining isoniazid, rifampin, pyrazinamide, and/or ethambutol. In this study, a single, coformulated dose of isoniazid 5mg/kg, rifampin 10mg/kg, pyrazinamide 30mg/kg, and ethambutol 30mg/kg was administered orally to six Asian elephants, and rectally to five elephants using a cross-over design. Blood samples were collected serially over 24h. Pyrazinamide and ethambutol concentrations were determined using validated gas chromatography assays. Isoniazid and rifampin concentrations were determined using validated high-performance liquid chromatography assays. Rectal isoniazid produced an earlier T-max compared with oral

To Drug Monograph Index To Ophthalmic Product Index

administration. Oral isoniazid resulted in a comparatively lower C-max, but higher AUC values compared with rectal isoniazid. Oral rifampin and oral ethambutol were well absorbed while rectal rifampin was not. Oral pyrazinamide produced comparatively higher C-max and AUC values compared with rectal pyrazinamide. Results of this study indicate that currently recommended therapeutic monitoring sample collection times for rectal isoniazid and oral rifampin do not provide an accurate assessment of exposure for these drugs. This study demonstrates notable individual variability, indicating that dosing of these medications requires individual monitoring and provides additional information to guide the clinician when treating elephants.

**Serum concentrations of antimycobacterial drugs in Asian Elephants (Elephas maximus).** 2016. L. Young, S. Scott, M. Salfinger and E. Ramsay. Proc. AAZV / EAZWV / IZW Joint Conference 2016

Mycobacterium tuberculosis is an important disease of captive Asian elephants (Elephas maximus.) In this study six adult Asian elephants which had Mycobacterium tuberculosis cultured from trunk wash samples or had reactive DPP/MAPIA serologic responses were treated, concurrently, with one to three antimycobacterial drugs. Enrofloxacin hydrochloride, 2.5 mg/kg p.o., s.i.d., was administered to all animals in various foodstuffs for 9-15 mo. Serum enrofloxacin concentrations ranged from 230-2380 µg/ml (targeted concentrations = 125-1000 µg/ml).1 Pyrazinamide (PZA), 30 mg/kg p.o., s.i.d., was administered to five elephants in various foodstuffs for 9-12 mo. Serum PZA concentrations ranged from 26-57 µg/ml (targeted concentrations = 20- 60 µg/ml).2 **Ethambutol (EMB**), 30 mg/kg p.o., s.i.d., was administered to one elephant for 12 mo. **A serum EMB concentration of 4.07 µg/ml was achieved (targeted concentration = 2-6 µg/ml).**2 Rifampin (RIF), 10 mg/kg p.o., s.i.d., was administered to one elephant for 9 mo. A serum RIF concentration of 16 µg/ml was achieved (targeted concentration = 8-24 µg/ml). All elephants were monitored for adverse clinical effects throughout treatments. Notable side effects were limited to excess, foamy lacrimation, believed to have occurred secondary to PZA administration. Clinical chemistries and complete blood counts were monitored in all animals and values remained within reference intervals throughout treatments. This study shows antimycobacterial drug dosages may require individuation, but concurrent, long-term, multidrug regimens for the treatment of Mycobacterium tuberculosis in Asian elephants can achieve appropriate therapeutic levels with minimal detrimental side effects.

Also see:
Using therapeutic drug monitoring to dose the antimycobacterial drugs. C. Peloquin.
Clinics in Chest Medicine 1997 Vol. 18 Pages 79-97

Clinical pharmacology of the anti-tuberculoisis drugs. C. A. Peloquin.In: Clinical Tuberculosis, edited by P. D. O. Davies. Arnold Publishers 2003

Tuberculosis treatment protocols and complications for elephants. G. Dumonceaux and S. Mikota. Proceedings International Elephant Conservation and Research Symposium 2006 Pages 84-85. Request full paper from smikota@elephantcare.org.

**Monitoring –** The efficacy of antituberculosis drug administration should be monitored by measurement of serum concentrations. Ideally, serum concentrations should be ascertained over a range of times to determine both the pharmacokinetics (as a means to monitor total area under the curve (AUC)) and the time (Tmax) of occurrence individual peak serum concentration (Cmax). For elephants administered rectal ethambutol, peak serum concentrations occur at 1 hr. For bongo antelope levels should be determined a 2.5 hrs after subcutaneous administration. Based on studies in humans, a serum concentration of 2-6 mcg/ml is associated with therapeutic success (Peloquin, 1997).

## ETORPHINE HYDROCHLORIDE

To Drug Monograph Index To Ophthalmic Product Index

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

**SPECIAL NOTE REGARDING ETORPHINE:** Opioid narcotics elevate blood pressure and have been implicated in the etiology of pink foam syndrome in wild African elephants. This emergency situation can be fatal. The syndrome manifests as pink froth from the trunk and is caused by pulmonary edema and capillary bleeding. Several authors recommend that azaperone be combined with opioid narcotics to counteract these hypertensive effects (see Hattingh and Knox, 1994 below). See azaperone monograph for further information.

**Elephant doses:**
a) African elephants: 0.003 mg/kg etorphine; antagonize with 3 mg diprenorphine per mg etorphine given; Asian elephants: 0.003 mg/kg; supplement with 2 mg etorphine as needed to maintain immobilization; antagonize with 0.012 mg/kg diprenorphine. Kreeger,T.J., Arnemo,J.M., and Raath,J.P., 2002. **Handbook of wildlife chemical immobilization**. Wildlife Pharmaceuticals Inc., Fort Collins, Colorado, U.S.A., pp. 183-184

b) 1 mg/1000kg IM for recumbency and surgical anesthesia in captive Asian elephants. Nayar,K.N.M., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Management of surgical affections in captive elephants**. Journal of Indian Veterinary Association Kerala 7:(3):55-59

c) 12 mg etorphine and 150 mg azaperone for capture of wild African elephant bulls. See original work for cow and juvenile doses. The author notes that old females and lactating females tend to recycle etorphine and should be reversed first prior to loading and transfer. du Toit,J.G., 2001. **Veterinary Care of African Elephants**. Novartis, Pretoria, Republic of South Africa, 1-59 pp

d) Five adult female wild African elephants (approx. 3000-3500kg) were immobilized with 10 or 12 mg (28-40 µg/kg) etorphine and reversed with 1000 or 1200 mg naltrexone (100 times the etorphine dose). (Horne et.al. 2001). Horne,W.A., Tchamba,M.N., and Loomis,M.R. 2001. **A simple method of providing intermittent positive-pressure ventilation to etorphine-immobilized elephants (Loxodonta africana) in the field**. Journal of Zoo and Wildlife Medicine 32:(4):519-522 **Abstract:** Five African elephants (Loxodonta africana) were immobilized with etorphine in Waza National Park, Cameroon, for the purpose of deploying radio/satellite tracking collars. A portable ventilator constructed from two high-flow demand valves and the Y-piece of a large animal anesthesia circuit was used to provide intermittent positive-pressure ventilation with 100% oxygen. Oxygenation status improved dramatically in all five elephants. In one hypoxemic elephant, arterial PaO2 increased from 40 to 366 mm Hg. The results of this study demonstrate that both oxygenation and ventilation can be readily controlled in etorphine-immobilized elephants even under remote field conditions.

e,f) A 2817 kg female Asian elephant was induced with 1.75 mg etorphine IM, followed by 0.75 mg etorphine at 40 minutes. The elephant was intubated with a 30 mm endotracheal tube and maintained with 1.5-2.0% isoflurane. Additional etorphine (total additional 1.4 mg) was supplemented IV during the procedure to surgically remove P-3. Thirty minutes prior to the completion of the procedure isoflurane was discontinued, but oxygen continued to flow. Additional etorphine was given intermittently IV (0.4 mg total) during the remaining 45 minutes of recumbency. Naltrexone (250 mg) was given IV and the elephant was standing within 3 minutes. Fowler,M.E., Steffey,E.P., Galuppo,L., and Pascoe,J.R. 2000. **Facilitation of Asian elephant (Elephas maximus) standing immobilization and anesthesia with a sling**. Journal of Zoo and Wildlife Medicine 31:(1):118-123 **Abstract:** An Asian elephant (Elephas maximus) required general anesthesia for orthopedic foot surgery. The elephant was unable to lie down, so it was placed in a custom-made sling, administered i.m. etorphine

To Drug Monograph Index To Ophthalmic Product Index

hydrochloride in the standing position, and lowered to lateral recumbency. General anesthesia was maintained with isoflurane administered through an endotracheal tube. After surgery, the isoflurane anesthesia was terminated, with immobilization maintained with additional i.v. etorphine. The elephant was lifted to the vertical position, and the immobilizing effects of etorphine were reversed with naltrexone. The suspension system and hoist for the sling were designed specifically for the elephant house. f) Fowler,M.E., Steffey,E.P., Galuppo,L., and Pascoe,J.R. 1999. **Standing immobilization and anesthesia in an Asian elephant (*Elephas maximus*)**. Proc. Am. Assoc. Zoo Vet. Pages: 107-110

g) For capture of adult, wild African elephants, etorphine in combination with azaperone as follows (the peripheral vasodilation effects of azaperone help to reduce the hypertension caused by the narcotic) :
adult females: 12 mg etorphine and 100 mg azaperone
adult males: 15 mg etorphine and 200 mg azaperone
For captive elephants, reduce dosage by 25 %.

For capture of wild African calves, etorphine in combination with azaperone according to shoulder height as follows:
Shoulder height 90 – 115 cm: 2 mg etorphine and 20 mg azaperone
Shoulder height 116 – 140 cm: 5 mg etorphine and 50 azaperone
Shoulder height 141 – 165 cm: 7 mg etorphine and 70 mg azaperone
Shoulder height 166 – 200 cm: 9 mg etorphine and 90 mg azaperone
For captive elephants, reduce dosage by 25 %

To reverse the effects of etorphine, give diprenorphine IV as a single bolus at three times the etorphine dose. Raath,J.P., 1999. **Relocation of African elephants**. In: Fowler,M.E. and Miller,R.E. (Editors), Zoo and Wild Animal Medicine: Current Therapy 4. W.B. Saunders, Philadelphia, PA, USA pp. 525-533

h) Following premedication with 120 mg azaperone, two 5-year-old African elephants were given 1 mg etorphine IM as a “walking dose,” and 2 mg etorphine to induce anesthesia. Stegmann,G.F. 1999. **Etorphine-halothane anaesthesia in two five-year-old African elephants (Loxodonta africana)**. Journal of the South African Veterinary Medical Association 70:(4):164-166 **Abstract:** Anaesthesia of 2 five-year-old female African elephants (Loxodonta africana) was required for dental surgery. The animals were each premedicated with 120 mg of azaperone 60 min before transportation to the hospital. Before offloading, 1 mg etorphine was administered intramuscularly (i.m.) to each elephant to facilitate walking them to the equine induction/recovery room. For induction, 2 mg etorphine was administered i.m. to each animal. Induction was complete within 6 min. Surgical anaesthesia was induced with halothane-in-oxygen after intubation of the trunk. During surgery the mean heart rate was 61 and 45 beats/min respectively. Systolic blood pressures increased to 27.5 and 25.6 kPa respectively, and were treated with intravenous azaperone. Blood pressure decreased thereafter to a mean systolic pressure of 18.1 and 19.8 kPa, respectively. Rectal temperature was 35.6 and 33.9 degrees C at the onset of surgery, and decreased to 35.3 and 33.5 degrees C, respectively, at the end of anaesthesia. Etorphine anaesthesia was reversed with 5 mg diprenorphine at the completion of 90 min of surgery.

i,n) Twenty free-ranging adult wild African elephants in northern Botswana were immobilized with a mean (±SD) of 9.5 ± 0.5 mg etorphine hydrochloride and 2000 IU hyaluronidase by i.m. dart and recovered uneventfully following reversal with diprenorphine at 23.3±1.5 mg IV and 11.7±0.5 mg IM or 24 mg all IV. Osofsky,S.A. 1997. **A practical anesthesia monitoring protocol for free-ranging adult African elephants (Loxodonta africana)**. Journal of Wildlife Diseases 33:(1):72-77
**Abstract:** Twenty free-ranging adult African elephants in northern Botswana were immobilized with a mean (± SD) of 9.5 ± 0.5 mg etorphine hydrochloride and 2000 IU hyaluronidase by i.m. dart. The mean time to recumbency was 8.7 ± 2.4 min. All animals were maintained in lateral recumbency. The anaesthesia monitoring protocol included cardiothoracic auscultation; palpation of auricular pulse for quality and regularity; checking of rectal temperature, and monitoring of respiratory and heart rates. Results of basic physiological measurements were similar to those of previous field studies of African elephants immobilized

To Drug Monograph Index To Ophthalmic Product Index

with etorphine or etorphine-hyaluronidase. In addition, continuous real-time pulse rate and percent oxygen saturation of haemoglobin ($SpO_2$) readings were obtained on 16 elephants with a portable pulse oxygen meter. Duration of pulse oximetry monitoring ranged from 3 to 24 min (mean ±SD = 8.2 ± 4.8 min). Differences between minimum and maximum $SpO_2$ values for any given elephant ranged from 1 to 6 percentage points, evidence for relatively stable trends. The SpO2 readings ranged from 70% to 96% among the 16 elephants, with a mean of 87.3 ± 2.8%. 15 of 16 elephants monitored with a pulse oximeter had mean $SpO_2$ values ≥ 81 ± 2.4%, with 11 having mean $SpO_2$ values ≥ 85 ± 1.5%. All 20 animals recovered uneventfully following reversal: diprenorphine at 23.3 ± 1.5 mg (IV) with 11.7 ± 0.5 mg IM, or 24 mg diprenorphine given all IV. Osofsky,S.A. 1995. **Pulse oximetry monitoring of free-ranging African elephants (*Loxodonta africana*) immobilized with an etorphine/hyaluronidase combination antagonized with diprenorphine.** Joint Conference AAZV/WDA/AAWV. Pages: 237-277

j) Etorphine (7-15 mg) was combined with azaperone (60-100 mg) and hyaluronidase 1500-3000 IU) in a translocation operation of 26 wild African elephants in central Kenya. Induction time was 7-15 minutes. Five elephants died from metabolic changes unrelated to drugs doses administered. Njumbi,S.T., Waithaka,J., Gachago,S., Sakwa,J., Mwathe,K., Mungai,P., Mulama,M., Mutinda,H., Omondi,P., and Litoroh,M. 1996. **Translocation of elephants: the Kenyan experience**. Pachyderm 22:61-65. Author's (Mikota) note: hyalase is incorrectly described as a tranquilizer in this article.

k) For capture of wild African elephants ≤ 600 kg: etorphine 0.35 ± 0.13 µg/(kg/min) and azaperone 3.11 ± 1.10 µg/(kg/min). For capture of wild African elephants > 600 kg: etorphine 0.23 ± 0.09 and azaperone 2.01 ± 0.8 µg/(kg/min) Note: Total doses of etorphine and azaperone [µg/(kg/min)] were calculated as a sum of the induction (dart) dose and any following supplements divided by the elephant's body mass and calculated anesthetic/recumbent time. Body mass of smaller elephants was determined by weighing. Body mass of larger elephants (>1000 kg) was estimated from shoulder height. Still,J., Raath,J.P., and Matzner,L. 1996. **Respiratory and circulatory parameters of African elephants (Loxodonta africana) anesthetized with etorphine and azaperone**. Journal of the South African Veterinary Medical Association 67:(3):123-127 **Abstract:** Respiratory rate, heart rate, blood-gas tensions ($PO_2$ and $PCO_2$) and pH of arterial (a) and peripheral venous (v) blood, concentration of haemoglobin in arterial blood (Hb), saturation of arterial haemoglobin with oxygen and the end-expiratory concentration of oxygen were measured in 22 juvenile African elephants anaesthetized with etorphine and azaperone during 35 to 65 min after they assumed lateral recumbency. Based on these parameters the alveolar-arterial and arterial-peripheral venous differences of $PO_2$ [$P(A\text{-}a)O_2$ and $P(a\text{-}v)O_2$, respectively], and oxygen content of arterial blood ($CaO_2$) were calculated. Elephants with body mass of ≤ 600 kg showed significant changes in the following parameters compared with elephants with a body mass of more than 600 kg (x ± SD) : $PO_2$ (64 ± 11 compared with 82 ± 8 mmHg), $P(a\text{-}v)O_2$ (9 ± 5 compared with 22 ± 9 mmHg), P(A-a)O2 (37 ± 16 compared with 15 ± 8 mmHg) and Hb (148 ± 20 compared with 130 ± 10 g/litre) ($p< 0.05$). These findings suggested a tendency towards impaired oxygen exchange in the lungs, reduced peripheral extraction of oxygen and elevated oxygen-carrying capacity of arterial blood in smaller elephants. These changes were theoretically attributed to the respiratory-depressant and sympathomimetic effects of higher dosages of etorphine used in the smaller elephants to maintain a clinically acceptable anaesthetic plane. Individual elephants spent 35 to 150 min under anaesthesia and all recovered uneventfully after reversal of etorphine with diprenorphine.

l) Immobilon® (etorphine + acepromazine): 1mg/450 kg IM for captive Asian elephants. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants** . In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

m) For immobilization of captive Asian elephants: 0.002-0.004 mg/kg (6-20 mg total dose); For immobilization of captive African elephants: 0.0015-0.0030 mg/kg (4-20 mg total dose). Fowler,M.E., 1995. **Elephants**. In: Restraint and handling of wild and domestic animals. Iowa State University Press, Ames, Iowa, USA pp. 265-269

To Drug Monograph Index To Ophthalmic Product Index

n) see i above

o) Eight African elephants were immobilized with etorphine at a dosage of 3.2 ± 0.5 µg/kg IM. Schumacher,J., Heard,D.J., Caligiuri,R., Norton,T., and Jacobson,E.R. 1995. **Comparative effects of etorphine and carfentanil on cardiopulmonary parameters in juvenile African elephants (*Loxodonta africana*).** Journal of Zoo and Wildlife Medicine 26:(4):503-507
**Abstract:** Fourteen African elephants (Loxodonta africana) were immobilized with either etorphine hydrochloride (3.2 ± 0.5 µg/kg i.m.) or carfentanil citrate (2.4 µg/kg i.m.). Induction time with etorphine was significantly longer (30 ± 21 min) than with carfentanil (8 ± 2 min). Immediately following immobilization all elephants were placed in lateral recumbency and respiratory rate, heart rate, and rectal body temperature were monitored every 5 min throughout the immobilization period. Arterial blood samples, collected from an auricular artery, were taken 10 min after immobilization and every 15 min thereafter for up to 1 hr. At the first sampling, mean values for arterial blood gas variables for etorphine immobilized elephants were pHa, 7.29 ± 0.03; $PaCO_2$, 53.4 ± 5.2 mmHg; $PaO_2$, 71.8 ± 13.8 mmHg; standard base excess (SBE), -1.6 ± 2.9 mEq/L; and HCO3, 25.7 ± 2.7 mEq/L. After 1 hr of immobilization, mean arterial blood gas values were pHa, 7.32 ± 0.06; $PaCO_2$ , 57.2 ± 9.6 mm Hg; and $PaO_2$ , 53.8 ± 10.5 mm Hg; SBE, 2.7 ± 1.4 mEq/L; and $HCO_{3-}$, 30.6 ± 1.6 mEq/L.

For carfentanil immobilized elephants, blood gas values at the first time of collection were pHa, 7.28 ± 0.04; $PaCO_2$, 52.1 ± 2.8 mmHg; $PaO_2$, 78.3 ± 14.7 mmHg; SBE, -2.3 ± 24 mEq/L; and $HCO_{3-}$, 24.3 ± 2.1 mEq/L. Sixty minutes after the first sampling, blood gas values of one elephant were pHa, 7.38; $PaCO_2$, 48.7 mmHg; $PaO_2$, 52 mmHg; SBE, 3.4 mEq/L, and $HCO_{3-}$, 28.8 mEq/L. Over time there was a progressive decline in arterial PO2 in all elephants. It is concluded that elephants immobilized with either etorphine HCl or carfentanil developed hypoxemia ($PaO_2$ < 60 mmHg) after 30 min of immobilization. It is recommended that the administration of one of these opioid drugs be accompanied by supplemental oxygen, or followed by an inhalant anesthetic in 100% oxygen for prolonged procedures. Diprenorphine or nalmefene reversal was rapid and uneventful in both the etorphine and carfentanil group. No cases of renarcotization were noted. **Additional excerpt:** All elephants in the etorphine group (n=8) received diprenorphine at a mean dosage of 8.3 ± 1.1 µg/kg IV. Two elephants in the carfentanil group (n=6) were administered diprenorphine at a dosage of 8.9 µg/kg IV and IM. Three elephants in this group received nalmefene hydrochloride. One of the three elephants was given nalmefene 166.7 µg/kg both IV and SC. Two of the three elephants were given nalmefene IV and IM. The dosage was 88.9 µg/kg IV and IM in one elephant and 53.3 µg/kg IV and IM in the other. One elephant in the carfentanil group was administered nalmefene (88.9 µg/kg IV) followed by diprenorphine (8.9 µg/kg IM).

p) Six adult, male wild African elephants (bodyweight approximately 5000 kg) were immobilized, with 8 mg etorphine (M99) for semen collection by electroejaculation. Hattingh,J., Knox,C.M., and Raath,J.P. 1994. **Arterial blood pressure of the African elephant (Loxodonta africana) under etorphine anaesthesia and after remobilisation with diprenorphine**. Veterinary Record 135:(19):458-459 **Abstract:** Six adult, male elephants (bodyweight approximately 5000 kg) were immobilized, with 8 mg etorphine (M99) for semen collection by electroejaculation. Before electrostimulation (about 10 minutes after the elephants initially became recumbent) their mean arterial pressure was 186 ± 25 mm Hg. During the electrostimulation procedure to which each elephant was subjected intermittently over a period of about 20 minutes using a rectal probe, the mean was 263 ± 30 mm Hg. After 10 to 15 minutes stabilization, 26 mg diprenorphine (M50/50) was administered i.v. The elephants adopted a rocking motion in an attempt to stand up. This motion was accompanied by wide fluctuations in arterial pressure which peaked at 245 ± 19 mm Hg immediately before they rose. Arterial pressure subsequently decreased to a mean of 200 ± 28 mgHg once they were standing. Since these values were higher than that previously observed in standing, conscious elephants (145 ± 3 mmHg) it appears the standing, remobilized elephants in this study were hypertensive. Possible reasons for this are discussed. It is suggested that in view of the observed and possible detrimental increase in arterial pressure during electrostimulation simultaneous blood pressure monitoring should be carried out when this procedure is employed.

To Drug Monograph Index  To Ophthalmic Product Index

q) Etorphine in combination with azaperone to reduce blood pressure Hattingh,J. and Knox,C.M. 1994. **Arterial blood pressure in anesthetized African elephants**. South African Journal of Wildlife Research 24:(1/2) **Abstract:** A number of elephants previously captured in the Krueger National Park developed a pink frothy discharge from the external nares. Some of these elephants subsequently died and histopathological examinations indicated severe lung oedema. In view of the current hypothesis that high blood pressure could be a causative factor, arterial blood pressure was measured in elephants immobilized with etorphine alone (n=71) and with etorphine/azaperone (n=109) and with carfentanil/azaperone (n=26) mixtures. Arterial pressure was found to be significantly lower in the groups immobilized with azaperone mixtures than in the group immobilized with etorphine alone ($p < 0.05$). In addition, no cases of lung oedema were observed in animals immobilized with etorphine/azaperone and carfentanil/azaperone mixtures. It is strongly recommended, therefore, that azaperone be added to immobilization mixtures when elephants are subjected to herding prior to darting. Additional excerpt: all elephants in this study were juveniles 200 to 1300 kg. Group 1 (n=71) was immobilized with 4-8 mg etorphine; group 2 (n=109) was immobilized with 4-8 mg etorphine and 50-90 mg azaperone; and group 3 (n=26) was immobilized with 4-8 mg carfentanil and 50-90 mg azaperone.

r) Sixteen adult female free-ranging African elephants were immobilized with 11.6 ± 0.3 mg of etorphine (M99) mixed with a standard dose of hyaluronidase (4500 IU). The 16 elephants were reimmobilized again using higher doses of etorphine (standardized at 15 mg total dose) with hyaluronidase (4500 IU). Kock,M.D., Martin,R.B., and Kock,N. 1993. **Chemical immobilization of free-ranging African elephants (Loxodonta africana) in Zimbabwe, using etorphine (M99) mixed with hyaluronidase, and evaluation of biological data collected soon after immobilization**. Journal of Zoo and Wildlife Medicine 24:(1):1-10 **Abstract:** Sixteen adult female free-ranging elephants were immobilized in July 1990, using a mean (±SE) dose per animal of 11.6 ± 0.3 mg of etorphine (M99) mixed with a standard dose of hyaluronidase (4500 IU), at the Sengwa Wildlife Research Area, Zimbabwe, to attach telemetry and infrasound detection collars. The 16 elephants were reimmobilized in December 1990, using higher doses of etorphine (standardized at 15 mg total dose) with hyaluronidase (4500 IU), to remove the collars. The higher doses of etorphine produced more rapid inductions. Biological data were collected on both occasions. Significant differences in selected measures indicative of stress, including lactic dehydrogenase and aspartate transaminase, were seen between immobilizations. Comparisons were made of selected health measures between samples collected in the early winter and late winter/early spring season. Significant differences were seen with total protein, albumin, urea nitrogen, creatinine, calcium, magnesium, inorganic phosphorus, chloride, and alanine transaminase.

s) Adult male African elephants: 6-20 mg; adult female African elephants: 4-15 mg. Use lower range doses for elephants under controlled conditions and higher range doses for elephants that are excited, angry, or exerted. The addition of hyaluronidase (4500 IU total dose) is recommended to reduce induction time. The average induction time in free-ranging elephants with doses of 14 mg (females) and 20 mg (males) is 5.38 minutes (range 3.15-10.4 minutes).
Reverse with diprenorphine at 4 times the etorphine dose in mg. The average recovery time is 3 minutes. Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants**. In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441

t) For adult wild African bull elephants: 16 mg etorphine (reverse with 48 mg diprenorphine); for adult cows: 12 mg etorphine (reverse with 36 mg diprenorphine). Raath,J.P., 1993. **Chemical capture of the African elephant**. In: The Capture and care manual : capture, care, accommodation and transportation of wild African animals. Pretoria : Wildlife Decision Support Services : South African Veterinary Foundation, Pretoria pp. 484-511

u) For the capture of wild Asian elephants: adult elephants weighing 4 to 4.5 tons require an average of 6.75 mg etorphine; subadult elephants weighing 2.5 to 3.0 tons may require 6 mg. Can use in combination with acepromazine (Immobilon®). Induction time is 10-12 minutes but will be delayed if injection is SC.

To Drug Monograph Index To Ophthalmic Product Index

Appayya,M.K. and Khadri,S.S.M.S., 1992. **Chemical capture of wild elephants and their translocation carried out in Karnataka state**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 107-112

v) Can be combined with hyaluronidase to reduce induction time (see hyaluronidase monograph for doses). Hyaluronidase activity remains high for at least 48 hr, provided storage temperatures can be maintained at ≤ 30°C. Storage at ≥ 40°C is associated with rapid loss of enzyme activity. Morton,D.J. and Kock,M.D. 1991. **Stability of hyaluronidase in solution with etorphine and xylazine**. J.Zoo and Wildlife Medicine 22:(3):345-347 **Abstract:** During capture of free-living wildlife, stress is potentially the greatest problem encountered. For this reason, reduction in induction time during immobilization is of paramount importance. Hyaluronidase reduces induction times, although no reports have assessed stability of the enzyme in drug mixtures used for chemical capture. This report presents information on the stability of hyaluronidase in combination with etorphine and xylazine, one of the most common drug mixtures used in chemical immobilization of wildlife. Hyaluronidase activity remains high for at least 48 hr, provided storage temperatures can be maintained at less than or equal to 30º C. Storage at greater than or equal to 40ºC is associated with rapid loss of enzyme activity in the mixture.

w) One African elephant was premedicated with an IM combination of 0.27 mg/kg ketamine and 0.23 mg/kg xylazine followed 20 minutes later by 0.9 µg/kg etorphine IV and then halothane. Two elephants weighing 900 and 3000 kg were trained to lay in lateral recumbency and were given etorphine (mean dose 2.2 µg/kg) IV. One elephant was intubated and maintained with halothane and the other was maintained by repeated administration of IV etorphine. Two elephants weighing 750 and 1500 kg received 3.3 µg/kg etorphine IM and following immobilization were intubated and maintained with halothane Welsch,B., Jacobson,E.R., Kollias,G.V., Kramer,L., Gardner,H., and Page,C.D. 1989. **Tusk extraction in the African elephant (*Loxodonta africana*)**. Journal of Zoo and Wildlife Medicine 20:(4):446-453 **Abstract:** Unilateral dentoalveolar abscesses and/or tusk fractures were identified and tusk extractions performed in seven 3.5-21-yr-old African elephants (*Loxodonta africana*) of both sexes weighing 650-3,000 kg. Following immobilization with etorphine hydrochloride or carfentanil citrate, six of seven elephants were intubated and maintained on a 1-1.5% halothane in oxygen mixture; one elephant was maintained in lateral recumbency by multiple i.v. injections of etorphine. All elephants were positioned with the affected tusk up. For one elephant, two surgical procedures were required to remove the tusk. In six of seven elephants, the tusks were sectioned transversely and the tusk wall thinned by enlarging the pulp cavity with carbide burs. In those tusks with remaining pulp, the pulp was removed with stainless steel rods and hooks. Next, the tusk was sectioned longitudinally into three or four segments using a wood saw within the pulp chamber. bone gouges, osteotomes, and a mallet were used to free the outer epithelial and alveolar attachments from the tusk. Starting with the smallest segment, the sections were removed using long screwdriver-shaped stainless steel rods. The alveolar chamber was then periodically flushed postsurgically with a dilute organic iodine solution. For six of seven elephants, complete granulation of the alveolar chamber was evident by 4 mo postsurgery; the seventh elephant showed partial healing with granulation tissue at 2 mo following surgery.

x) Sixteen 3- to 5-year-old African elephants were anesthetized one or more times for a total of 27 diagnostic and surgical procedures. Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing juvenile elephants during a 45-minute transport period before administration of general anesthesia. After IM or IV administration of etorphine (1.9 ± 0.56 micrograms/kg), the mean time to lateral recumbency was 20 ± 6.6 and 3 ± 0.0 minutes, respectively. Heard,D.J., Kollias,G.V., Webb,A.I., Jacobson,E.R., and Brock,K.A. 1988. **Use of halothane to maintain anesthesia induced with etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 193:254-256 **Excerpts:** Sixteen 3- to 5-year-old African elephants were anesthetized one or more times for a total of 27 diagnostic and surgical procedures. Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM

To Drug Monograph Index To Ophthalmic Product Index

induced good chemical restraint in standing juvenile elephants during a 45-minute transport period before administration of general anesthesia. After IM or IV administration of etorphine (1.9 ± 0.56 micrograms/kg), the mean time to lateral recumbency was 20 ± 6.6 and 3 ± 0.0 minutes, respectively. The mean heart rate, systolic blood pressure, and respiration rate during all procedures was 50 ± 12 beats/min, 106 ± 19 mm of Hg, and 10 ± 3 breaths/min, respectively.

Cardiac arrhythmias were detected during 2 procedures. In one elephant paroxysmal ventricular tachycardia was detected and the procedure terminated when the arrhythmia failed to stabilize after multiple doses of lidocaine (1 mg/kg, IV). In another elephant, second degree atrioventricular block returned to normal sinus rhythm after IV administration of atropine (0.04 mg/kg).

In one elephant, low mean blood pressure (54 mm of Hg) responded to reduction in halothane (vaporizer setting 1 to 0.75%) and slow infusion of dobutamine HCl ((250 mg/1,000 ml) given to effect. The systolic blood pressure increased to 90 mm of Hg and remained high with a continuous infusion of dobutamine (5 µg/kg/min).

Immediately after induction in another elephant, profound respiratory depression (< 1 breath / minute) and palpably weak arterial pulse were identified. Intravenous administration of diprenorphine at half the recommended reversal dose resulted in improvement of respiration and palpable arterial pulse, without the elephant developing signs of complete anesthetic reversal.

Alterations in systolic blood pressure, ear flapping, and trunk muscle tone were useful for monitoring depth of anesthesia. Results indicated that halothane in oxygen was effective for maintenance of surgical anesthesia in juvenile African elephants after induction with etorphine. in performing major invasive surgical procedures in African elephants. Note: A correction appeared in a later volume 193(6): p.721.

y) Fourteen African elephants were immobilized with etorphine (2.9 ± 0.7 µg/kg) and physiological effects compared. Jacobson,E.R., Heard,D.J., Caligiuri,R., and Kollias,G.V. 1987. **Physiologic effects of etorphine and carfentanil in African elephants**. Proc.1st.Intl.Conf.Zool.Avian Med. Pages: 525-527
**Abstract:** (Full text): The effects of etorphine hydrochloride and carfentanil citrate on blood pressure, heart rate, respiration and body temperature were determined in a group of captive African elephants (Loxodonta africana). Fourteen African elephants, weighing 450 kg to 4000 kg, divided into 2 groups of 6 and 8 elephants each, received either etorphine hydrochloride (2.9 ± 0.7 µg/kg of body weight; mean ± SD) or carfentanil citrate (2.0 ± 0.2 µg/kg of body weight) respectively. The mean time for lateral recumbency in elephants which received etorphine was 31 ± 9.1 minutes while the mean time for lateral recumbency in elephants which received carfentanil was 10.3 ± 4.1 minutes. Following immobilization, a 18 gauge catheter was inserted into an auricular artery, the catheter connected to a pressure transducer system and systolic, diastolic, and mean arterial pressures were monitored by use of a multichannel oscilloscope. Systolic, diastolic, mean arterial pressures, heart rate, respiration, and temperature were recorded every 5 minutes over a 45 to 60 minute period. Elephants were maintained in lateral recumbency over the period of monitoring by intravenous injections of either etorphine or carfentanil.

Following immobilization with etorphine, mean physiological values for elephants were: systolic pressure, 229 ± 33 mm Hg; diastolic pressure, 141 ± 30 mm Hg; mean arterial pressure, 177 ± 30 mm Hg; heart rate 64 ± 10 beats/minute; respiratory rate 10 ± 4 breaths/minute; body temperature, 97 ± 2°F. Mean physiological values at the final time period of monitoring prior to antagonism were: systolic pressure, 217 ± 40 mm Hg; diastolic pressure, 147 ± 36 mm Hg; mean arterial pressure, 176 ± 38mm Hg; heart rate 77 ± 13 beats/minute; respiratory rate 12 ± 1 breaths/minute; body temperature, 98 ± 2°F. Immediately following the last recording, all 8 elephants received the experimental opioid antagonist, nalmefene hydrochloride, administered at 38 ± 11 µg/kg of body weight given both subcutaneously and intravenously. The mean standing time following administration of nalmefene was 1.4 ± 0.7 minutes.

To Drug Monograph Index To Ophthalmic Product Index

Immediately following immobilization with carfentanil, mean physiological values for elephants were: systolic pressure, 232 ± 28 mm Hg; diastolic pressure, 148 ± 14 mm Hg; mean arterial pressure, 183 ± 24 mm Hg; heart rate 57 ± 11 beats/minute; respiratory rate 11 ± 3 breaths/minute; body temperature, 99 ± 1°F. Mean physiological values at the final time period of monitoring prior to antagonism were: systolic pressure, 224 ± 29 mm Hg; diastolic pressure, 146 ± 13 mm Hg; mean arterial pressure, 179 ± 18mm Hg; heart rate 65 ± 11 beats/minute; respiratory rate 12 ± 1 breaths/minute; body temperature, 99 ± 1°F. Immediately following the last recording, all 6 elephants received the opioid antagonist, nalmefene hydrochloride administered at 62 ± 17 µg/kg of body weight given both subcutaneously and intravenously. The mean standing time following administration of nalmefene was 2.6 ± 1.6 minutes.

The results of this study indicated that both etorphine and carfentanil resulted in high blood pressure over the duration of the period of monitoring. Based upon these findings, both etorphine hydrochloride and carfentanil citrate are not recommended as the primary agent

z) Serum etorphine levels were measured in 11 African elephants Jacobson,E.R., Chen,C.-L., Gronwall,R., and Tiller,A. 1986. **Serum concentrations of etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 189:(9):1079-1081 **Abstract:** Eleven juvenile African elephants were given etorphine hydrochloride (2.19 + 0.11 micrograms/kg body weight, mean +SD) as a single IM injection; 3 elephants were given additional etorphine (0.42+0.09) IV. After immobilization, each elephant was maintained in lateral recumbency by administration of a 0.5% halothane/oxygen mixture or by administration of multiple IV injections of etorphine. At postinjection hours 0.25 and 0.5 and at 30-minute intervals thereafter, blood samples were collected via an auricular artery, and serum concentrations of etorphine were determined by use of radioimmunoassay. The highest mean serum concentration of etorphine in 6 elephants given a single IM injection and subsequently maintained on halothane and oxygen was 1.62+0.97 ng/ml at postinjection hours 0.5; thereafter, the mean serum concentration decreased steadily. In 4 elephants maintained in lateral recumbency with multiple IV administrations of etorphine, a correlation was not found between the time to develop initial signs of arousal and serum concentrations of etorphine before arousal. After administration of the initial immobilizing dose of etorphine, the interval between successive IV administrations of etorphine decreased.

aa) 1 mg/450 kg for Asian elephants IV or IM; 1 mg/600 kg for African elephants IV or IM. Reverse with 2 mg diprenorphine for every mg of etorphine. It is better to overdose with etorphine than to underdose. Schmidt,M.J., 1986. **Proboscidea (Elephants)**. In: Fowler,M.E. (Editor), Zoo and wild animal medicine. W.B. Saunders, Philadelphia,PA, USA pp. 884-923

bb) An Asian bull in musth (estimated weight 4500 kg) was immobilized six times. Three drugs were used either alone or in combination. A mixture of etorphine and acetylpromazine (Immobilon®) was used effectively on three occasions at an average dose of 0.48 ml/1000kg. Xylazine (0.1 mg/kg) used alone was ineffective on two occasions and was supplemented with Immobilon. When Immobilon® was used after the xylazine, the dose was reduced to 0.2 ml / 1000 kg. Author's (Mikota) note: xylazine dose given as mg/kg and etorphine dose given as ml in original article. Kock,N., Kock,M., Arif,A., and Wahid,M.N.S.A. 1984. **Immobilization techniques and complications associated with a bull Indian elephant (*Elephas maximus indicus*) during musth**. Proc.Am.Assoc.Zoo Vet. Pages: 68-74

cc) Etorphine (4 mg/ml) was used as the immobilizing agent at a dose of 1 mg per foot (30cm) shoulder height (estimated) on 3 male Asian elephants aged 40-45 years and 255-300 cm shoulder height. Immobilon® ( 2.45 mg/ml etorphine and 10 mg/ml acepromazine) was used on four subsequent occasions at a dosage of 2.45 mg etorphine and 10 mg acepromazine per 4 ft (120 cm) shoulder height on male elephants aged 30-50 years and 240 –270 cm shoulder height. Drugs were given IM. Induction times were

To Drug Monograph Index To Ophthalmic Product Index

11-18 minutes for Immobilon® and 13-25 minutes for etorphine. Bongso,T.A. and Perera,B.M.A.O. 1978. **Observations on the use of etorphine alone and in combination with acepromazine maleate for immobilization of aggressive Asian elephants (*Elephas maximus*)**. Veterinary Record 102:(15):339-340

dd) Etorphine (5-8 mg) adequately immobilized four adult Asian male elephants with estimated weights of 3300-3700 kg. Induction times varied from 8 to 19 minutes. Jainudeen,M.R., Bongso,T.A., and Perera,B.M.O.A. 1971. **Immobilisation of aggressive working elephants (*Elephas maximus*)**. Veterinary Record 89:(26):686-688 **Abstract:** The capture of aggressive working elephants, *Elephas maximus*, by the drug immobilisation technique is described. Doses of 5 mg to 8 mg etorphine hydrochloride alone, satisfactorily immobilised four adult elephants. Cyprenorphine hydrochloride reversed the immobilising effects almost immediately and completely. Recovery was uncomplicated. The value of this method of capture is discussed in relation to aggressive working elephant.

**See also:**

Hoare,R. 1999. **Reducing drug immobilization time in the field immobilization of elephants**. Pachyderm 27:(Jan-Dec):49-54

Elkan,P.W., Planton,H.P., Powell,J.A., Haigh,J.A., and Karesh,W.B. 1998. **Chemical immobilization of African elephant in lowland forest, southwestern Cameroon**. Pachyderm 25:(Jan-July):32-37

Singh,L.A.K., Nayak,B.N., and Acharjya,S.K. 1996. **Chemical capture of a problem-elephant in Bolangir, Orissa**. Indian Forester. Special issue: wildlife management. 122:(10):955-960
**Abstract:** A detailed account is given of the method used to capture an elephant which had been regularly (over 18 yr) entering villages in the Bolangir and Padampur areas of NW Orissa, and causing damage to buildings, eating stored grains and injuring humans. Some 45 people took part in the capture operation which involved the use of darts containing Immobilon (etorphine hydrochloride and acepromazine maleate) to the animal, and of (diprenorphine hydrochloride) for revival. The human antidote for (Narcan) was kept on hand. The communication system, the operational strategies used, and then care and revival processes adopted for the animal are described. It is thought that the animal (with a female) had originally been in the care of a mahout who was taken into custody for some crime so that the animals were abandoned. The female appeared to have been accepted back into the wild, while the male continued to follow the routes used by the mahout. The purpose of capture was to control or translocate the animal.

Dunlop,C.I., Hodgson,D.S., Cambre,R.C., Kenny,D.E., and Martin,H.D. 1994. **Cardiopulmonary effects of three prolonged periods of isoflurane anesthesia in an adult elephant**. Journal of the American Veterinary Medical Association 205:(10):1439-1444
**Abstract:** An adult 3500-kg female African elephant (Loxodonta africana) was anaesthetized 3 times for treatment of subcutaneous fistulas over the lateral aspect of each cubitus (anaesthesia 1 and 2) and for repair of a fractured tusk (anaesthesia 3). Lateral recumbency and anaesthesia were achieved with etorphine (anaesthesia 1 and 2) or etorphine and azaperone (anaesthesia 3). The trachea was intubated and anaesthesia was maintained by isoflurane and oxygen delivered through 2 standard large animal anaesthesia machines joined in parallel. The range of total recumbency time was 2.4 to 3.3 h. Breathing and heart rates, systemic arterial pressure, rectal temperature, PaO2, pH and end-tidal gases were monitored. After administration of etorphine, measurements were made while the elephant was recumbent and breathing air, then every 5 min (cardiovascular) or 15 min (blood gases) after the start of administration of isoflurane and oxygen. Tachycardia and hypertension were detected after administration of etorphine, but heart rate and systemic arterial pressure decreased to within normal ranges after administration of isoflurane and oxygen. The elephant remained well oxygenated while anaesthetized and breathing a high oxygen mixture. The elephant had an uneventful recovery from each anaesthesia.

To Drug Monograph Index To Ophthalmic Product Index

Still,J. 1993. **Etorphine-azaperone anaesthesia in an African elephant (Loxodonta africana)**. Journal of Veterinary Anaesthesia 20:54-55

Johnsingh,A.J.T., Joshua,J., Ravi,C., Ashraf,N.V.K., Krishnamurthy,V., Khati,D.V.S., and Chellam,R. 1993. **Etorphine and acepromazine combination for immobilising wild Indian elephants (Elephas maximus)**. Journal of the Bombay Natural History Society 90:(2):45-49

Lahiri-Choudhury,D.K., 1992. **Translocation of wild elephants**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 91-106

Ashraf,N.V.K., Johnsingh,A.J.T., Panwar,H.S., Sale,J.B., Joshua,J., Ravi,C., and Krishnamurth,V. 1991. **Chemical immobilization of wild Asian elephants: pharmacological, biological and ecological considerations**. International Seminar on Veterinary Medicine in Wild and Captive Animals, Nov. 8-10, Bangalore, India. Pages: 21

Jacobson,E.R. 1988. **Chemical restraint and anesthesia of elephants**. Proc.Ann.Elephant Workshop 9. Pages: 112-119

Mihm,F.G., Machado,C., and Snyder,R. 1988. **Pulse oximetry and end-tidal $CO_2$ monitoring of an adult Asian elephant**. Journal of Zoo Animal Medicine 19:106-109
**Abstract:** The adequacy of ventilation during etorphine anesthesia of a 20-yr-old Asian (3050 kg) elephant (*Elephas maximus*) was monitored with a pulse oximeter to measure arterial hemoglobin oxygen saturation ($SaO_2$) and a $CO_2$ analyzer to measure end-tidal $CO_2$ concentrations ($PetCO_2$). Immediately after the first anesthetic induction (8 mg etorphine IV), $SaO_2$ values of 45% were noted while the animal was breathing room air at a rate of 6/min. The $SaO_2$ readings increased to 93% 15 min after administration of 5 liters/min of oxygen via the trunk. Seven arterial blood gas samples obtained during two anesthetics, and once while unanesthetized, provided $PaO_2$ and $PaCO_2$ values which compared favorably with $SaO_2$ and $PetCO_2$. In the anesthetized animal, $PaO_2$ ranged between 31 and 70 mmHg while $SaO_2$ values were 70-95%. At the same time, measurements of $PaCO_2$ ranged from 42 to 57 mmHg while values of $PetCO_2$ ranged from 35 to 57 mmHg. Pulse oximetry and end-tidal $CO_2$ monitoring are easy to apply and should increase the safety of anesthesia for these animals. Note: Atropine (120 mg) IV was given after induction. Duration of surgery was 60 minutes. Diprenorphine (16 mg) was given IV for reversal and the elephant stood in 9 minutes.

Heard,D.J., Jacobson,E.R., and Brock,K.A. 1986. **Effects of oxygen supplementation on blood gas values in chemically restrained juvenile African elephants**. Journal of the American Veterinary Medical Association 189:(9):1071-1074 **Abstract:** Arterial oxygen and carbon dioxide tensions were determined in sedated immature African elephants and in elephants immobilized with etorphine hydrochloride or with an etorphine-ketamine combination. For manipulative and surgical procedures, the Hudson demand value was used for oxygen supplementation during 6 procedures, and insufflation was used during 2 procedures. The Hudson demand value was more effective than insufflation in sustaining adequate arterial oxygenation.

Lateur,N. and Stolk,P. 1986. **Repeated general anesthesia in a male Indian elephant**. Proc.Am.Assoc.Zoo Vet. Pages: 128-131

Hattingh,J. 1984. **Effects of etorphine and succinyldicholine on blood composition in elephant and buffalo**. South African Journal of Zoology 19:286-290

Tamas,P.M. and Geiser,D.R. 1983. **Etorphine analgesia supplemented by halothane anesthesia in an adult African elephant**. Journal of the American Veterinary Medical Association 183:(11):1312-1314

To Drug Monograph Index To Ophthalmic Product Index

Fowler,M.E. 1981. **Problems with immobilizing and anesthetizing elephants**. Proceedings of the American Association of Zoo Veterinarians 87-91

Jarofke,D. 1981. **Etorphine anesthesia in the elephant**. Journal of Zoo Animal Medicine 12: 93-95

von Richter,W., Drager,N., Patterson,L., and Sommerlatte,M. 1978. **Observations on the immobilization and marking of African elephants (*Loxodonta africana*) in Botswana**. Akademie-Verlag 14:185-191
**Abstract:** 58 elephants were successfully immobilized in their natural environment in the Chobe Nation Park and on privately owned farms in Botswana using a drug mixture of etorphine (M99 Reckitt) and acetylpromazine. The specific antidote cyprenorphine (M285 Reckitt) was used in most cases to resuscitate the animals. One known mortality occurred. For the long term monitoring of social organization and long and short term movements collars manufactured from machine belting and fitted with colour codes or symbols proved most satisfactory. Stamping the tusks near the lip provided a permanent marking although not useful for field observation. Various other marking techniques were tested but were considered unsatisfactory for long term identification. Various behavioral aspects associated with the immobilizing of elephants are described and discussed.

Ebedes,H. 1975. **The immobilization of adult male and female elephant, *Loxodonta africana*, with etorphine and observation on the action of diprenorphine**. Madogua 9:19-24

Alford,B.T., Burkhart,R.L., and Johnson,W.P. 1974. **Etorphine and diprenorphine as immobilizing and reversing agents in captive and free-ranging mammals**. Journal of the American Veterinary Medical Association 164:(7):702-705

Fowler,M.E. and Hart,R. 1973. **Castration of an Asian elephant, using etorphine anesthesia**. Journal of the American Veterinary Medical Association 163:(6):539-543
**Abstract:** A 9-year-old Asian elephant was castrated, using etorphine HCl for anesthesia. The intra-abdominal surgery was completed in 2 stages. Respiratory and heart rates were normal throughout each surgical procedure. Normal $PaCO_2$ and $PaO_2$ were maintained without the need of intermittent positive pressure ventilation.

Jainudeen,M.R., Bongso,T.A., and Perera,B.M.O.A. 1971. **Immobilisation of aggressive working elephants (*Elephas maximus*)**. Veterinary Record 89:(26):686-688
**Abstract:** The capture of aggressive working elephants, *Elephas maximus*, by the drug immobilisation technique is described. Doses of 5 mg to 8 mg etorphine hydrochloride alone, satisfactorily immobilised four adult elephants. Cyprenorphine hydrochloride reversed the immobilising effects almost immediately and completely. Recovery was uncomplicated. The value of this method of capture is discussed in relation to aggressive working elephant.

Gray,C.W. and Nettasinghe,A.P.W. 1970. **A preliminary study of immobilization of the Asiatic elephant (*Elephas maximus*) utilizing etorphine (M-99)**. Zoologica 55:51-53
**Ref Type:** Journal **Language:** English **Abstract:** A preliminary study of M-99 for the immobilization of the Ceylonese elephant indicates the effective dosage is approximately twice that used in the African elephant, based on comparative body weights. A dosage rate of 7 to 8 mgs of M-99 was necessary to immobilize the Ceylonese elephant as compared to 5 or 6 mgs of M-99 for African elephants of almost double the weight.

Jainudeen,M.R. 1970. **The use of etorphine hydrochloride for restraint of a domesticated elephant (*Elephas maximus*)**. Journal of the American Veterinary Medical Association 157:(5):624-626 **Abstract:** A domestic male Asian elephant (*Elephas maximus*) in "musth" (aggressive state) was successfully immobilized with 8 mg. of etorphine hydrochloride (M.99). The clinical signs of immobilization were comparable to those reported in the African elephant (*Loxodonta africana*). Cyprenorphine hydrochloride (M.285) reversed the immobilizing effects almost immediately and completely. Recovery was uncomplicated.

To Drug Monograph Index To Ophthalmic Product Index

Gandal,C.P. 1968. **M-99 usage in African elephant, okapi and blesbok**. American Association of Zoo Veterinarians Newsletter 1:

Gray,C.W. 1968. **The use of M-99 in wild Asian elephant**. American Association of Zoo Veterinarians Newsletter March 25:

Wallach,J.D. and Anderson,J.L. 1968. **Oripavine (M.99) combinations and solvents for immobilization of the African elephant**. Journal of the American Veterinary Medical Association 153:(7):793-797 **Abstract:** The oripavine derivative, M.99, alone or in combination with small amounts of tranquilizer, satisfactorily immobilized 21 adult African elephants. The addition of scopolamine to M.99 solutions in doses high enough to produce a physiologic effect prolonged the recovery period unnecessarily. There was no reduction of the induction period when dimethyl sulfoxide was used as a solvent for M.99 given subcutaneously or by deep intramuscular injections. Cyprenorphine (M.285) reversed the immobilizing effects of M.99 alone or in combination with small amounts of tranquilizer.

Pienaar,U.d.V., Van Niekerk,J.W., and Young,E. 1966. **The use of oripavine hydrochloride (M.99) in the drug immobilization and marking of wild African elephant (*Loxodonta africana* Blumenbach) in the Kruger national park**. Koedoe 9:108-124

Harthoorn,A.M. and Bligh,J. 1965. **The use of a new oripavine derivative with potent morphine-like activity for the restraint of hoofed wild animals**. Research in Veterinary Science 6:290-299 **Abstract:** The use of one of a series of oripavine derivatives (No. M.99) for the immobilization and capture of hoofed wild animals is described. This substance, usually injected in combination with tranquilizer and hyoscine, is suitable for the restraint of all hoofed wild animals on which it has been used. The very low mortality achieved originally with the use of tranquilizer/synthetic morphine/hyoscine mixtures has been maintained, while the speed of reaction has greatly increased. The much smaller bulk of this substance (approximately 0.2 ml compared with 10 ml equivalent of solution formerly needed) has considerably increased the ease of injection through the use of much smaller projectile syringes. The effect of this oripavine substance may be reversed with nalorphine.

## EUTHANASIA AGENTS CONTAINING PENTOBARBITAL

For therapeutic uses (other than euthanasia) of pentobarbital, see the main pentobarbital monograph for this agent. The sections on chemistry, storage, pharmacokinetics, overdosage, drug interactions, and monitoring parameters can be found in the main pentobarbital monograph also.

**Pharmacology** - Pentobarbital causes death by severely depressing the medullary respiratory and vasomotor centers when administered at high doses. Cardiac activity may persist for several minutes following administration.

Phenytoin is added to *Beuthanasia*®*-D Special* (Schering) and lidocaine to *FP-3*® (Vortech) for their added cardiac depressant effects and to denature the compounds from a Class-II controlled substance to Class-III drugs. Pentobarbital is also known as pentobarbitone.

**Uses/Indications** - For rapid, humane euthanasia in animals not intended for food purposes. Individual products may be approved for use in specific species. Barbituric acid derivatives are considered to be the “preferred method of euthanasia of individual dogs, cats, and other small animals.” (AVMA Panel on Euthanasia, 1986).

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions** - Must not be used in animals to be used for food purposes (human or animal consumption). Should be stored in such a manner that these products will not be confused with therapeutic agents. Extreme care in handling filled syringes and proper disposal of used injection equipment must be undertaken. Avoid any contact with open wounds or accidental injection. Keep out of reach of children. Prior use of a tranquilizing agent may be necessary when the animal is in pain or agitated.

**Adverse Effects/Warnings** - Minor muscle twitching may occur after injection. Death may be delayed or not accomplished if injection given perivascularly.

**Doses** - Because different products have different concentrations, please refer to the information provided with the product in use.
**Large Animals**: (Note: **must not** be used in animals to be consumed by either humans or other animals). Depending on product concentration, most animals require 10 - 15 ml per 100 pounds of body weight.

**Monitoring Parameters** -

1) Respiratory, cardiac rate, corneal reflex

**Client Information** - Must be administered by an individual familiar with its use. Inform client observing euthanasia, that animal may give a terminal gasp after becoming unconscious.

**Dosage Forms/Preparations** - See other pentobarbital dosage forms under the main monograph for lower concentration products.

Pentobarbital Sodium for Injection (Euthanasia)

*Sleepaway*® (Fort Dodge) 260 mg/ml; 100 ml vials; C-II

*Euthanasia-6*® (Anthony) 390 mg/kg; 100 ml, 250 ml vials; C-II
*Euthanasia Solution* (Vet-Labs)324 mg/ml; 100 ml vials; C-II

Pentobarbital Sodium 390 mg/ml/Phenytoin Sodium 50 mg/ml for Injection (Euthanasia)

*Beuthanasia*® *-D Special* (Schering) 100 ml vials; C-III

Pentobarbital Sodium 390 mg/ml/Lidocaine 20 mg/ml for Injection (Euthanasia)

*FP-3*® (Vortech) 100ml vials; C-III

All products are controlled substances and require a prescription. Pentobarbital alone is a Class-II controlled substance, combination products are generally Class-III.

Another barbiturate combination product similar to *Beuthanasia*®*-D* or *FP-3*® is: *Repose*® (Syntex) which contains 400 mg/ml secobarbital and 25 mg/ml dibucaine. The suggested dose for euthanasia in dogs and cats is: 0.22 ml/kg body weight IV.

## FAMCICLOVIR PK

Famciclovir is a human anti-viral drug that has been used to treat endotheliotrophic herpesvirus (EEHV) infection in Asian elephants. EEHV infections in elephants are acute, severe and often fatal. Only those references that include treatment information are listed below. For a complete list of EEHV references see the Bibliographic Database at www.elephantcare.org.

a) Montali,R.J., Richman,L.K., Mikota,S.K., Schmitt,D.L., Larsen,R.S., Hildebrandt,T.B., Isaza,R., and Lindsay,W.A. 2001. **Management Aspects of Herpesvirus Infections and Tuberculosis in Elephants**. A Research Update on Elephants and Rhinos; Proceedings of the International Elephant and Rhino Research Symposium, Vienna, June 7-11, 2001. Pages: 87-95 **Abstract:** Elephant endotheliotropic herpesvirus (EEHV) infections and tuberculosis have emerged as causes of illness and mortality in captive

To Drug Monograph Index To Ophthalmic Product Index

elephants. Twenty-six confirmed EEHV cases are documented. Since 1995, 7 have occurred in North America, 10 in Europe and 2 in Asia. A PCR test was used to detect the virus in symptomatic animals; a serological test to identify carrier elephants is under development. The African elephant is a potential source of the EEHV that is lethal for Asian elephants. Fatal infections have also occurred in Asian elephants without African elephant contacts. Three of 6 elephants recovered after treatment with antiviral famciclovir; however, more research is needed to improve the usefulness of this drug. Asian elephants that are less than 10-years old and have been moved to another facility and/or have had contact with African elephants are at increased risk for contracting EEHV. Animals traveling between facilities with a history of EEHV cases may be at greater risk. All young elephants should be monitored daily for anorexia, lethargy, body swellings and blue discoloration (bruising) of the tongue, and be trained for blood sampling and potential oral and rectal treatment with famciclovir.

b) Schaftenaar,W., Mensink,J.M.C.H., Deboer,A.M., Hildebrandt,T.B., and Fickel,J. 2001. **Successful treatment of a sub adult Asian elephant bull (Elephas maximus) infected with elephant herpes virus**. Proc. of the International Symposium for Diseases of Zoo and Wildlife Animals (Rotterdam).

c) Schmitt,D.L., Hardy,D.A., Montali,R.J., Richman,L.K., Lindsay,W.A., Isaza,R., and West,G. 2000. **Use of famciclovir for the treatment of endotheliotrophic herpesvirus infections in Asian elephants (Elephas maximus)**. Journal of Zoo and Wildlife Medicine 31:(4):518-522
**Abstract:** Two juvenile Asian elephants (E. maximus) presented with an acute onset of facial oedema and lethargy. Examination of the oral cavity of each animal revealed cyanosis of the tip and distal margins of the tongue suggestive of endothelial inclusion body disease (EIBD) of elephants. Whole-blood samples were obtained, and polymerase chain reaction tests confirmed the presence of elephant herpesvirus. The animals were administered famciclovir (Flamvir; 500 mg/70 kg body weight, with a loading dose of 1000 mg/70 kg body weight) a potent human anti-herpesvirus drug, in the course of their disease, and recovery followed a treatment regime of 3-4 wk. These are the first known cases of elephants surviving EIBD.

d) Schmitt,D.L., Hardy,D.A. 1998. **Use of famciclovir for the treatment of herpesvirus in an Asian elephant**. Journal of the Elephant Managers' Association 9:103-104

**e) Famciclovir pharmacokinetics in young Asian elephants (Elephas maximus).** R. Isaza, R. P. Hunter, L. K. Richman, R. J. Montali, D. L. Schmitt, D. E. Koch, et al.Proc. American Assoc. of Zoo Veterinarians 2003 Pages: 82-83

Asian elephants (Elephas maximus) are susceptible to a unique infection caused by elephant endotheliotropic herpesvirus (EEHV).3,4 Worldwide, between the years 1983 and 2000, there have been 26 confirmed deaths from this virus in Asian elephants.2 Although most cases have been fatal, treatment with famciclovir (Famvir, SmithKline Beecham Pharmaceuticals, Philadelphia,PA 19101 USA) has been associated with survival in three cases of six cases of EEHV infection proven by PCR.2,5,6 Dose selections for surviving elephants (5.5 - 8.0 mg/kg, p.o. every 8 hr) were made without the benefit of elephant pharmacokinetics and were a direct extrapolation from recommended human dosages (7 mg/kg, p.o. every 8 hr).5,6 In this study, famciclovir was administered both orally and rectally in healthy young Asian elephants. The doses tested in this study were 5 mg/kg orally, 5 mg/kg rectally, and 15 mg/kg rectally. Blood samples were analyzed for famciclovir and penciclovir using a validated LC/MS assay. Famciclovir was absorbed well by both routes and underwent rapid biotransformation to the active compound penciclovir. None of the plasma samples had detectable famciclovir. Pharmacokinetic parameters for penciclovir were determined using non-compartmental analysis. After a single oral dose of 5 mg/kg the Cmax was 1.3 ìg/mL with a Tmax at 1.1 h. After a rectal dose of 5 mg/kg the Cmax was 1.2 ìg/mL with a Tmax at 0.34 hr. After a rectal dose of 15 mg the t½ was 2.6 h, with a Cmax of 3.6 ìg/mL at Tmax 0.66 h. These results were similar to those reported in humans where an oral dose of 500 mg (7 mg/kg) had a t½ of about 2 h with a Cmax of 3.3 ìg/mL. A dose range of 8 -15 mg/kg given orally or rectally every 8 hours should produce penciclovir concentrations in Asian elephants that are considered therapeutic in humans.

To Drug Monograph Index To Ophthalmic Product Index

## LITERATURE CITED

1. Hardman, J.G., L.E. Limbird and A.G. Gilman. 2001. In: Goodman and Gilman's The pharmacological basis of therapeutics, Tenth edition. McGraw-Hill Co. New York, New York. USA. Pp. 1322-1324.

2. Montali, R.J., Richman, L.K., Mikots,S.K., Schmitt,D.L., Larsen, R.S., Hildebrandt,T.B., Isaza,R., Lindsay,W.A. Management Aspects of Herpesvirus Infections and Tuberculosis in Elephants. International Elephant and Rhino Research Symposium, Vienna, June 7-11, 2001.

3. Richman, L.K., R.J. Montali, R.L. Garber, M.A. Kennedy, J. Lehnhardt, T. Hildebrandt, D. Schmitt, D. Hardy, D.J. Alcendor, G.S. Hayward. 1999a. Novel endotheliotropic herpesvirus fatal for Asian and African elephants. Science. 283:1171-1176.

4. Richman, L.K., R.J. Montali, R.C. Cambre, D. Schmitt, D. Hardy, T. Hildebrandt, F.M. Hamzeh, A. Shahkolahi, G.S. Hayward. 2000. Clinical and pathological findings of a newly recognized disease of elephants caused by endotheliotrophic herpesvirus. J. Wild. Dis. 36:1-12.

5. Schaftenaar, W., J.M.C.H. Mensink, A.M. de Boer, T.B. Hildebrandt, and J. Fickel. 2001. Successful treatment of a subadult Asian elephant bull (Elephas maximus) infected with the endotheliotropic elephant herpes virus. Verhber. Erkrg. Zootiere. P. 40.

6. Schmitt, D., D.A. Hardy, R.J. Montali, LK Richman, Lindsay WA, R. Isaza, G. West. 2000. Use of famciclovir for the treatment of endotheliotropic herpesvirus infections in Asian elephants (Elephas maximus). J. Zoo Wild. Med. 31:518-522.

f) **Estimates of the pharmacokinetics of famciclovir and its active metabolite penciclovir in young Asian elephants (Elephas maximus).** A. P. Brock, R. Isaza, R. P. Hunter, L. K. Richman, R. J. Montali, D. L. Schmitt, et al. Am J Vet Res 2012 Vol. 73 Issue 12 Pages 1996-2000. Accession Number: 23176429 PMCID: PMC3886626 DOI: 10.2460/ajvr.73.12.1996.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3886626/pdf/nihms-531733.pdf

OBJECTIVE: To determine plasma pharmacokinetics of penciclovir following oral and rectal administration of famciclovir to young Asian elephants (Elephas maximus). ANIMALS: 6 healthy Asian elephants (5 females and 1 male), 4.5 to 9 years old and weighing 1,646 to 2,438 kg. PROCEDURES: Famciclovir was administered orally or rectally in accordance with an incomplete crossover design. Three treatment groups, each comprising 4 elephants, received single doses of famciclovir (5 mg/kg, PO, or 5 or 15 mg/kg, rectally); there was a minimum 12-week washout period between subsequent famciclovir administrations. Serial blood samples were collected after each administration. Samples were analyzed for famciclovir and penciclovir with a validated liquid chromatography-mass spectroscopy assay. RESULTS: Famciclovir was tolerated well for both routes of administration and underwent complete biotransformation to the active metabolite, penciclovir. Mean maximum plasma concentration of penciclovir was 1.3 mug/mL at 1.1 hours after oral administration of 5 mg/kg. Similar results were detected after rectal administration of 5 mg/kg. Mean maximum plasma concentration was 3.6 mug/mL at 0.66 hours after rectal administration of 15 mg/kg; this concentration was similar to results reported for humans receiving 7 mg/kg orally. CONCLUSIONS AND CLINICAL RELEVANCE: Juvenile Asian elephants are susceptible to elephant endotheliotropic herpesvirus. Although most infections are fatal, case reports indicate administration of famciclovir has been associated with survival of 3 elephants. In Asian elephants, a dose of 8 to 15 mg of famciclovir/kg given orally or rectally at least every 8 hours may result in penciclovir concentrations that are considered therapeutic in humans

**FAMOTIDINE**

To Drug Monograph Index  To Ophthalmic Product Index

**Chemistry** - An $H_2$-receptor antagonist, famotidine occurs as a white to pale yellow, crystalline powder. It is odorless, but has a bitter taste. 740 micrograms are soluble in one ml of water.

**Storage/Stability/Compatibility** - Tablets should be stored in well-closed, light-resistant containers at room temperature. Tablets are assigned an expiration date of 30 months after date of manufacture.

The powder for oral suspension should be stored in tight containers at temperatures less than 40°C. After reconstitution, the resultant suspension is stable for 30 days when stored at temperatures less than 30°C.; do not freeze.

Famotidine injection should be stored in the refrigerator (2-8°C). It is compatible with most commonly used IV infusion solutions and is stable for 48 hours at room temperature when diluted in these solutions.

**Pharmacology** - At the $H_2$ receptors of the parietal cells, famotidine competitively inhibits histamine, thereby reducing gastric acid output both during basal conditions and when stimulated by food, pentagastrin, histamine or insulin. Gastric emptying time, pancreatic or biliary secretion, and lower esophageal pressures are not altered by famotidine . By decreasing the amount of gastric juice produced, $H_2$-blockers also decrease the amount of pepsin secreted.

**Uses/Indications** - In veterinary medicine, famotidine may be useful for the treatment and/or prophylaxis of gastric, abomasal and duodenal ulcers, uremic gastritis, stress-related or drug-induced erosive gastritis, esophagitis, duodenal gastric reflux and esophageal reflux.

Although there is less veterinary experience with this agent than with either ranitidine or cimetidine, it has some potential advantages in that it suffers from fewer documented drug interaction problems and may suppress acid production longer than with either cimetidine or ranitidine. The clinical advantage of using famotidine over either drug has not been confirmed.

**Pharmacokinetics** - Famotidine is not completely absorbed after oral administration, but undergoes only minimal first-pass metabolism. In humans, systemic bioavailability is about 40-50%. Distribution characteristics are not well described. In rats, the drug concentrates in the liver, pancreas, kidney and submandibular gland. Only about 15-20% is bound to plasma proteins. In rats, the drug does not cross the blood brain barrier nor the placenta. It is distributed into milk. When the drug is administered orally, about 1/3 is excreted unchanged in the urine and the remainder primarily metabolized in the liver and then excreted in the urine. After intravenous dosing, about 2/3's of a dose is excreted unchanged.

The pharmacokinetics of famotidine, ranitidine, and cimetidine have been investigated (Duran and Ravis 1993) in horses After a single IV dosage, elimination half lives of cimetidine, ranitidine and famotidine all were in the 2-3 hour range and were not significantly different. Of the three drugs tested, famotidine had a larger volume of distribution (4.28 L/kg) than either cimetidine (1.14 L/kg) or ranitidine (2.04 L/kg). Bioavailability of each of the drugs was low; famotidine (13%), ranitidine (13.5%) and cimetidine (30%).

**Contraindications/Precautions/Reproductive Safety** - Famotidine is contraindicated in patients with known hypersensitivity to the drug.

Famotidine should be used cautiously in geriatric patients and in patients with significantly impaired hepatic or renal function. Famotidine may have negative inotropic effects and have some cardioarrhythmogenic properties. Use with caution in patients with cardiac disease.

In lab animal studies, famotidine demonstrated no detectable harm to offspring. Large doses may affect the mother's food intake and weight gain during pregnancy which may indirectly be harmful. Use in pregnancy

To Drug Monograph Index To Ophthalmic Product Index

when potential benefits outweigh the risks. In rats nursing from mothers receiving very high doses of famotidine, transient decreases in weight gain occurred.

**Adverse Effects/Warnings** - Because there is limited experience with this drug, its adverse effect profile has not been determined for veterinary species. Other H2 blockers have been demonstrated to be relatively safe and exhibit minimal adverse effects. Potential adverse effects (documented in humans) that could be seen include GI effects (anorexia, vomiting, diarrhea), headache, or dry mouth or skin. Rarely, agranulocytosis may develop particularly when used concomitantly with other drugs that can cause bone marrow depression.

There have been reports of famotidine causing intravascular hemolysis when given intravenously to cats.

**Overdosage/Acute Toxicity** - The minimum acute lethal dose in dogs is reported to be >2 grams/kg for oral doses and approximately 300 mg/kg for intravenous doses. IV doses in dogs ranging from 5-200 mg/kg IV caused vomiting, restlessness, mucous membrane pallor and redness of the mouth and ears. Higher doses caused hypotension, tachycardia and collapse.
Because of this wide margin of safety associated with the drug, most overdoses should require only monitoring. In massive oral overdoses, gut emptying protocols should be considered and supportive therapy initiated when warranted.

**Drug Interactions** - Stagger doses (separate by 2 hours if possible) of famotidine with **antacids, metoclopramide, sucralfate, digoxin,** and **ketoconazole**. Famotidine may exacerbate leukopenias when used with other **bone marrow suppressing drugs**.
Unlike cimetidine or ranitidine, famotidine does not appear to inhibit hepatic cytochrome P-450 enzyme systems and dosage adjustments of other drugs (*e.g.,* warfarin, theophylline, diazepam, procainamide, phenytoin) that are metabolized by this metabolic pathway should usually not be required.

**Laboratory Considerations -** Histamine$_2$ blockers may antagonize the effects of histamine and pentagastrin in the **evaluation gastric acid secretion**. After using **allergen extract skin tests**, histamine$_2$ antagonists may inhibit histamine responses. It is recommended that histamine$_2$ blockers be discontinued at least 24 hours before performing either of these tests.

**Doses** -
**Horses**:

As an adjunct in ulcer treatment:

a) IV doses: 0.23 mg/kg IV q8h or 0.35 mg/kg IV q12h. Oral doses: 1.88 mg/kg PO q8h or 2.8 mg/kg PO q12h. (Duran and Ravis 1993)

**Monitoring Parameters** - 1) Clinical efficacy (dependent on reason for use); monitored by decrease in symptomatology, endoscopic examination, blood in feces, etc.; 2) Adverse effects, if noted

**Client Information** - To maximize the benefit of this medication, it must be administered as prescribed by the veterinarian; symptoms may reoccur if dosages are missed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Famotidine Film-coated Tablets 10 mg, 20 mg, 40 mg; *Pepcid*®. (Merck) (Rx);*Pepcid AC Acid Controller*® (J & J Merck); (Rx)

To Drug Monograph Index To Ophthalmic Product Index

Famotidine Oral Powder for Suspension 40 mg/5 ml (400 mg total); *Pepcid*®. (Merck); (Rx)
Famotidine Injection 10 mg/ml in 2 ml single dose vials and 4 ml multidose vials; premixed - 20 mg per 50 ml in 0.9% NaCl *Pepcid*® *I.V.*.(Merck) (Rx)

## FEBANTEL

**Chemistry** - A phenylguanidine anthelmintic, febantel occurs as a colorless powder. It is insoluble in water and alcohol. Structurally, febantel is related to the benzimidazoles. As febantel is at least partially metabolized to fenbendazole and oxibendazole *in vivo*, it is sometimes categorized as a probenzimidazole agent.

**Storage/Stability/Compatibility** - Febantel (alone) should be stored at room temperature. Partially used febantel (*Rintal*®) syringes may be stored for up to one year if capped tightly and expiration date is not exceeded. When mixed extemporaneously with trichlorfon (*Combot*®), it should be stored tightly sealed and used within 6 days if kept at room temperature and within 2 months if refrigerated. Mix well before administering.

**Pharmacology** - The mode of action of this agent is thought to be via inhibition of fumarate reductase in the worm, thereby blocking glucose uptake. The majority of the activity is believed to be derived from the active metabolites, fenbendazole and oxfendazole.

**Uses/Indications** - Febantel paste and oral (tube) suspension is indicated (labeled) for the treatment of large and small strongyles (*Strongulus vulgaris, S. edentatus, S. equinus*), ascarids (*P. equorum*—adult and sexually immature forms), and pinworms (*Oxyuris equi*—adult and 4th stage larva) in horses. In combination with trichlorfon (*Combotel*®), it is indicated (labeled) for the removal of the mouth and stomach stages of bots (*Gastrophilus intestinalis, G. nasalis*).

Febantel (in combination with praziquantel—*Vercom*®) is indicated (labeled) for the following intestinal parasites in dogs and puppies: hookworms (*Ancylostoma caninum*), roundworms (*Toxocara canis*), whipworms (*Trichuris vulpus*) and tapeworms (*Dipylidium caninum & Taenia pisiformis*).

Febantel (in combination with praziquantel—*Vercom*®) is indicated (labeled) for the following intestinal parasites in cats and kittens: hookworms (*Ancylostoma tubaeforme*), roundworms (*Toxocara canti*) and tapeworms (*Dipylidium caninum & Taenia taeniaeformis*).

Although not approved for use in cattle or sheep, febantel has greater than 85% efficacy against the following helminths in those species: Abomasal nematodes, small intestinal nematodes, large intestinal nematodes (*Oesophogostomum spp.*), lungworms and trematodes (*F. hepatica*— 4 week to 15 week stages; not in sheep).

**Pharmacokinetics** - In the horse, febantel is apparently readily absorbed from the GI tract and is rapidly metabolized to fenbendazole-sulphone, fenbendazole and oxibendazole. Febantel is also absorbed from the intestine in cattle and sheep. Sheep apparently absorb and metabolize the drug faster than do cattle. Maximum plasma concentrations occur 6-12 hours after dosing in sheep and 12-24 hours in cattle.

**Contraindications/Precautions** - When used alone in horses, the manufacturer lists no contraindications to the use of the drug. It is considered to be safe in breeding stallions and pregnant mares. The combination product (*Combotel*®) is labeled as being contraindicated in horses "...suffering from colic, diarrhea,

constipation, or infectious disease until such conditions have been corrected." The combination product (*Vercom*®) is contraindicated in pregnant small animals.

**Adverse Effects/Warnings** - When used at recommended dosages in horses, adverse reactions are unlikely to occur. Anaphylaxis is listed as a possible reaction, but case reports documenting this were not found in the literature. At very high doses (8 times labeled), a self-limiting diarrhea has been described.

Adverse effects in horses with the combination product *Combotel*®, include mouth irritation with resultant salivation, occasional diarrhea and colic. Adverse effects are more likely to occur if given on an empty stomach or if feed is withheld prior to dosing.

In dogs and cats, *Vercom*® (febantel & praziquantel) is unlikely to cause serious adverse effects at usual doses. Dogs may exhibit salivation, anorexia, emesis or gagging, and diarrhea or soft stools. Incidence of these effects was less than 3% of dogs treated in clinical trials. Cats may show signs (less than 10% incidence) of salivation, vomiting, depression and rejection of the paste. These effects are described as mild and self-limiting.

**Overdosage/Toxicity** - In horses, febantel has a reported 40X margin of safety after a single oral dose. Slightly decreased red blood cell counts, hemoglobin and hematocrit may be noted for 3 weeks after this dosage. Repeated doses of 8X recommended resulted only in a self-limiting diarrhea.

While, in horses there is a considerable safety factor for febantel, there is much less so for trichlorfon (in *Combotel*®). For more information on the toxicity for this compound (trichlorfon) refer to its monograph found later in this section.

The $LD_{50}$ in dogs is greater than 10 g/kg of febantel. When administered at 15X recommended dose to mature dogs and cats, or 10X recommended dose to puppies or kittens for 6 days, transient salivation, diarrhea, vomiting and anorexia were noted. In dogs receiving 5 or 10 mg/kg PO for 90 days, testicular and prostatic hypoplasia were noted.

**Drug Interactions**, **Drug/Laboratory Interactions** - None reported.

**Doses** -
**Horses**:

For labeled indications:

a) 6 mg/kg PO or tube; retreat in 6-8 weeks if reinfection is likely to occur. (Robinson 1987), (Package Inserts; *Rintal*® Paste & Suspension—Miles)

**Monitoring Parameters** -1) Efficacy; 2) Adverse effects, if severe

**Client Information** - Clients should be informed on general measures to reduce exposure to helminth eggs and larva. Dogs with concomitant flea and *Dipylidium caninum* infestations should have measures taken to remove the fleas from the animal and the environment.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**:

Febantel Oral Paste 45.5%; 6 gram, and 36 gram (multi-dose) syringe

*Rintal*® *Paste* (Bayer), (OTC) Approved for use in horses.

Febantel Suspension 93 mg/ml (9.3%) in 26 fl. oz. bottles

To Drug Monograph Index To Ophthalmic Product Index

*Rintal*® *Suspension* (Bayer); (Rx)  Approved for use in horses.

Febantel 3.4% (34 mg/gram) and Praziquantel 0.34% (3.4 mg/gram) Oral paste syringe; 4.8 g, 12 g, and 36 g syringes

*Vercom*® *Paste* (Bayer); (Rx)  Approved for use in dogs, cats, puppies, and kittens.

Praziquantel/pyrantel pamoate plus febantel; *Drontal Plus Tablets*® (Bayer) (Rx) small, medium and large dog sizes

May also be known as *Amatron*® or *Bayverm*® in the U.K..

**Human-Approved Products:** None

## FENBENDAZOLE

**Chemistry** - A benzimidazole anthelmintic, fenbendazole occurs as a white, crystalline powder. It is only slightly soluble in water.

**Storage/Stability/Compatibility** - Fenbendazole products should be stored at room temperature.

**Uses/Indications** - Fenbendazole is indicated (labeled) for the removal of the following parasites in **dogs**: ascarids (*Toxocara canis, T. leonina*), Hookworms (*Ancylostoma caninum, Uncinaria stenocephala*), whipworms (*Trichuris vulpis*), and tapeworms (*Taenia pisiformis*). It is not effective against *Dipylidium caninum*. Fenbendazole has also been used clinically to treat *Capillaria aerophilia*:, *Filaroides hirthi* and *Paragonimus kellicoti* infections in dogs.

Fenbendazole is indicated (labeled) for the removal of the following parasites in **cattle**: Adult forms of: *Haemonchus contortus, Ostertagia ostertagi, Trichostrongylus axei, Bunostomum phlebotomum, Nematodirus helvetianus, Cooperia spp., Trichostrongylus colubriformis, Oesophagostomum radiatum* and *Dictyocaulus vivaparus*. It is also effective against most immature stages of the above listed parasites. Although not approved, it also has good activity against *Moniezia spp*., and arrested 4th stage forms of *Ostertagia ostertagi*.

Fenbendazole is indicated (labeled) for the removal of the following parasites in **horses**: large strongyles (*S. edentatus, S. equinus, S. vulgaris*), small strongyles (*Cyathostomum spp., Cylicocylus spp., Cylicostephanus spp.,Triodontaphorus spp.*) and pinworms (*Oxyuris equi*).

Fenbendazole is indicated (labeled) for the removal of the following parasites in **swine**: large roundworms (*Ascaris suum*), lungworms (*Metastrongylus apri*), nodular worms (*Oesphagostomum dentatum, O. quadrispinulatum*), small stomach worms (*Hyostrongylus rubidus*), whipworms (*Trichuris suis*) and kidney worms (*Stephanuris dentatus*; both mature and immature).

Although not approved, fenbendazole has been used in **cats, sheep, goats, pet birds and llamas**. See Dosage section for more information.

Fenbendazole is considered to be safe to use in pregnant bitches and is generally considered to be safe to use in pregnancy for all species.

**Pharmacokinetics** - Fenbendazole is only marginally absorbed after oral administration. After oral dosing in calves and horses, peak blood levels of 0.11 micrograms/ml and 0.07 micrograms/ml respectively, were measured. Absorbed fenbendazole is metabolized (and vice-versa) to the active compound, oxfendazole

To Drug Monograph Index  To Ophthalmic Product Index

(sulfoxide) and the sulfone. In sheep, cattle, and pigs, 44-50% of a dose of fenbendazole is excreted unchanged in the feces, and <1% in the urine.

**Contraindications/Precautions** - Fenbendazole is not approved for use in lactating dairy cattle or for horses intended for food purposes.

**Adverse Effects/Warnings** - At usual doses, fenbendazole generally does not cause any adverse effects. Hypersensitivity reactions secondary to antigen release by dying parasites may occur; particularly at high dosages. Vomiting may infrequently occur in dogs or cats receiving fenbendazole.

Single doses (even at exaggerated doses) are not effective in dogs and cats; must treat for 3 days.

**Overdosage/Toxicity** - Fenbendazole is apparently well tolerated at doses up to 100X recommended. The $LD_{50}$ in laboratory animals exceeds 10 grams/kg when administered PO. It is unlikely an acute overdosage would lead to clinical symptoms.

**Drug Interactions** - Oxfendazole or fenbendazole should not be given concurrently with the **bromsalan flukicides (Dibromsalan, Tribromsalan**). Abortions in cattle and death in sheep have been reported after using these compounds together.

**Doses** -
**Horses**:

For susceptible parasites:

a) 5 mg/kg PO; 10 mg/kg once daily for 5 days to treat *S. vulgaris* in foals. (Robinson 1987)
b) 5 mg/kg PO; 10 mg/kg for ascarids. (Roberson 1988b)
c) For treatment of migrating large strongyles: 50 mg/kg PO for 3 consecutive days, or 10 mg/kg for 5 consecutive days. (Herd 1987)

**Elephants:**

For strongylosis:
a) 5 mg/kg po. Raman,M., Jayathagaraj,M.G., Rajavelu,G., and John,M.C. 2000. **Strongylosis in captive elephants - a report**. Indian Journal of Animal Health 39:(2):85-86 **Summary:** Strongylosis was observed in a group of elephants (n=4) maintained in a private circus in Chennai, Tamil Nadu, India [date not given]. Examination of faecal samples showed larvae which were identified as Murshidia sp., Quilonia sp., and Decrusia sp. larvae. All elephants were treated with fenbendazole at a dose of 5 mg/kg body weight. A decline of egg count was observed after 1-2 days of treatment. Identification at the earlier stages of infection, good nutrition and hygiene, and less exertion might be the cause of absence of significant clinical signs like anaemia, dehydration and others. It is concluded that use of fenbendazole at the rate of 5 mg/kg body weight in the mega herbivores with repetition after 3 weeks, and regular deworming every 3-6 months, yield satisfactory results.

b) 2.5 mg/kg orally as a single dose Chandrasekharan,K. 2002. **Specific diseases of Asian elephants**. Journal of Indian Veterinary Association Kerala 7:(3):31-34; Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T., 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference to Kerala**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-449

c) 2.0 –2.5 mg/kg orally as a single dose mixed with jaggery or rice. Chandrasekharan,K., 1992. **Prevalence of infectious diseases in elephants in Kerala and their treatment**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management

To Drug Monograph Index To Ophthalmic Product Index

(Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 148-155

d) 5 mg/kg po in feed as a single dose. Strao,D., Yathiraj,S., Choudhuri,P.C., and Reddy,P.K. 1992. **Treatment of helminthiosis in elephants**. Indian Journal of Animal Science 62:(12):1155-1156 **Summary:** Drug containing 25% fenbendazole powder was given orally mixed in jaggery @ 5 mg/kg to 3 elephants. The body weight of the 3 elephants were 2530, 2925, and 3400 kg, and the total dose of Panacur for each elephant was 52, 58, and 68 kg respectively. Body weight was calculated using the formula W=12.8 (n+ng) – 4281, where W = weight in kg; g = chest girth (cm), and ng = neck girth (cm). One elephant had severe diarrhea. The egg count for strongyles was reduced to nil by 7 days indicating 100% efficacy against strongyles. NOTE: First author's name unclear and may be Trao, D.S. or Rao,D.S.T.

e) Chronic murshidiasis in an Asian elephant was resolved with 50 g fenbendazole repeated at 30 days. Tripathy,S.B., Acharjyo,L.N.M., and Padhi,N.K. 1991. **Use of fenbendazole against murshidiasis in zoo elephant**. International Seminar on Veterinary Medicine in Wild and Captive Animals, Nov. 8-10, Bangalore, India. Pages: 29 **Abstract:** Treatment of a chronic case of murshidiasis in a captive elephant with fenbendazole has been reported. Large numbers (epg 4200) of Murshidia eggs were detected in the faeces. Differential count of the blood revealed lymphocytosis (63%) and neutropenia (27%). Reduction in feed intake, oedematous swelling on dependent parts of the body, debility and reduction in body weight were recorded. Oral administration of 50 g of Panacur (25% fenbendazole) repeated after 30 days, 50 g of Minamil (mineral mixture) once daily for 30 days and 100 g of Livol (liver tonic) daily for 15 days along with 30 ml of Neurobiocin IM every third day for 5 injections brought clinical recovery and gain in body weight 2 months and 4 months after initiation of treatment respectively. The number of Murshidia eggs reduced by 70% and 100% in per gram of faeces when examined 5 and 10 days post treatment with anthelmintic, respectively.

f) 5 mg/kg po as a single dose. Roy,S. and Mazumdar,B.K. 1988. **Anthelmintic activity of fenbendazole (Panacur) against Murshidia murshida in zoo elephants**. Indian Veterinary Journal 65:(6):531-532 S**ummary:** Three Indian elephants, Elephas maximus, infected with M. murshida were treated with a single dose of fenbendazole at 5 mg/kg mixed into feed (cooked rice). Faecal samples were negative in one elephant 3 days after treatment, and in all animals 7 days after treatment. No side effects were recorded.

g) 12 g of Panacur dissolved in 2000 ml water in 2 divided doses at a 3 -day interval. Lahkar,B.C. and Das,M.R. 1988. **A note on the successful treatment of trichostrongyle infection of elephants (Elephas maximus) with Panacur (fenbendazole)**. Indian Veterinary Journal 65:(6):538 **Summary:** Six Indian elephants, E. maximus infected with gastrointestinal nematodes (700-1400 epg faeces) were given 12 g Panacur (fenbendazole) in the form of a bolus with flour, in 2 doses 3 days part. Faecal samples from all animals were negative 3 days after the second dose. No side effects were recorded.

**Dosage Forms/Preparations/FDA Approval Status** -
**Veterinary-Approved Products:**

Fenbendazole Granules 222 mg/gram (22.2%) in 0.18 oz & 1 g, 2 g, 4 g packets and 1 lb jars; *Panacur*® *Granules* 22.2% (Hoechst). (Rx) Approved for use in dogs.

Fenbendazole Granules 222 mg/gram (22.2%); *Panacur*® *Granules* 22.2% (Hoechst). (OTC) Approved for use in horses not intended for food.

Fenbendazole Suspension 100 mg/ml (10%); available in both equine and bovine labeled products; *Panacur*® *Suspension* (Hoechst). (Rx) Approved for use in horses (not intended for food) and cattle Slaughter withdrawal=8 days (cattle). *Safe-Guard*® Suspension (Hoechst) (OTC) Approved for use in beef and dairy cattle. Slaughter withdrawal = 8 days

To Drug Monograph Index To Ophthalmic Product Index

Fenbendazole Paste 100 mg/gram (10%); available in both equine and bovine labeled products and sizes. *Panacur® Paste* (Hoechst). (OTC) Approved for use in horses (not intended for food) and cattle. Slaughter withdrawal=8 days (cattle). *Safe Guard Paste®* (Hoechst) (OTC) Approved for use in horses not intended for food and cattle. Slaughter withdrawal = 8 days; no milk withdrawal time.

Fenbendazole Medicated Block 750 mg/lb.; 25 lb. block; *Safe-Guard Sweetlix®* (Hoechst); (OTC) Approved for use in beef cattle. Slaughter withdrawal= 16 days.

Fenbendazole Type B Medicated Feed

*Safe-Guard EZ Scoop Swine Dewormer®* (Hoechst) (OTC). 1.8% Fenbendazole No slaughter withdrawal time required

*Safe-Guard 0.96% Scoop Dewormer®* (Hoechst) (OTC) Approved for use in cattle. No milk withdrawal time; slaughter withdrawal time=13 days

Fenbendazole Type C Medicated Feed

*Safe-Guard Free-choice Cattle Dewormer®* (Hoechst) (OTC). 0.50% Fenbendazole (2.27 g/lb) Approved for use in beef and dairy cattle. No milk withdrawal time.

*Safe-Guard 35% Salt Free-choice Cattle Dewormer®* (Hoechst) (OTC) 1.9 g/lb Fenbendazole. Approved for use in dairy and beef cattle. Slaughter withdrawal time=13 days; no milk withdrawal time.

Fenbendazole Pellets

*Safe-Guard 0.5% Cattle Top Dress®* (Hoechst) (OTC) Slaughter withdrawal time=13 days; no milk withdrawal period

*Safe-Guard 1.96% Scoop Dewormer Mini Pellets®* (Hoechst) (OTC) Approved for use in beef and dairy cattle. No milk withdrawal time; slaughter withdrawal time=13 days

Fenbendazole Premix 20% Type A (200 mg/gram)

*Safe-Guard Premix®* (Hoechst). (OTC) Approved for use in swine. dairy and beef cattle, zoo & wildlife animals. Slaughter withdrawal for cattle = 13 days; no milk withdrawal time. Slaughter withdrawal for swine=none. Wildlife animal slaughter (hunting) withdrawal = 14 days.

**Human-Approved Products**: None

## FERROUS SULFATE

**Chemistry** - An orally available iron supplement, ferrous sulfate occurs as odorless, pale-bluish-green, crystals or granules having a saline, styptic taste. In dry air the drug is efflorescent. If exposed to moisture or moist air, the drug is rapidly oxidized to a brownish-yellow ferric compound which should not be used medicinally. Exposure to light or an alkaline medium will enhance the conversion from the ferrous to ferric state.

Ferrous sulfate is available commercially in two forms, a “regular” and a “dried” form. Regular ferrous sulfate contains 7 molecules of water of hydration and is freely soluble in water and insoluble in alcohol. Ferrous sulfate contains approximately 200 mg of elemental iron per gram.
Dried ferrous sulfate consists primarily of the monohydrate with some tetrahydrate. It is slowly soluble in water and insoluble in water. Dried ferrous sulfate contains 300 mg of elemental iron per gram. Ferrous sulfate, dried may also be know as ferrous sulfate, exsiccated.

**Storage/Stability/Compatibility** - Unless otherwise instructed, store ferrous sulfate preparations in tight, light-resistant containers.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Iron is necessary for myoglobin and hemoglobin in the transport and utilization of oxygen. While neither stimulating erythropoiesis nor correcting hemoglobin abnormalities not caused by iron deficiency, iron administration does correct both physical symptoms and decreased hemoglobin levels secondary to iron deficiency.

Ionized iron is also a component in the enzymes cytochrome oxidase, succinic dehydrogenase, and xanthine oxidase.

**Uses/Indications -** While iron is a necessary trace element in all hemoglobin-utilizing animals, the use of therapeutic dosages of ferrous sulfate (or other oral iron) preparations in veterinary medicine is limited primarily to the treatment of iron-deficiency anemias in dogs (usually due to chronic blood loss), although it may occasionally be used in other species. Injectable iron products are usually used in the treatment of iron deficiency anemias associated with newborn animals.

**Pharmacokinetics** - Oral absorption of iron salts is complex and is determined by a variety of factors, including diet, iron stores present, degree of erythropoiesis, and dose. Iron is thought to be absorbed throughout the GI tract, but is most absorbed in the duodenum and proximal jejunum. Food in the GI tract may reduce the amount absorbed.

After absorption, the ferrous iron is immediately bound to transferrin, and is transported to the bone marrow and eventually incorporated into hemoglobin. Iron metabolism occurs in a nearly closed system. Because iron liberated by the destruction of hemoglobin is reused by the body and only small amounts are lost by the body via hair and nail growth, normal skin desquamation and GI tract sloughing, normal dietary intake usually is sufficient to maintain iron homeostasis.

**Contraindications/Precautions/Reproductive Safety** - Ferrous sulfate (or other oral iron products) are considered contraindicated in patients with hemosiderosis, hemochromotosis, hemolytic anemias, or known hypersensitivity to any component of the product. Because of the GI irritating properties of the drugs, oral iron products are also considered contraindicated by some clinicians in patients with GI ulcerative diseases.

**Adverse Effects/Warnings** - Adverse effects associated with non-toxic doses are usually limited to mild gastrointestinal upset. Division of the daily dosage may reduce this effect, but dosage reduction may also be necessary in some animals.

**Overdosage/Acute Toxicity** - Ingestion of iron containing products may result in serious toxicity. While lethal doses are not readily available in domestic species, as little as 400 mg (of elemental iron) is potentially fatal in a child. Initial symptoms of acute iron poisoning usually present as an acute onset of gastrointestinal irritation and distress (vomiting—possibly hemorrhagic, abdominal pain, diarrhea). The onset of these effects may be seen within 30 minutes of ingestion, but also can be delayed for several hours. Peripheral vascular collapse may rapidly follow with symptoms of depression, weak and/or rapid pulse, hypotension, cyanosis, ataxia, and coma possible. Some patients do not exhibit this phase of toxicity and may be asymptomatic for 12-48 hours after ingestion, when another critical phase may occur.
This phase may be exhibited by pulmonary edema, vasomotor collapse, cyanosis, pulmonary edema, fulminant hepatic failure, coma and death. Animals who survive this phase may exhibit long-term sequelae, including gastric scarring and contraction and have persistent digestive disturbances.

Because an acute onset of gastroenteritis may be associated with a multitude of causes, diagnosis of iron intoxication may be difficult unless the animal has been observed ingesting the product or physical evidence suggests ingestion. Ferrous sulfate (and gluconate) tablets are radiopaque, and often can be observed on abdominal radiographs. Serum iron levels and total iron binding capacity (TIBC) may also be helpful in determining the diagnosis, but must be done on an emergency basis to have any clinical benefit.

To Drug Monograph Index  To Ophthalmic Product Index

Treatment of iron intoxication must be handled as an emergency. In humans who have ingested 10 mg/kg or more of elemental iron within 4 hours of presentation, the stomach is emptied, preferably using gastric lavage with a large bore tube to remove tablet fragments. It is generally recommended to avoid using emetics in patients who already have had episodes of hemorrhagic vomiting. These patients are lavaged using tepid water or 1-5% sodium bicarbonate solution.

In dogs, one author (Mount 1989), has recommended using oral milk of magnesia to help bind the drug, administering apomorphine if appropriate to help dislodge tablets, and to instill a gastric lavage slurry of 50% sodium bicarbonate with a portion left in the stomach.

**Deferoxamine** is useful in chelating iron that has been absorbed. After chelation, a water soluble complex forms that is rapidly eliminated by the kidneys. Dosage recommendations for iron intoxicated dogs are:

a) In severely affected animals: 40 mg/kg IV at a rate not exceeding 15 mg/kg/hr (avoiding hypotension); repeat every 4-12 hours at 20 mg/kg as determined by animal's response.
In less acutely afflicted animals: 20 mg/kg q4-12h IM or SQ q3-12h.
Three days of therapy may be required in severely poisoned animals. (Mount 1989)
b) Initially, 10 mg/kg IM or IV for 2 doses, 2 hours apart. After the second dose has been given, the urine should be examined. If no color change is seen after the second dose and the animal is not exhibiting clinical signs or symptoms or intoxication, no further treatment is required. If the urine is a reddish-orange color, a significant amount of iron has been ingested and treatment should continue at 10 mg/kg q8h for 24 hours. Do not exceed 80 mg/kg total dose of deferoxamine in 24 hours. Continue to monitor carefully, particularly for shock. (Papich 1990)

In addition to chelation therapy, other supportive measures may be necessary, including treatment of acidosis, prophylactic antibiotics, oxygen, treatment for shock, coagulation abnormalities, seizures and/or hyperthermia. After the acute phases have resolved, dietary evaluation and management may be required.

**Drug Interactions** - Oral iron preparations can bind to orally administered **tetracyclines**, thereby decreasing the absorption of both compounds. If both drugs are necessary, give the tetracycline dose 2 hours before or 3 hours after the iron dose. Because **chloramphenicol** may delay the response to iron administration, avoid using chloramphenicol in patients with iron deficiency anemia. Iron can decrease the efficacy of **penicillamine**, probably by decreasing its absorption. Doses of the two drugs should be spaced as far apart as possible, should both be required. **Antacids**, **eggs**, or **milk** administered concurrently with oral iron preparations can reduce the bioavailability of the iron. Separate iron doses from these items as far apart as possible. Iron salts may precipitate **phosphate** in the GI tract.

**Drug/Laboratory Interactions -** Large doses of oral iron can color the feces black and cause false-positives with the **guiaic test for occult blood** in the feces. Iron does not usually affect the benzidine test for occult blood.

**Doses** - **Caution**: Unless otherwise noted, doses are for ferrous sulfate (regular—not dried). Dosing of oral iron products can be confusing; some authors state doses in terms of the iron salt and some state doses in terms of elemental iron. For the doses below, assume that the doses are for ferrous sulfate and not elemental iron, unless specified.

**Horses**:

As a hematinic:

a) 2 - 8 g PO per day for 2 weeks or more. (Adams 1988a)

**Monitoring Parameters** -

1) Efficacy; adverse effects
   a) hemograms

To Drug Monograph Index To Ophthalmic Product Index

b) serum iron and total iron binding capacity, if necessary. Normal serum iron values for dogs and cats are reported as 80-180 micrograms/dl and 70-140 micrograms/dl, respectively. Total iron binding for dogs and cats are reported as 280-340 micrograms/dl and 270-400 micrograms/dl, respectively. (Morgan 1988)

**Client Information** - Because of the potential for serious toxicity when overdoses of oral iron-containing products are ingested by either children or animals, these products should be kept well out of reach of children and pets.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: No veterinary-approved products containing only ferrous sulfate could be located, but there are many multivitamin with iron containing products available.

**Human-Approved Products**:

Ferrous Sulfate Tablets (20% elemental iron) 195 mg (39 mg iron), 300 mg (60 mg iron), 324 mg (65 mg iron); *Mol-Iron*®(Schering-Plough); *Feratab*® (Upsher-Smith); generic (OTC)

Ferrous Sulfate Caplets: 160 mg (50 mg iron); *Fe50* ® (Northampton) (OTC)

Ferrous Sulfate Capsules: 250 mg (50 mg iron);*Ferospace*® (Hudson); generic, (OTC)

Ferrous Sulfate Tablets Timed-Release 525 mg (105 mg iron); *Fero-Gradumet*® *Filmtabs*® (Abbott) (OTC)

Ferrous Sulfate Syrup 18 mg/ml (3.6 mg iron/ml) in pints; *Fer-In-Sol*® (Mead Johnson Nutritionals); (OTC)

Ferrous Sulfate Elixir 44 mg/ml (8.8 mg iron/ml) in pints and gallons 220 mg (44 mg iron) per 5 ml in pints and gallons

*Feosol*® (SKBeecham); (OTC); generic (OTC)

Ferrous Sulfate Drops 125 mg/ml (25 mg iron/ml) in 50 ml *Fer-In-Sol*® (Mead Johnson Nutritionals), *Fer-Iron*® (various generics), (OTC)

Ferrous Sulfate, Dried (exissicated) Capsules 190 mg (60 mg iron); *Fer-In-Sol*® (Mead Johnson Nutritionals); (OTC)

Ferrous Sulfate, Dried (exissicated) Capsules Timed-Release 159 mg (50 mg iron); 250 mg dried ferrous sulfate equivalent (50 mg iron); *Feosol*®(SK-Beecham); *Ferralyn Lanacaps*® (Lannett); *Ferra-TD*® (Goldline); generic (OTC)

Ferrous Sulfate, Dried (exissicated) Tablets 200 mg (65 mg iron); *Feosol*® (SK-Beecham); (OTC)

Ferrous Sulfate, Dried (exissicated) Tablets, Slow-Release 160 mg (50 mg iron); *Slow FE*® (Ciba Consumer); (OTC)

## Firocoxib

**SERUM DISPOSITION OF A SINGLE DOSE OF ORALLY ADMINISTERED FIROCOXIB IN AFRICAN ELEPHANTS (LOXODONTA AFRICANA).** J. Kottwitz, U. Bechert, C. Cruz-Espindola, J. M. Christensen and D. Boothe. Journal of zoo and wildlife medicine : official publication of the American Association of Zoo Veterinarians 2023 Vol. 54 Issue 2 Pages 350-359.
Accession Number: MEDLINE:37428699 DOI: 10.1638/2022-0117

To Drug Monograph Index To Ophthalmic Product Index

The time course of serum firocoxib concentrations was described after administration of two single oral doses (0.01 and 0.1 mg/kg) of commercially available firocoxib tablet (n = 4) and paste (n = 2) formulations to six healthy adult female African (Loxodonta africana) elephants. Firocoxib was quantitated by high-performance liquid chromatography. Firocoxib serum concentrations were below detectable levels after administration of 0.01 mg/kg of both formulations. A dose of 0.1 mg/kg (n = 4) of the tablet formulation had the following mean ± SD of pharmacokinetic parameters: area under the curve (AUC) 1,588 ± 362 h * ng/ml, maximum plasma concentration (Cmax) 31 ± 6.6 ng/ml at 6.4 ± 1.8 h, and disappearance half-life (T1/2) 66 ± 59 h, Elephant compliance to oral administration of the paste formulation was challenging, with only two elephants accepting administration of the paste at 0.1 mg/kg. Pharmacokinetic parameters determined included AUC of 814 h * ng/ml, Cmax of 44 ng/ml at Tmax of 7.0 h, and T1/2 of 36.4 h. Based on mean AUC, the relative bioavailability of paste compared to tablet formulations was 50%. Limitations of this study were the small number of participants and elephant compliance with the paste formulation. This study supports an oral dose of 0.1 mg/kg every 24 h. Multidose and IV trials are indicated to confirm firocoxib dosing requirements for African elephants.

## FLORFENICOL

**Chemistry/Storage/Stability/Compatibility** - A fluorinated analog of thiamphenicol, florfenicol is commercially available as light yellow to straw-colored injectable solution also containing n-ethyl-2-pyrolidone, propylene glycol and polyethylene glycol. It should be stored between 2°-30°C (36°-86°F).

**Pharmacology** - Like chloramphenicol, florfenicol is a broad spectrum antibiotic that has activity against many bacteria. It acts by binding to the 50S ribosome, thereby inhibiting bacterial protein synthesis.

**Uses/Indications** - The drug is approved for use in cattle only (in the USA) for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica*, *Pasteurella multocida* and *Haemophilus somnus*.

Because florfenicol has activity against a wide range of microorganisms (e.g., Mycoplasma), it may be useful for treating other infections in cattle (or other species) as well, but specific data supporting these uses is presently lacking.

**Pharmacokinetics** - After IM injection, approximately 79% of the dose is bioavailable. The drug appears to be well distributed throughout the body, including achievement of therapeutic levels in the CSF. In cattle, only about 13% is bound to serum proteins. Mean serum half life is 18 hours, but wide interpatient variation exists.

**Contraindications/Precautions/Reproductive Safety -** No contraindications are listed in the package insert, but see residue warnings (below). Safety or effects when used in breeding cattle, during pregnancy or during lactation are unknown and the manufacturer states that the drug is not for use in cattle of breeding age. Caution: Do not give this drug IV.

**Adverse Effects/Warnings** - Noted transient adverse reactions in cattle include anorexia, decreased water consumption or diarrhea. Injection site reactions can occur that may result in trim loss. Reactions may be more severe if injected at sites other than the neck.

**Overdosage** - In toxicology studies where feeder calves were injected with up to 10X of the recommended dosage, the adverse effects noted above were seen, plus increased serum enzymes were noted. These effects were generally transient in nature. Long term (43 day) standard dosage studies showed a transient decrease in feed consumption, but no long-term negative effects were noted.

To Drug Monograph Index To Ophthalmic Product Index

**Drug Interactions** - No specific drug interactions for florfenicol were located, but the drug may behave similarly to chloramphenicol. If so, florfenicol could antagonize the bactericidal activity of the **penicillins** or **aminoglycosides**. This antagonism has not been demonstrated *in vivo*, and these drug combinations have been used successfully many times clinically. Other antibiotics that bind to the 50S ribosomal subunit of susceptible bacteria (**erythromycin, clindamycin, lincomycin, tylosin**, etc.) may potentially antagonize the activity of chloramphenicol or vice versa, but the clinical significance of this potential interaction has not been determined. For other drug interactions that florfenicol may share with chloramphenicol, see that monograph or refer to other drug information resources.

**Doses** -
**Cattle**:

For treatment of BRD:

a) 20 mg/kg IM (in neck muscle only); repeat in 48 hours. Alternatively, a single 40 mg/kg SubQ dose (in neck) may be used. Note: 20 mg/kg equates to 3 ml of the injection per 100 lb. of body weight. Do not exceed 10 ml per injection site. (*Nuflor*® Package Insert—Schering Plough)

**Monitoring Parameters** -1) Clinical efficacy 2) Injection site reactions

**Client Information - Residue Warnings**: Slaughter withdrawal is 28 days post injection if using the IM route; 38 days after the SubQ route. Not to be used in female dairy cattle 20 months of age or older. A withdrawal period has not been established in preruminating calves. Do not use in calves to be processed for veal.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products**:

Florfenicol Injection 300 mg/ml in 100 ml, 250 ml and 500 ml multi-dose vials; NuFlor® (Schering-Plough); (Rx). Approved for use in cattle; see residue warnings above.

**Human-Approved Products**: None

## FLUMETHASONE

Note: For more information refer to the monograph: Glucocorticoids, General Information.

**Chemistry** - Flumethasone occurs as an odorless, white to creamy white, crystalline powder. Its chemical name is 6alpha,9alpha-difluoro-16alpha methylprednisolone.

**Pharmacokinetics** - No information was located for this agent.

**Contraindications/Precautions** - Flumethasone is contraindicated during the last trimester of pregnancy. Refer to the General Statement on the glucocorticoids for more information.

**Doses** -
**Horses**:

For labeled indications (musculoskeletal conditions due to inflammation, where permanent changes do not exist..., and also for allergic states such as hives, urticaria and insect bites):

a) 1.25 - 2.5 mg daily by IV, IM or intra-articular injection. If necessary, the dose may be repeated. (Package insert; *Flucort*®—Syntex)
b) 1.0 - 2.5 mg/450 kg IV or IM (Robinson 1987)

To Drug Monograph Index To Ophthalmic Product Index

**Dosage Forms/Preparations/Approval Status/Withdrawal Times**-

**Veterinary-Approved Products: None**

Flumethasone Tablets 0.0625 mg; *Flucort® Tablets* (Fort Dodge); (Rx) Approved for use in dogs and cats. Note: may not presently be available.

Flumethasone Injection 0.5 mg/ml in 100 ml vials; *Flucort® Solution* (Fort Dodge); (Rx) Approved for use in dogs, cats, and horses.

**Human-Approved Products:** None

## FLUNIXIN MEGLUMINE PK

**Chemistry** - Flunixin meglumine, a nonsteroidal anti-inflammatory agent that is a highly substituted derivative of nicotinic acid, is unique structurally when compared to other NSAIDs. The chemical name for flunixin is 3-pyridine-carboxylic acid.

**Storage/Stability/Compatibility** - All flunixin products should be stored between 2-30°C (36-86°F). It has been recommended that flunixin meglumine injection not be mixed with other drugs because of unknown compatibilities.

**Pharmacology** - Flunixin is a very potent inhibitor of cyclooxygenase and like other NSAIDs, it exhibits analgesic, anti-inflammatory and antipyrexic activity. Flunixin does not appreciably alter GI motility in horses and may improve hemodynamics in animals with septic shock.

**Pharmacokinetics** - In the horse, flunixin is rapidly absorbed following oral administration with an average bioavailability of 80% and peak serum levels in 30 minutes. The onset of action is generally within 2 hours; peak response occurs between 12-16 hours and the duration of action lasts up to 36 hours. It is unknown how extensively flunixin is bound to plasma proteins or where it distributes in the body. It is unclear if the drug is extensively metabolized and exactly how the drug is removed from the body. Serum half-lives have been determined in horses ≈ 1.6 hours, dogs ≈ 3.7 hours; cattle ≈ 8.1 hours. Flunixin is detectable in equine urine for at least 48 hrs. after a dose.

**Uses/Indications** - In the United States, flunixin meglumine is approved for use in horses and cattle. However, it is approved for use in dogs in other countries. The approved indications for its use in the horse are for the alleviation of inflammation and pain associated with musculoskeletal disorders and alleviation of visceral pain associated with colic in the horse. In cattle it is approved for the control of pyrexia associated with bovine respiratory disease and endotoxemia, and for the control of inflammation in endotoxemia.

Flunixin has been touted for many other indications in various species, including: Horses: foal diarrheas, shock, colitis, respiratory disease, post-race treatment, and pre- and post ophthalmic and general surgery; Dogs: disk problems, arthritis, heat stroke, diarrhea, shock, ophthalmic inflammatory conditions, pre- and post ophthalmic and general surgery, and treatment of parvovirus infection; Cattle: acute respiratory disease, acute coliform mastitis with endotoxic shock, pain (downer cow), and calf diarrheas; Swine: agalactia/hypogalactia, lameness, and piglet diarrhea. It should be noted that the evidence supporting some of these indications is equivocal and flunixin may not be appropriate for every case.

**Contraindications/Precautions** - The only contraindication the manufacturer lists for flunixin's use in horses is for patients with a history of hypersensitivity reactions to it. It is suggested, however, that flunixin be used cautiously in animals with preexisting GI ulcers, renal, hepatic or hematologic diseases. When

To Drug Monograph Index To Ophthalmic Product Index

using to treat colic, flunixin may mask the behavioral and cardiopulmonary signs associated with endotoxemia or intestinal devitalization and must be used with caution.

In cattle, the drug is contraindicated in animals who have shown prior hypersensitivity reactions to it and is not recommended to be used in breeding bulls (lack of reproductive safety data).
Although reports of teratogenicity, effects on breeding performance, or gestation length have not been noted, flunixin should be used cautiously in pregnant animals.
Flunixin is usually considered to be contraindicated in cats, but some clinicians may use it short term (see doses).

**Adverse Effects/Warnings** - In horses following IM injection, reports of localized swelling, induration, stiffness, and sweating have been reported. Do not inject intra-arterially as it may cause CNS stimulation (hysteria), ataxia, hyperventilation, and muscle weakness. Symptoms are transient and generally do not require any treatment. Flunixin appears to be a relatively safe agent for use in the horse, but the potential does exist for GI intolerance, hypoproteinemia, and hematologic abnormalities to occur. Flunixin is not to be used in horses intended for food.

In horses and cattle, rare anaphylactic-like reactions have been reported, primarily after rapid IV administration.

In dogs, GI distress is the most likely adverse reaction. Symptoms may include, vomiting, diarrhea, and ulceration with very high doses or chronic use. There have been anecdotal reports of flunixin causing renal shutdown in dogs when used at higher dosages pre-operatively.

**Overdosage** - No clinical case reports of flunixin overdoses were discovered. It is suggested that acute overdosage be handled by using established protocols of emptying the gut (if oral ingestion and practical or possible) and treating the patient supportively.

**Drug Interactions** - Drug/drug interactions have not been appreciably studied for flunixin, but if it follows other NSAIDs it should be used cautiously with highly protein bound drugs such as **phenytoin, valproic acid, oral anticoagulants**, other **anti-inflammatory agents, salicylates, sulfonamides**, and the **sulfonylurea antidiabetic agents.** Additionally, use flunixin cautiously with **warfarin, methotrexate**, and **aspirin** or other ulcerigenic agents. Flunixin could theoretically reduce the saluretic and diuretic effects of **furosemide**. Use with caution in patients with severe cardiac failure.

**Doses** -
**Horses**:

a) Injectable: 1.1 mg/kg IV or IM once daily for up to 5 days. For colic cases, use IV route and may redose when necessary.

Oral Paste: 1.1 mg/kg PO (see markings on syringe—calibrated in 250 lb. weight increments) once daily. One syringe will treat a 1000 lb. horse for 3 days. Do not exceed 5 days of consecutive therapy.

Oral Granules:1.1 mg/kg PO once daily. One packet will treat 500lbs of body weight. May apply on feed. Do not exceed 5 consecutive days of therapy. (Package Inserts - Schering Animal Health for *Banamine*®)

b) 1.1 mg/kg IM or IV q12h to treat moderate to severe pain. (Clark and Becht 1987)

c) 1.1 mg/kg IM or IV; duration of effect averages 4-36 hrs depending upon cause and severity of abdominal pain. (Muir 1987)

**Elephants:**

a) Anecdotal doses of 1 mg/kg every 24 hours (route of administration not specified) have

To Drug Monograph Index To Ophthalmic Product Index

been reported. This is based on a survey of 20 zoo veterinarians in the U.S.

Mortenson,J., 2001. **Determining dosages for antibiotic and anti-inflammatory agents**. In: Csuti,B., Sargent,E.L., and Bechert,U.S. (Editors), The Elephant's Foot. Iowa State University Press, Ames pp. 141-144

Mortenson,J. 1998. **Determining dosages for anti-inflammatory agents in elephants.** Proceedings AAZV and AAWV Joint Conference. Pages: 477-479

Mortenson,J. and Sierra S. 1998. **Determining dosages for antibiotic and anti-inflammatory agents in elephants**. Proceedings of the First North American Conference on Elephant Foot Care and Pathology. Pages: 50-55

b) **PHARMACOKINETICS OF ORALLY ADMINISTERED FLUNIXIN MEGLUMINE IN AFRICAN (LOXODONTA AFRICANA) AND ASIAN (ELEPHAS MAXIMUS) ELEPHANTS.** U. Bechert, J. M. Christensen, J. Kottwitz, D. Boothe, S. Alshahrani and S. Mohammed. J Zoo Wildl Med 2021 Vol. 51 Issue 4 Pages 905-914. Accession Number: 33480571 DOI: 10.1638/2020-0053

https://bioone.org/journals/journal-of-zoo-and-wildlife-medicine/volume-51/issue-4/2020-0053/PHARMACOKINETICS-OF-ORALLY-ADMINISTERED-FLUNIXIN-MEGLUMINE-IN-AFRICAN-LOXODONTA-AFRICANA/10.1638/2020-0053.short

Flunixin meglumine is the most commonly used nonsteroidal anti-inflammatory drug used to treat elephants; however, no pharmacokinetic study for flunixin has yet been conducted in these species, and dosages used range widely. Pharmacokinetic parameters of flunixin were determined in African (Loxodonta africana) and Asian (Elephas maximus) elephants after single-dose oral administration of 0.8 and 1.5 mg/kg flunixin paste in each species. Elephant compliance to oral administration of banamine was occasionally challenging, especially among older, female African elephants. After administration of 0.8 mg/kg flunixin, mean serum concentrations peaked in approximately 1.3 hr at 2.1 ± 0.8 µg/ml for Asian (n = 8) and 2.8 hr at 2.5 ± 0.7 µg/ml for African (n = 8) elephants. Dosages of 1.5 mg/kg flunixin resulted in mean serum concentration peaks of 7.2 ± 1.5 µg/ml in Asian elephants (n = 7) and 4.4 ± 0.7 µg/ml in African elephants (n = 6). However, multiple-dose trials using 1.1 mg/kg flunixin resulted in peak serum concentrations that were again less in Asian than African elephants (2.7 µg/ml versus 4.4 µg/ml, respectively). Asian elephants consistently had lower time to maximal concentration, greater area under the curve, and longer mean residence times compared with African elephants. In other species, flunixin is excreted unchanged primarily via hepatic routes with small amounts in the urine. Asian elephants may engage in some level of enterohepatic recycling of flunixin, as was previously reported for phenylbutazone. This study supports that different oral dosing regimens should be used for Asian (1.0 mg/kg SID) and African (1.2 mg/kg SID) and oral administration techniques used should ensure complete dosage delivery.

**Monitoring Parameters** -

1) Analgesic/anti-inflammatory/antipyrexic effects
2) GI effects in dogs
3) CBC's, occult blood in feces with chronic use in horses

**Client Information** - If injecting IM, do not inject into neck muscles.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: Flunixin is approved only for use in horses not intended for food; for beef cattle and non-lactating dairy cattle. Slaughter withdrawal time in cattle = 4 days.

Flunixin Meglumine for Injection 50 mg/ml; in 50 and 100 ml vials; *Banamine*® (Schering); (Rx)

To Drug Monograph Index To Ophthalmic Product Index

Flunixin Meglumine Oral Paste 1500 mg/syringe; 30 gram syringe containing 1500 mg flunixin in boxes of 6; *Banamine*® (Schering); (Rx)

Flunixin Meglumine Oral Granules 250 mg: 10 gram sachets, each sachet contains 250 mg flunixin in boxes of 50. 500 mg: 20 g sachets, each sachet contains 500 mg flunixin in boxes of 25; *Banamine*® (Schering); (Rx)

Flunixin may also be known as *Finadyne*®.

**Human-Approved Products**: None

## FLUPROSTENOL SODIUM

**Chemistry** - A synthetic analogue of prostaglandin F□alpha, fluprostenol sodium occurs as a white or almost white hygroscopic powder that is soluble in water and alcohol. The drug's potency is expressed in terms of fluprostenol; 52.4 micrograms of fluprostenol sodium is equivalent to 50 micrograms of fluprostenol.

**Storage/Stability/Compatibility** - Fluprostenol should be stored in airtight containers and protected from light. The manufacturer recommends discarding any unused product after opening the vial.

**Pharmacology** - Fluprostenol exhibits pharmacologic effects similar to those of the other agents in this class. Effects on the female reproductive system include stimulation of myometrial activity, relaxation of the cervix, inhibition of steroidogenesis by corpora lutea, and potential lysing of corpora lutea. Fluprostenol reportedly has less smooth muscle stimulant activity and, therefore, may be safer to use to induce parturition in the mare.

**Uses/Indications -** The labeled indications for fluprostenol are to synchronize estrus for breeding management and for postpartum breeding. Suggested therapeutic uses by the manufacturer include: induction of luteolysis following early fetal death and resorption; termination of persistent diestrus; termination of pseudopregnancy; termination of lactational anestrus; establishing estrous cycles in barren/maiden mares; and to determine if a mare is cycling. The drug has also been used as an induction agent for parturition and as an abortifacient.

**Pharmacokinetics** - No information was located for this agent.

**Contraindications/Precautions** - Fluprostenol should not be used in pregnant mares unless parturition induction or abortion is desired. It should also not be used in mares with acute or sub-acute disorders of the GI tract or respiratory disease.

The manufacturer states that mares receiving non-steroidal antiinflammatory drugs should not receive fluprostenol, as this drug can inhibit the synthesis and release of prostaglandins. The clinical significance of such an interaction is in doubt, however.

The manufacturer recommends conducting a through breeding exam prior to the use of this drug.

**Adverse Effects/Warnings** - In horses, sweating, increased respiration, mild abdominal discomfort, uneasiness and defecation may be seen after fluprostenol injection. Adverse effects are more likely at doses above those recommended by the manufacturer.
See the warnings regarding the handling of the agent under Client Information below.

To Drug Monograph Index To Ophthalmic Product Index

**Overdosage** - No specific information was located. It would be expected that mild overdoses would result in the adverse effects listed above (sweating, diarrhea, increased respiratory rate). The animal should be treated supportively if necessary.

**Drug Interactions** - Other **oxytocic agents**' activity may be enhanced by fluprostenol. Reduced effect of fluprostenol would be expected with concomitant administration of a **progestin**.

**Doses** -
**Horses**:

Manufacturer's suggested dosage for all labeled indications (see above or package insert):

a) 0.55 micrograms/kg (average dose 250 micrograms or 5 ml) IM

To induce parturition in the mare:

a) 2.2 micrograms/kg (0.0022 mg/kg) IM; delivery generally occurs in about 4 hours (Carleton and Threlfall 1986)
b) Pony mares 250 micrograms IM, full-sized mares 1000 micrograms IM. First stage of labor ensues in 30 minutes, onset of second stage labor occurs in about 1/2 -3 hours. Duration of second stage labor varies from about 5-35 minutes. Author recommends further studies before recommending procedure. (Hillman 1987)

As an abortifacient:

a) Prior to the 12th day of pregnancy: 250 micrograms IM (Lofstedt 1986)
b) Prior to day 35 of gestation: 250 micrograms IM one time; after day 35: 250 micrograms IM daily for 3-5 days are required. (Squires and McKinnon 1987)

For estrus synchronization in normally cycling mares:

a) Two injection method: On day 1 give 250 micrograms (*Note: The text from this reference reads: 0.250 micrograms; it is believed that this is an error as the manufacturer's recommended dose is approximately 250 micrograms*) and again on day 16. Most (60%) mares will begin estrus 4 days after the second injection and about 90% will show estrous behavior by the 6th day after the second injection. Breed using AI every second day during estrus or inseminated at predetermined times without estrus detection. Alternatively, an IM injection of HCG (2500-3300 Units) can be added on the first or second day (usually day 21) of estrus to hasten ovulation. Breed using AI on days 20, 22, 24, and 26. This may be of more benefit when used early in the breeding season. (Bristol 1987)

**Client Information** - Fluprostenol should only be used by individuals familiar with its use and precautions. Pregnant women, asthmatics or other persons with bronchial diseases should handle this product with extreme caution. Any accidental exposure to skin should be washed off immediately using soap and water.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Fluprostenol sodium for Injection, equivalent to 50 micrograms/ml fluprostenol in 5 ml vials; *Equimate*® (Bayer); (Rx) Approved for use in horses. It is not for use in horses intended for food.

**Human-Approved Products**: None

## FOLLICLE STIMULATING HORMONE-PITUITARY

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - Follicle stimulating hormone-pituitary (FSH-P) is available commercially as a lyophilized powder. It is obtained from the pituitary glands of food producing animals. Reportedly, FSH-P may also have small amounts of luteinizing hormone present.
One mg of FSH-P = 1 Armour Unit. One Armour Unit, however, can contain from 9.4 - 14.2 International Units (IU) of FSH. When using to induce estrus in the bitch, one clinician (Barton and Wolf 1988) recommends contacting the manufacturer to determine how many IU of FSH are contained per Armour Unit in the lot number of the product obtained.

**Storage/Stability/Compatibility** - FSH-P should be stored at room temperature; protect from light, heat and moisture. After reconstituting, the manufacturer (Schering) recommends disposing of any unused drug, but it has been reported that it is relatively stable in the frozen state after reconstitution.

**Pharmacology** - FSH is produced by the anterior pituitary gland by the same cells that produce luteinizing hormone (LH). Its actions include stimulation of follicular growth and estrogen production in the female, and spermatogenesis in the male.

**Uses/Indications -** Although labeled for "use in cattle, horses, swine, sheep and dogs as a supplemental source of FSH when there is a general deficiency", its primary use in veterinary medicine has been to induce follicular growth for the purposes of superovulation and out-of-season breeding.

**Pharmacokinetics** - No specific information was located.

**Contraindications/Precautions** - FSH should not be used in animals with preexisting endometrial hyperplasia or follicular cysts.

**Adverse Effects/Warnings** - Cystic endometrial hyperplasia, undesired superovulation and follicular cysts are all potential adverse effects with FSH therapy. High dosages and prolonged treatment increase the likelihood of these effects developing.
Although not reported, hypersensitivity reactions are potentially possible with this product.

**Overdosage** - No specific information was located; refer to Adverse effects section above.

**Doses** -
**Horses**:
For labeled indications (FSH deficiency):
a) 10 - 50 mg IV, IM or SQ (Package Insert; *F.S.H.-P.* —Schering)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: Note: The ongoing availability of FSH-P products has been reported to be an issue; these products may or may not be avialable in the marketplace. Check with suppliers for more information.

Follicle Stimulating Hormone-Pituitary (FSH-P) lyophilized powder for reconstitution and injection. Each vial contains 50 mg Armour Standard and is packaged with one 10 ml vial of diluent (sodium chloride injection).; *F.S.H.-P.* (Schering) (Rx) Approved for use in cattle, horses, swine, sheep, and dogs.

Follicle Stimulating Hormone Each vial contains 75 mg NIH-FSH-S1 Standard and is packaged with one 10 ml vial of buffered diluent .; Super-OV® (AUSA Int.) (Rx) Approved for use in cattle. No milk or meat withdrawal periods are required when used as directed.

**Human-Approved Products**: None

To Drug Monograph Index To Ophthalmic Product Index

## FURAZOLIDONE

**Chemistry** - A synthetic nitrofuran-derivative antibacterial/antiprotozoal, furazolidone occurs as a bitter-tasting, yellow, crystalline powder. It is practically insoluble in water.

**Storage/Stability/Compatibility** - Store protected from light in tight containers. Do not expose the suspension to excessive heat.

**Pharmacology** - Furazolidone interferes with susceptible bacterial enzyme systems. Its mechanism against susceptible protozoa is not well determined. Furazolidone has activity against *Giardia, Vibrio cholerae, Trichomonas,* Coccidia and many strains of *E. Coli, Enterobacter, Campylobacter, Salmonella* and *Shigella*. Not all strains are sensitive, but resistance is usually limited and develops slowly. Furazolidone also inhibits monoamine oxidase.

**Uses/Indications** - Furazolidone is usually a drug of second choice in small animals to treat enteric infections caused by the organisms listed above.

**Pharmacokinetics** - Conflicting information on furazolidone's absorption characteristics are published. As colored metabolites are found in the urine, it is clearly absorbed to some extent. Because furazolidone is used to treat enteric infections, absorption becomes important only when discussing adverse reactions and drug interaction issues. Furazolidone is reported to be distributed into the CSF. Absorbed furazolidone is rapidly metabolized in the liver and the majority of absorbed drug is eliminated in the urine.

**Contraindications/Precautions/Reproductive Safety** - Furazolidone is contraindicated in patients hypersensitive to it. While the safe use of furazolidone during pregnancy has not been established, neither have there been any teratogenic problems reported for the drug. It is unknown if furazolidone enters maternal milk.

**Adverse Effects/Warnings** - Adverse effects noted with furazolidone are usually minimal. Anorexia, vomiting, cramping and diarrhea may occasionally occur. Some human patients are reported to be hypersensitive to the drug. Because furazolidone also inhibits monoamine oxidase, it may potentially interact with several other drugs and foods (see Drug Interactions below). The clinical significance of these interactions is unclear, particularly in light of the drug's poor absorptive characteristics.

**Overdosage/Acute Toxicity** - No information was located; but moderate overdoses are unlikely to cause significant toxicity. Gut emptying may be considered for large overdoses.

**Drug Interactions** - Because furazolidone inhibits monoamine oxidase, its use concurrently with **buspirone, sympathomimetic amines (phenylpropanolamine, ephedrine, etc.), tricyclic antidepressants, other monamine oxidase inhibitors, and fish or poultry** (high tyramine content) is not recommended because dangerous hypertension could occur. **Alcohol** used concurrently with furazolidone may cause a disulfiram-like reaction.

**Laboratory Considerations -** Furazolidone may cause a false-positive urine glucose determination when using the cupric sulfate solution test (*e.g.*, *Clinitest*®).

**Doses** -
**Horses**:

a) 4 mg/kg PO *tid* (Robinson 1992)

**Monitoring Parameters** - Efficacy (stool exams for parasitic infections)

To Drug Monograph Index To Ophthalmic Product Index

**Client Information** - Furazolidone may discolor urine to a dark yellow to brown color; this is not significant. Have clients report prolonged or serious GI effects.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Furazolidone Oral Liquid 3.34 mg/ml (50 mg/15 ml) in 60 ml and pint bottles; *Furoxone*® (Procter & Gamble Pharm);(Rx)

Furazolidone Oral Tablets 100 mg; *Furoxone*® (Procter & Gamble Pharm); (Rx)

## FUROSEMIDE

**Chemistry** - A loop diuretic related structurally to the sulfonamides, furosemide occurs as an odorless, practically tasteless, white to slightly yellow, fine, crystalline powder. Furosemide has a melting point between 203° - 205° with decomposition, and a $pK_a$ of 3.9. It is practically insoluble in water, sparingly soluble in alcohol and freely soluble in alkaline hydroxides. The injectable product has its pH adjusted to 8 - 9.3 with sodium hydroxide. Furosemide may also be known as frusemide.

**Storage/Stability/Compatibility** - Furosemide tablets should be stored in light-resistant, well-closed containers. The oral solution should be stored at room temperature and protected from light and freezing. Furosemide injection should be stored at room temperature. A precipitate may form if the injection is refrigerated, but will resolubolize when warmed without alteration in potency. The human injection (10 mg/ml) should not be used if it is a yellow-color. The veterinary injection (50 mg/ml) normally has a slight yellow color. Furosemide is unstable at an acid pH, but is very stable under alkaline conditions.

Furosemide injection (10 mg/ml) is reportedly **compatible** with all commonly used intravenous solutions and the following drugs: amikacin sulfate, cimetidine HCl, kanamycin sulfate, tobramycin sulfate and verapamil.

It is reportedly **incompatible** with the following agents: ascorbic acid solutions, dobutamine HCl, epinephrine, gentamicin sulfate, netilmicin sulfate and tetracylines. It should generally not be mixed with antihistamines, local anesthetics, alkaloids, hypnotics, or opiates.

**Pharmacology** - Furosemide reduces the absorption of electrolytes in the ascending section of the loop of Henle, decreases the reabsorption of both sodium and chloride and increases the excretion of potassium in the distal renal tubule, and directly effects electrolyte transport in the proximal tubule. The exact mechanisms of furosemide's effects have not been established. It has no effect on carbonic anhydrase nor does it antagonize aldosterone.

Furosemide increases renal excretion of water, sodium, potassium, chloride, calcium, magnesium, hydrogen, ammonium, and bicarbonate. It causes some renal venodilation and transiently increases glomerular filtration rates (GFR). Renal blood flow is increased and decreased peripheral resistance may occur. Furosemide can cause hyperglycemia, but to a lesser extent than the thiazides.

**Uses/Indications -** Furosemide is used for its diuretic activity in all species. It is used in small animals for the treatment of congestive cardiomyopathy, pulmonary edema, hypercalcuric nephropathy, uremia, as adjunctive therapy in hyperkalemia and, occasionally, as an antihypertensive agent. In cattle, it is approved

for use for the treatment of post-parturient udder edema. It has been used to help prevent or reduce epistaxis (exercise-induced pulmonary hemorrhage; EIPH) in race horses.

**Pharmacokinetics** - The pharmacokinetics of furosemide have been studied in a limited fashion in domestic animals. In dogs, the oral bioavailability is approximately 77% and the elimination half-life approximately 1 - 1.5 hours.

In humans, furosemide is 60-75% absorbed following oral administration. The diuretic effect takes place within 5 minutes after IV administration and within one hour after oral dosing. Peak effects occur approximately 30 minutes after IV dosing, and 1-2 hours after oral dosing. The drug is approximately 95% bound to plasma proteins in both azotemic and normal patients. The serum half-life is about 2 hours, but is prolonged in patients with renal failure, uremia, CHF, and in neonates.

**Contraindications/Precautions** - Furosemide is contraindicated in patients with anuria or who are hypersensitive to the drug. The manufacturer states that the drug should be discontinued in patients with progressive renal disease if increasing azotemia and oliguria occur during therapy.

Furosemide should be used with caution in patients with preexisting electrolyte or water balance abnormalities, impaired hepatic function (may precipitate hepatic coma) and diabetetes mellitus. Patients with conditions that may lead to electrolyte or water balance abnormalities (*e.g.,* vomiting, diarrhea, etc.) should be monitored carefully. Patients hypersensitive to sulfonamides may also be hypersensitive to furosemide (not documented in veterinary species).

**Adverse Effects/Warnings** - Furosemide may induce fluid and electrolyte abnormalities. Patients should be monitored for hydration status and electrolyte imbalances (especially potassium, calcium and sodium). Other potential adverse effects include ototoxicity (especially in cats with high dose IV therapy), gastrointestinal disturbances, hematologic effects (anemia, leukopenia), weakness and restlessness.

**Overdosage** - The $LD_{50}$ in dogs after oral administration is > 1000 mg/kg and after IV injection > 300 mg/kg. Chronic overdosing at 10 mg/kg for six months in dogs led to development of calcification and scarring of the renal parenchyma.

Acute overdosage may cause electrolyte and water balance problems, CNS effects (lethargy to coma and seizures) and cardiovascular collapse.

Treatment consists of emptying the gut after recent oral ingestion, using standard protocols. Avoid giving concomitant cathartics as they may exacerbate the fluid and electrolyte imbalances that can occur. Aggressively monitor and treat electrolyte and water balance abnormalities supportively. Additionally, monitor respiratory, CNS, and cardiovascular status. Treat supportively and symptomatically if necessary.

**Drug Interactions** - Pharmacologic effects of **theophylline** may be enhanced when given with furosemide. Ototoxicity and nephrotoxicity associated with the **aminoglycoside antibiotics** may be increased when furosemide is also used. If used concomitantly with **corticosteroids, corticotropin or amphotericin B,** furosemide may increase the chance of hypokalemia development. Furosemide-induced hypokalemia may increase chances of **digitalis** toxicity.
Patients on **aspirin** therapy may need dosage adjustment as furosemide competes for renal excretory sites. Furosemide may inhibit the muscle relaxation qualities of **tubocurarine**, but increase the effects of **succinylcholine**. Enhanced effects may occur if furosemide is used concomitantly with **other diuretics**. The uricosuric effects of **probenecid** or **sulfinpyrazone** may be inhibited by furosemide. Furosemide may alter the requirements of **insulin** or other anti-diabetic agents in diabetic patients.

**Doses** -

To Drug Monograph Index To Ophthalmic Product Index

**Horses**:

As a diuretic:

a) 0.25 - 1.0 mg/kg IV (Muir and McGuirk 1987)
b) 1 mg/kg IV (Robinson 1987)

For epistaxis prevention:

a) 0.3 - 0.6 mg/kg 60-90 minutes prior to race. (Robinson 1987) (Note: Refer to state guidelines for use of furosemide in racing animals)

**Elephants:**

a) Furosemide: 300-500 mg/animal IM. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants**. In: Daniel,J.C. (Editor), **A Week with Elephants; Proceedings of the International Seminar on Asian Elephants.** Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

**Monitoring Parameters** -

1) Serum electrolytes, BUN, creatinine, glucose
2) Hydration status
3) Blood pressure, if indicated
4) Symptoms of edema, patient weight, if indicated
5) Evaluation of ototoxity, particularly with prolonged therapy or in cats

**Client Information** - Clients should contact veterinarian if symptoms of water or electrolyte imbalance occur. Symptoms such as excessive thirst, lethargy, lassitude, restlessness, oliguria, GI distress or tachycardia may indicate electrolyte or water balance problems.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Furosemide Tablets 12.5 mg, 50 mg ; *Lasix*® (Hoechst); Generic; (Rx) Approved for use in dogs and cats.

Furosemide Oral Solution: 10 mg/ml in 60 ml btls; *Lasix*® (Hoechst) (Rx) Approved for use in dogs.

Furosemide 2 gram boluses; *Lasix*® (Hoechst); (Rx) Approved for use in cattle. A 48 hour withdrawal time has been assigned for both milk and slaughter for cattle.

Furosemide 50 mg/ml (5%) for Injection in 50 ml vials; *Lasix*® (Hoechst), *Diuride*® (Anthony), Generic (Rx) Approved for use in dogs, cats, horses not intended for food, and cattle. Milk withdrawal time = 48 hours; slaughter withdrawal = 48 hours.

**Human-Approved Products**:

Furosemide Tablets 20 mg, 40 mg, 80 mg; *Lasix*® (Hoechst Marion Roussel); Generic (Rx)

Furosemide Oral Solution: 8 mg/ml in 5, 10, & 500 ml btls; 10 mg/ml in 60 ml & 120 ml bottles; *Lasix*® (Hoechst Marion Roussel); Generic (Rx)

Furosemide 10 mg/ml for Injection in 2, 4, & 10 ml amps, vials and syringes; *Lasix*® (Hoechst Marion Roussel); Generic (Rx)

## GENTAMICIN SULFATE

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - An aminoglycoside obtained from cultures of *Micromonaspora purpurea*, gentamicin sulfate occurs as a white to buff powder that is soluble in water and insoluble in alcohol. The commercial product is actually a combination of gentamicin sulfate $C_1$, $C_2$ and $C_3$, but all these compounds apparently have similar antimicrobial activities. Commercially available injections have a pH from 3 - 5.5.

**Storage/Stability/Compatibility** - Gentamicin sulfate for injection and the oral solution should be stored at room temperature (15-30°C); freezing or temperatures above 40°C should be avoided. The soluble powder should be stored from 2-30°C. Do not store or offer medicated drinking water in rusty containers or the drug may be destroyed.

While the manufacturer does not recommend that gentamicin be mixed with other drugs, it is reportedly **compatible** and stable in all commonly used intravenous solutions and with the following drugs: bleomycin sulfate, cefoxitin sodium, cimetidine HCl, clindamycin phosphate, methicillin sodium, metronidazole (with and without sodium bicarbonate), penicillin G sodium and verapamil HCl.

The following drugs or solutions are reportedly **incompatible** or only compatible in specific situations with gentamicin: amphotericin B, ampicillin sodium, carbenicillin disodium, cefamandole naftate, cephalothin sodium, cephapirin sodium, dopamine HCl, furosemide, and heparin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

*In vitro* inactivation of aminoglycoside antibiotics by beta-lactam antibiotics is well documented. Gentamicin is very susceptible to this effect and it is usually recommended to avoid mixing these compounds together. Refer to the Drug Interaction section in the amikacin sulfate monograph for more information.

**Pharmacology** - Gentamicin has a mechanism of action and spectrum of activity (primarily gram negative aerobes) similar to the other aminoglycosides. This information is outlined in more detail in the amikacin monograph. Gentamicin resistance by certain bacteria, principally *Klebsiella*, *E. coli* and *Pseudomonas aeruginosa* is a continuing concern for many areas. However, most strains of gentamicin-resistant bacteria of these species remain susceptible to amikacin.

**Uses/Indications** - The inherent toxicity of the aminoglycosides limit their systemic (parenteral) use to the treatment of serious gram negative infections when there is either a documented lack of susceptibility to other less toxic antibiotics or when the clinical situation dictates immediate treatment of a presumed gram negative infection before culture and susceptibility results are reported.

Various gentamicin products are approved for parenteral use in dogs, cats, chickens, turkeys and swine. Although routinely used parenterally in horses, gentamicin is only approved for intrauterine infusion in that species. Oral products are approved for gastrointestinal infections in swine and turkeys. For more information refer to the Dosage section below.

**Pharmacokinetics** - Gentamicin, like the other aminoglycosides is not appreciably absorbed after oral or intrauterine administration, but is absorbed from topical administration (not skin or urinary bladder) when used in irrigations during surgical procedures. Patients receiving oral aminoglycosides with hemorrhagic or necrotic enteritises may absorb appreciable quantities of the drug. After IM administration to dogs and cats, peak levels occur from 1/2 to 1 hour later. Subcutaneous injection results in slightly delayed peak levels and with more variability than after IM injection. Bioavailability from extravascular injection (IM or SQ) is greater than 90%.

After absorption, aminoglycosides are distributed primarily in the extracellular fluid. They are found in ascitic, pleural, pericardial, peritoneal, synovial and abscess fluids and high levels are found in sputum,

bronchial secretions and bile. Aminoglycosides are minimally protein bound (<20%, streptomycin 35%) to plasma proteins. Aminoglycosides do not readily cross the blood-brain barrier or penetrate ocular tissue. CSF levels are unpredictable and range from 0-50% of those found in the serum. Therapeutic levels are found in bone, heart, gallbladder and lung tissues after parenteral dosing. Aminoglycosides tend to accumulate in certain tissues, such as the inner ear and kidneys, which may help explain their toxicity. Volumes of distribution have been reported to be 0.15-0.3 L/kg in adult cats and dogs, and 0.26-0.58 L/kg in horses. Volumes of distribution may be significantly larger in neonates and juvenile animals due to their higher extracellular fluid fractions. Aminoglycosides cross the placenta. Fetal concentrations range from 15-50% of those found in maternal serum.

Elimination of aminoglycosides after parenteral administration occurs almost entirely by glomerular filtration. The elimination half-lives for gentamicin have been reported to be 1.82- 3.25 hours in horses, 2.2-2.7 hours in calves, 2.4 hours in sheep, 1.8 hours in cows, 1.9 hours in swine, 1 hour in rabbits, and 0.5-1.5 hours in dogs and cats. Patients with decreased renal function can have significantly prolonged half-lives. In humans with normal renal function, elimination rates can be highly variable with the aminoglycoside antibiotics.

**Contraindications/Precautions/Reproductive Safety** - Aminoglycosides are contraindicated in patients who are hypersensitive to them. Because these drugs are often the only effective agents in severe gram-negative infections there are no other absolute contraindications to their use. However, they should be used with extreme caution in patients with preexisting renal disease with concomitant monitoring and dosage interval adjustments made. Other risk factors for the development of toxicity include age (both neonatal and geriatric patients), fever, sepsis and dehydration.

Because aminoglycosides can cause irreversible ototoxicity, they should be used with caution in “working” dogs (*e.g.,* “seeing-eye”, herding, dogs for the hearing impaired, etc.).

Aminoglycosides should be used with caution in patients with neuromuscular disorders (*e.g.,* myasthenia gravis) due to their neuromuscular blocking activity.

Because aminoglycosides are eliminated primarily through renal mechanisms, they should be used cautiously, preferably with serum monitoring and dosage adjustment in neonatal or geriatric animals.

Aminoglycosides are generally considered contraindicated in rabbits as they adversely affect the GI flora balance in these animals.

Aminoglycosides can cross the placenta and while rare, may cause 8th cranial nerve toxicity or nephrotoxicity in fetuses. Because the drug should only be used in serious infections, the benefits of therapy may exceed the potential risks.

**Adverse Effects/Warnings** - The aminoglycosides are infamous for their nephrotoxic and ototoxic effects. The nephrotoxic (tubular necrosis) mechanisms of these drugs are not completely understood, but are probably related to interference with phospholipid metabolism in the lysosomes of proximal renal tubular cells, resulting in leakage of proteolytic enzymes into the cytoplasm. Nephrotoxicity is usually manifested by increases in BUN, creatinine, nonprotein nitrogen in the serum and decreases in urine specific gravity and creatinine clearance.
Proteinuria and cells or casts may also be seen in the urine. Nephrotoxicity is usually reversible once the drug is discontinued. While gentamicin may be more nephrotoxic than the other aminoglycosides, the incidences of nephrotoxicity with all of these agents require equal caution and monitoring.

Ototoxicity (8th cranial nerve toxicity) of the aminoglycosides can be manifested by either auditory and/or vestibular symptoms and may be irreversible. Vestibular symptoms are more frequent with streptomycin, gentamicin, or tobramycin. Auditory symptoms are more frequent with amikacin, neomycin, or kanamycin,

but either forms can occur with any of the drugs. Cats are apparently very sensitive to the vestibular effects of the aminoglycosides.

The aminoglycosides can also cause neuromuscular blockade, facial edema, pain/inflammation at injection site, peripheral neuropathy and hypersensitivity reactions. Rarely, GI symptoms, hematologic and hepatic effects have been reported.

**Overdosage/Acute Toxicity** - Should an inadvertant overdosage be administered, three treatments have been recommended. Hemodialysis is very effective in reducing serum levels of the drug, but is not a viable option for most veterinary patients. Peritoneal dialysis also will reduce serum levels, but is much less efficacious. Complexation of drug with either carbenicillin or ticarcillin (12-20 g/day in humans) is reportedly nearly as effective as hemodialysis.

**Drug Interactions** - Aminoglycosides should be used with caution with other nephrotoxic, ototoxic, and neurotoxic drugs. These include **amphotericin B**, **other aminoglycosides**, **acyclovir**, **bacitracin** (parenteral use), **cisplatin**, **methoxyflurane**, **polymyxin B**, or **vancomycin**. The concurrent use of aminoglycosides with **cephalosporins** is controversial. Potentially, cephalosporins could cause additive nephrotoxicity when used with aminoglycosides, but this interaction has only been well documented with cephaloridine (no longer marketed) and cephalothin. Concurrent use with loop (**furosemide**, **ethacrynic acid**) or osmotic diuretics (**mannitol**, **urea**) may increase the nephrotoxic or ototoxic potential of the aminoglycosides. Concomitant use with **general anesthetics** or **neuromuscular blocking agents** could potentiate neuromuscular blockade. Synergism against *Pseudomonas aeruginosa* and *enterococci* may occur with beta**-lactam antibiotics** and the aminoglycosides. This effect is apparently not predictable and its clinical usefulness is in question.

**Drug/Laboratory Interactions** - Gentamicin **serum concentrations** may be falsely decreased if the patient is also receiving beta-lactam antibiotics and the serum is stored prior analysis. It is recommended that if assay is delayed, samples be frozen and if possible, drawn at times when the beta-lactam antibiotic is at a trough.

**Doses** -Note: There is significant interpatient variability with regards to aminoglycoside pharmacokinetic parameters. To insure therapeutic levels and to minimize the risks for toxicity development, it is recommended to consider monitoring serum levels for this drug.
For small animals, one pair of authors (Aronson and Aucoin 1989) make the following recommendations with regard to minimizing risks of toxicity yet maximizing efficacy:

1) Dose according to animal size. The larger the animal, the smaller the dose (on a mg/kg basis).
2) The more risk factors (age, fever, sepsis, renal disease, dehydration) the smaller the dose.
3) In old patients or those suspected of renal disease, increase dosing interval from q8h to q16-24h.
4) Determine serum creatinine prior to therapy and adjust by changes in level even if it remains in "normal range".
5) Monitor urine for changes in sediment (*e.g.,* casts) or concentrating ability. (Not very useful in patients with UTI.)
6) Therapeutic drug monitoring is recommended when possible.

**Horses**:

For susceptible infections:

a) 1 - 3 mg/kg IM *qid* (Robinson 1987)
b) For gram negative respiratory infections: 2.2 mg/kg IM or IV 4 times a day in mature horses and 3 times a day in foals. (Beech 1987a)
c) In foals: 2 - 3 mg/kg IV q12h; use lower dose in premature foals or those less than 7 days of age. Monitor serum levels if possible. (Caprile and Short 1987)
d) For prophylaxis (with penicillin G) for surgical colic: 2.2. mg/kg *tid* IV. (Stover 1987)
e) 2.2 mg/kg IV q6h; animals must be well hydrated. (Sweeney et al. 1988)

To Drug Monograph Index To Ophthalmic Product Index

f) 2 - 4 mg/kg IM q8-12h (Baggot and Prescott 1987)
g) 4.4 mg/kg IV q12h (Duran 1992)
h) There is increased interest in giving gentamicin once daily at an initial dosage of 6.6 mg/kg preferably as an IV infusion over one hour. Therapeutic drug monitoring would be beneficial. Watch for futher references documenting the safety and efficacy of this dosing method. (Plumb)

**Elephants:**

a) 4.4 mg/kg IV (or IM) once daily. The IV injection can be diluted with 10% saline. Based on trough levels measured at 24 hours, this dose will maintain blood levels at 1.7 – 1.8 µg /ml (recommended trough levels for humans are < 2 µg /ml. Schmidt, M.J: Senior Research Veterinarian, Washington Park Zoo, Portland, Oregon, personal communication, 1986. In: Olsen,J.H., 1999. **Antibiotic therapy in elephants**. In: Fowler,M.E. and Miller R.E. (Editors), **Zoo and Wild Animal Medicine: Current Therapy 4.** W.B. Saunders, Philadelphia, PA,USA p. 537

**Monitoring Parameters** (parenteral use)-

1) Efficacy (cultures, clinical signs and symptoms associated with infection).
2) Renal toxicity; baseline urinalysis, serum creatinine/BUN. Casts in the urine are often the initial sign of impending nephrotoxicity. Frequency of monitoring during therapy is controversial. It can be said that daily urinalyses early in the course of treatment is not too often nor are daily creatinines once casts are seen or increases noted in serum creatinine levels.
3) Gross monitoring of vestibular or auditory toxicity is recommended.
4) Serum levels, if possible; see the reference by Aronson and Aucoin for more information.

**Client Information** - With appropriate training, owners may give subcutaneous injections at home, but routine monitoring of therapy for efficacy and toxicity must still be done. Clients should also understand that the potential exists for severe toxicity (nephrotoxicity, ototoxicity) developing from this medication.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products:**

Gentamicin Sulfate Injection 50 mg/ml & 100 mg/ml (horses only) in 50 ml & 100 ml vials ; *Gentocin*® (Schering);*Ultragex*® *100* (Anthony); Generic (Rx) Approved for use in dogs, cats, and horses (not for food).

Gentamicin Sulfate Injection 5 mg/ml in 250 ml vials; *Garacin*® *Piglet Injection* (Schering); (OTC) Approved for use in swine. Slaughter withdrawal = 40 days.

Gentamicin Sulfate Oral Solution 50 mg/ml in 80 ml bottles; *Garacin*® *Oral Solution* (Schering); (OTC) Approved for use in swine. Slaughter withdrawal = 3 days.

Gentamicin Sulfate Oral Solution 4.35 mg/ml in 115 ml pump bottles (1 pump delivers approximately 5 mg); *Garacin*® *Pig Pump Oral Solution* (Schering); (OTC) Approved for use in swine. Slaughter withdrawal = 14 days.

Gentamicin Sulfate Soluble Powder 2 g gentamicin/30 grams of powder in 360 gram jar or 2 g gentamicin in 120 gram packets; *Garacin*® *Soluble Powder* (Schering); (OTC) Approved for use in swine. Slaughter withdrawal = 10 days.

Veterinary-approved injections for chickens and turkeys plus a water additive for egg dipping are available. Ophthalmic, otic and topical preparations are also available with veterinary labeling.

**Human-Approved Products** (partial listing):

To Drug Monograph Index To Ophthalmic Product Index

Gentamicin Sulfate Injection 40 mg/ml & 10 mg/ml as sulfate and 2 mg/ml as sulfate in 2 & 20 ml vials and 1.5 & 2 ml cartridge-needle units/disp. syringes and 2 ml amps; *Garamycin*® (Schering); *Jenamicin*® (Hauck); *Pediatric Gentamicin Sulfate*® (Elkins-Sinn; *Garamycin Pediatric*® (Schering); *Garamycin Intratheca*l® (Schering); generic, (Rx)

Topical, otic and ophthalmic labeled products are also available.

## GLUCOCORTICOID AGENTS, GENERAL INFORMATION

### Glucocorticoid Comparison Table

| DRUG | EQUIV. ANTI-INFLAMMA-TORY DOSE (mg) | RELATIVE ANTI-INFLAMMA-TORY POTENCY | RELATIVE MINERALO-CORTICOID ACTIVITY | PLASMA HALF-LIFE DOGS (min) [Humans] | DURATION OF ACTION AFTER ORAL/IV [IM] ADMIN. |
|---|---|---|---|---|---|
| Hydrocortisone (Cortisol) | 20 | 1 | 1-2 | 52-57 [90] | <12 hrs |
| Betamethasone Sod. Succ./ Sod. Phos. | 0.6 | 25 | 0 | ?[300+] | >48 hrs |
| Dexamethasone Sod. Succ./ Sod. Phos. | 0.75 | 30 | 0 | 119-136 [200-300+] | >48 hrs |
| Flumethasone | 1.5 | 15-30 | ? | ? | |
| Isoflupredone | | 17 | | | |
| Methylpred-nisolone | 4 | 5 | 0 | 91 [200] | 12-36 hrs |
| Prednisolone | 5 | 4 | 1 | 69-197 [115-212] | 12-36 hrs |
| Prednisone | 5 | 4 | 1 | [60] | 12-36 hrs |
| Triamcinolone Acetonide | 4 | 5 | 0 | [200+] | 12-36 hrs [weeks] |

**Pharmacology** - Glucocorticoids have effects on virtually every cell type and system in mammals. An overview of the effects of these agents follows:

**Cardiovascular System**: Glucocorticoids can reduce capillary permeability and enhance vasoconstriction. A relatively clinically insignificant positive inotropic effect can occur after glucocorticoid administration. Increased blood pressure can result from both the drugs' vasoconstrictive properties and increased blood volume that may be produced.

**Cells**: Glucocorticoids inhibit fibroblast proliferation, macrophage response to migration inhibiting factor, sensitization of lymphocytes and the cellular response to mediators of inflammation. Glucocorticoids stabilize lysosomal membranes.

**CNS/Autonomic Nervous System**: Glucocorticoids can lower seizure threshold, alter mood and behavior, diminish the response to pyrogens, stimulate appetite and maintain alpha rhythm. Glucocorticoids are necessary for normal adrenergic receptor sensitivity.

**Endocrine System**: When animals are not stressed, glucocorticoids will suppress the release of ACTH from the anterior pituitary, thereby reducing or preventing the release of endogenous corticosteroids. Stress

factors (*e.g.,* renal disease, liver disease, diabetes) may sometimes nullify the suppressing aspects of exogenously administered steroids. Release of thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), prolactin and luteinizing hormone (LH) may all be reduced when glucocorticoids are administered at pharmacological doses. Conversion of thyroxine ($T_4$) to triiodothyronine ($T_3$) may be reduced by glucocorticoids and plasma levels of parathyroid hormone increased. Glucocorticoids may inhibit osteoblast function. Vasopressin (ADH) activity is reduced at the renal tubules and diuresis may occur. Glucocorticoids inhibit insulin binding to insulin-receptors and the post-receptor effects of insulin.

**Hematopoietic System**: Glucocorticoids can increase the numbers of circulating platelets, neutrophils and red blood cells, but platelet aggregation is inhibited. Decreased amounts of lymphocytes (peripheral), monocytes and eosinophils are seen as glucocorticoids can sequester these cells into the lungs and spleen and prompt decreased release from the bone marrow. Removal of old red blood cells is diminished. Glucocorticoids can cause involution of lymphoid tissue.

**GI Tract and Hepatic System**: Glucocorticoids increase the secretion of gastric acid, pepsin and trypsin. They alter the structure of mucin and decrease mucosal cell proliferation. Iron salts and calcium absorption are decreased while fat absorption is increased. Hepatic changes can include increased fat and glycogen deposits within hepatocytes, increased serum levels of alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (GGT). Significant increases can be seen in serum alkaline phosphatase levels. Glucocorticoids can cause minor increases in BSP (bromosulfophthalein) retention time.

**Immune System** (also see Cells and Hematopoietic System): Glucocorticoids can decrease circulating levels of T-lymphocytes; inhibit lymphokines; inhibit neutrophil, macrophage, and monocyte migration; reduce production of interferon; inhibit phagocytosis and chemotaxis; antigen processing; and diminish intracellular killing. Specific acquired immunity is affected less than nonspecific immune responses. Glucocorticoids can also antagonize the complement cascade and mask the clinical signs of infection. Mast cells are decreased in number and histamine synthesis is suppressed. Many of these effects only occur at high or very high doses and there are species differences in response.

**Metabolic effects**: Glucocorticoids stimulate gluconeogenesis. Lipogenesis is enhanced in certain areas of the body (*e.g.,* abdomen) and adipose tissue can be redistributed away from the extremities to the trunk. Fatty acids are mobilized from tissues and their oxidation is increased. Plasma levels of triglycerides, cholesterol and glycerol are increased. Protein is mobilized from most areas of the body (not the liver).

**Musculoskeletal**: Glucocorticoids may cause muscular weakness (also caused if there is a lack of glucocorticoids), atrophy, and osteoporosis. Bone growth can be inhibited via growth hormone and somatomedin inhibition, increased calcium excretion and inhibition of vitamin D activation. Resorption of bone can be enhanced. Fibrocartilage growth is also inhibited.

**Ophthalmic**: Prolonged corticosteroid use (both systemic or topically to the eye) can cause increased intraocular pressure and glaucoma, cataracts and exophthalmos.

**Reproductive Tract, Pregnancy, & Lactation**: Glucocorticoids are probably necessary for normal fetal development. They may be required for adequate surfactant production, myelin, retinal, pancreas and mammary development. Excessive dosages early in pregnancy may lead to teratogenic effects. In horses and ruminants, exogenous steroid administration may induce parturition when administered in the latter stages of pregnancy. Glucocorticoids unbound to plasma proteins will enter milk. High dosages or prolonged administration to mothers may potentially inhibit the growth of nursing newborns.

**Renal, Fluid, & Electrolytes**: Glucocorticoids can increase potassium and calcium excretion; sodium and chloride reabsorption and extracellular fluid volume. Hypokalemia and/or hypocalcemia occur rarely. Diuresis may occur following glucocorticoid administration.

To Drug Monograph Index  To Ophthalmic Product Index

**Skin**: Thinning of dermal tissue and skin atrophy can be seen with glucocorticoid therapy. Hair follicles can become distended and alopecia may occur.

**Uses/Indications -** Glucocorticoids have been used in attempt to treat practically every malady that afflicts man or animal. Among some of the uses for glucocorticoids are: endocrine (adrenal insufficiency), rheumatic (arthritis), collagen diseases (systemic lupus), allergic states, respiratory diseases (asthma), dermatologic diseases (pemphigus, allergic dermatoses), hematologic (thrombocytopenias, autoimmune hemolytic anemias), neoplasias, nervous system (increased CSF pressure), GI (ulcerative colitis exacerbations) and renal (nephrotic syndrome). Some glucocorticoids are used topically in the eye and skin for various conditions or are injected intra-articularly or intra-lesionally. The above listing is certainly not complete. For specific dosages and indications refer to the Doses section for each glucocorticoid drug monograph.

**Contraindications/Precautions** - Systemic use of glucocorticoids are generally considered to be contraindicated in systemic fungal infections (unless used for replacement therapy in Addison's), when administered IM in patient's with idiopathic thrombocytopenia and in patient's hypersensitive to a particular compound. Use of sustained-release injectable glucocorticoids are considered to be contraindicated for chronic corticosteroid therapy of systemic diseases.

Animals who have received glucocorticoids systemically other than with "burst" therapy, should be tapered off the drugs. Patients who have received the drugs chronically should be tapered off slowly as endogenous ACTH and corticosteroid function may return slowly. Should the animal undergo a "stressor" (*e.g.,* surgery, trauma, illness, etc.) during the tapering process or until normal adrenal and pituitary function resume, additional glucocorticoids should be administered.
Corticosteroid therapy may induce parturition in large animal species during the latter stages of pregnancy.

**Adverse Effects/Warnings** - Adverse effects are generally associated with long-term administration of these drugs, especially if given at high dosages or not on an alternate day regimen. Effects generally are manifested as symptoms of hyperadrenocorticism. When administered to young, growing animals, glucocorticoids can retard growth. Many of the potential effects, adverse and otherwise, are outlined above in the Pharmacology section.

In dogs, polydipsia (PD), polyphagia (PP) and polyuria (PU), may all be seen with short-term "burst" therapy as well as with alternate-day maintenance therapy on days when the drug is given. Adverse effects in dogs can include dull, dry haircoat, weight gain, panting, vomiting, diarrhea, elevated liver enzymes, pancreatitis, GI ulceration, lipidemias, activation or worsening of diabetes mellitus, muscle wasting and behavioral changes (depression, lethargy, viciousness). Discontin-uation of the drug may be necessary; changing to an alternate steroid may also alleviate the problem. With the exception of PU/PD/PP, adverse effects associated with antiinflammatory therapy are relatively uncommon. Adverse effects associated with immunosuppressive doses are more common and potentially more severe.

Cats generally require higher dosages than dogs for clinical effect, but tend to develop fewer adverse effects. Occasionally, polydipsia, polyuria, polyphagia with weight gain, diarrhea, or depression can be seen. Long-term, high dose therapy can lead to "Cushinoid" effects, however.

Administration of dexamethasone or triamcinolone may play a role in the development of laminitis in horses.

**Overdosage** - Glucocorticoids when given short-term are unlikely to cause harmful effects, even in massive dosages. One incidence of a dog developing acute CNS effects after accidental ingestion of glucocorticoids has been reported. Should symptoms occur, use supportive treatment if required.

To Drug Monograph Index To Ophthalmic Product Index

Chronic usage of glucocorticoids can lead to serious adverse effects. Refer to Adverse Effects above for more information.

**Drug Interactions** - **Amphotericin B** or potassium-depleting diuretics (**furosemide, thiazides**) when administered concomitantly with glucocorticoids may cause hypokalemia. When these drugs are used concurrently with **digitalis glycosides**, an increased chance of digitalis toxicity may occur should hypokalemia develop. Diligent monitoring of potassium and digitalis glycoside levels are recommended. Glucocorticoids may reduce **salicylate** blood levels. **Insulin** requirements may increase in patients taking glucocorticoids. **Phenytoin, phenobarbital, rifampin** may increase the metabolism of glucocorticoids. Concomitant administration of glucocorticoids and **cyclosporin** may increase the blood levels of each, by mutually inhibiting the hepatic metabolism of each other. The clinical significance of this interaction is not clear. Glucocorticoids may also inhibit the hepatic metabolism of **cyclophosphamide**. Dosage adjustments may be required. The hepatic metabolism of **methylprednisolone** may be inhibited by **erythromycin**. **Mitotane** may alter the metabolism of steroids; higher than usual doses of steroids may be necessary to treat mitotane-induced adrenal insufficiency.
Patients taking corticosteroids at immunosuppressive dosages should generally not receive **live attenuated-virus vaccines** as virus replication may be augmented. A diminished immune response may occur after **vaccine, toxoid, or bactrin** administration in patients receiving glucocorticoids. Administration of **ulcerogenic drugs** (*e.g.,* **non-steroidal antiinflammatory drugs**) with glucocorticoids may increase the risk of gastrointestinal ulceration.
The effects of **hydrocortisone**, and possibly other glucocorticoids, may be potentiated by concomitant administration with **estrogens**. In patients with myasthenia gravis, concomitant glucocorticoid and **anticholinesterase agent** (*e.g.,* pyridostigmine, neostigmine, etc.) administration may lead to profound muscle weakness. If possible, discontinue anticholinesterase medication at least 24 hours prior to corticosteroid administration.

**Drug/Laboratory Interactions** - Glucocorticoids may increase **serum cholesterol** and **urine glucose** levels. Glucocorticoids may decrease **serum potassium**. Glucocorticoids can suppress the release of thyroid stimulating hormone (TSH) and reduce **$T_3$ & $T_4$** values. Thyroid gland atrophy has been reported after chronic glucocorticoid administration. Uptake of **$I^{131}$** by the thyroid may be decreased by glucocorticoids. Reactions to **skin tests** may be suppressed by glucocorticoids. False-negative results the **nitroblue tetrazolium test** for systemic bacterial infections may be induced by glucocorticoids.

**Monitoring Parameters** - Monitoring of glucocorticoid therapy is dependent on its reason for use, dosage, agent used (amount of mineralocorticoid activity), dosage schedule (daily versus alternate day therapy), duration of therapy, and the animal's age and condition.The following list may not be appropriate or complete for all animals; use clinical assessment and judgement should adverse effects be noted:

1) Weight, appetite, signs of edema
2) Serum and/or urine electrolytes
3) Total plasma proteins, albumin
4) Blood glucose
5) Growth and development in young animals
7) ACTH stimulation test if necessary

**Client Information** - Clients should carefully follow the dosage instructions and should not discontinue the drug abruptly without consulting with veterinarian beforehand. Clients should be briefed on the potential adverse effects that can be seen with these drugs and instructed to contact the veterinarian should these effects become severe or progress.

## GLYCOPYRROLATE

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - A synthetic quaternary ammonium antimuscarinic agent, glycopyrrolate occurs as a bitter-tasting, practically odorless, white, crystalline powder with a melting range of 193 - 198°C. One gram is soluble in 20 ml of water; 30 ml of alcohol. The commercially available injection is adjusted to a pH of 2-3 and contains 0.9% benzyl alcohol as a preservative. Glycopyrrolate may also be known as glycopyrronium bromide.

**Storage/Stability/Compatibility** - Glycopyrrolate tablets should be stored in tight containers and both the injection and tablets should be stored at room temperature (15-30°C).

Glycopyrrolate is stable under ordinary conditions of light and temperature. It is most stable in solution at an acidic pH and undergoes ester hydrolysis at pH's above 6.

Glycopyrrolate injection is physically **stable** in the following IV solutions: $D_5W$, $D_5$/half normal saline, Ringer's injection, and normal saline. Glycopyrrolate may be administered via the tubing of an IV running lactated Ringer's, but rapid hydrolysis will occur if it is added to an IV bag of LRS. The following drugs are reportedly physically **compatible** with glycopyrrolate: atropine sulfate, benzquinamide, chlorpromazine HCl, codeine phosphate, diphenhydramine HCl, droperidol, droperidol/fentanyl, hydromorphone, hydroxyzine HCl, lidocaine HCl, meperidine HCl, meperidine HCl/promethazine HCl, morphine sulfate, neostigmine methylsulfate, oxymorphone HCl, procaine HCl, prochlorperazine HCl, promazine HCl, promethazine HCl, pyridostigmine Br, scopolamine HBr, trimethobenzamide HCl.

The following drugs are reportedly **incompatible** with glycopyrrolate: chloramphenicol sodium succinate, dexamethasone sodium phosphate, diazepam, dimenhydrinate, methohexital sodium, methylprednisolone sodium succinate, pentazocine lactate, pentobarbital sodium, secobarbital sodium, sodium bicarbonate, and thiopental sodium. Other alkaline drugs (*e.g.,* thiamylal) would also be expected to be incompatible with glycopyrrolate. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** - An antimuscarinic with similar actions as atropine, glycopyrrolate is a quaternary ammonium compound and, unlike atropine, does not cross appreciably into the CNS. It, therefore, should not exhibit the same extent of CNS adverse effects that atropine possesses. For further information, refer to the atropine monograph.

**Uses/Indications** - Glycopyrrolate injection is approved for use in dogs and cats. The FDA approved indication for these species is as a preanesthetic anticholinergic agent. The drug is also used to treat sinus bradycardia, sinoatrial arrest, incomplete AV block where anticholinergic therapy may be beneficial. When cholinergic agents such as neostigmine or pyridostigmine are used to reverse neuromuscular blockade due to non-depolarizing muscle relaxants, glycopyrrolate may administered simultaneously to prevent the peripheral muscarinic effects of the cholinergic agent.

**Pharmacokinetics** - Quaternary anticholinergic agents are not completely absorbed after oral administration, but quantitative data reporting the rate and extent of absorption of glycopyrrolate is not available. In dogs, following IV administration, the onset of action is generally within one minute. After IM or SQ administration, peak effects occur approximately 30-45 minutes post injection. The vagolytic effects persist for 2-3 hours and the antisialagogue (reduced salivation) effects persist for up to 7 hours. After oral administration, the anticholinergic effects of glycopyrrolate may persist for 8-12 hours.

Little information is available regarding the distributory aspects of glycopyrrolate. Being a quaternary ammonium compound, glycopyrrolate is completely ionized. Therefore, it has poor lipid solubility and does not readily penetrate into the CNS or eye. Glycopyrrolate crosses the placenta only marginally; it is unknown if it is excreted into milk.

To Drug Monograph Index  To Ophthalmic Product Index

Glycopyrrolate is eliminated rapidly from the serum after IV administration and virtually no drug remains in the serum 30 minutes to 3 hours after dosing. Only a small amount is metabolized and the majority is eliminated unchanged in the feces and urine.

**Contraindications/Precautions** - The manufacturer (Robins) of the veterinary product lists contraindications to glycopyrrolate's use in dogs and cats in animals hypersensitive to it and that it should not be used in pregnant animals. However, it would be prudent to refer to the recommendations listed in the atropine monograph regarding contraindications and precautions.

**Adverse Effects/Warnings** - With the exceptions of rare CNS adverse effects and being slightly less arrhythmogenic, glycopyrrolate can be expected to have a similar adverse effect profile as atropine. The manufacturer of the veterinary product (Robins) lists only mydriasis, tachycardia, and xerostomia as adverse effects in dogs and cats at the doses they recommend. For more information refer to the atropine monograph.

**Overdosage** - In dogs, the $LD_{50}$ for glycopyrrolate is reported to be 25 mg/kg IV. Doses of 2 mg/kg IV daily for 5 days per week for 4 weeks demonstrated no signs of toxicity. In the cat, the $LD_{50}$ after IM injection is 283 mg/kg. Because of its quaternary structure, it would be expected that minimal CNS effects would occur after an overdose of glycopyrrolate when compared to atropine. See the information listed in the atropine monograph for more information.

**Drug Interactions** - Glycopyrrolate would be expected to have a similar drug interaction profile as atropine. The following drugs may enhance the activity of glycopyrrolate and its derivatives: **antihistamines, procainamide, quinidine, meperidine, benzodiazepines, phenothiazines**.
The following drugs may potentiate the adverse effects of glycopyrrolate and its derivatives: **primidone, disopyramide, nitrates, long-term corticosteroid use** (may increase intraocular pressure).
Glycopyrrolate and its derivatives may enhance the actions of **nitrofurantoin, thiazide diuretics, sympathomimetics**. Glycopyrrolate and its derivatives may antagonize the actions of **metoclopramide**.

**Doses** -
**Horses**:

For treatment of bradyarrhythmias due to increased parasympathetic tone:

a) 0.005 mg/kg IV (Muir and McGuirk 1987a)

As a bronchodilator:

a) Initially, 2 -3 mg IM *bid-tid* for a 450 kg animal (Beech 1987)

**Monitoring Parameters** - Dependent on route of administration, dose, and reason for use. See the atropine monograph for more information.

**Client Information** - Parenteral glycopyrrolate administration is best performed by professional staff and where adequate cardiac monitoring is available. If animal is receiving glycopyrrolate tablets, allow animal free access to water and encourage drinking if dry mouth is a problem

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Glycopyrrolate for Injection 0.2 mg/ml in 20 ml vials; *Robinul®-V* (Veterinary - 20 ml vial only); (Fort Dodge) (Rx) Approved for use in dogs and cats.

**Human-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Glycopyrrolate Tablets 1 mg & 2 mg; *Robinul*® & *Robinul Forte*® (2 mg) (Robins); Generic; (Rx)

Glycopyrrolate for Injection 0.2 mg/ml in 1, 2, 5, & 20 ml vials; *Robinul*® (Robins); Generic; (Rx)

## GRISEOFULVIN

**Chemistry** - A fugistatic antibiotic produced by species of Penicillium (primarily *P. griseofulvum*), griseofulvin occurs as an odorless or nearly odorless, bitter tasting, white to creamy white powder. It is very slightly soluble in water and sparingly soluble in alcohol.
Two forms of the drug are available commercially. Microsize griseofulvin contains particles with a predominant size of 4 µm in diameter, while the ultramicrosize form particle size averages less than 1 micron in diameter.

**Storage/Stability/Compatibility** - Although griseofulvin is relatively thermostable, products should be stored at less than 40°C, preferably at 15-30°C. Griseofulvin suspension should be stored in tight, light-resistant containers. Microsize tablets and capsules should be stored in tight containers; the ultramicrosize tablets should be stored in well-closed containers.

**Pharmacology** - Griseofulvin acts on susceptible fungi by disrupting the structure of the cell's mitotic spindle, thereby arresting the metaphase of cell division. Griseofulvin has activity against species of *Trichophyton*, *Microsporum* and *Epidermophyton*. Only new hair or nail growth is resistant to infection. It has no antibacterial activity, and is not clinically useful against other pathogenic fungi.

**Uses/Indications** - In veterinary species, griseofulvin is approved for use in dogs and cats to treat dermatophytic fungal (see above) infections of the skin, hair and claws, and to treat ringworm (caused by *T. equinum* and *M. gypseum*) in horses. It has also been used in laboratory animals and ruminants for the same indications.

**Pharmacokinetics** - The microsized form of the drug is absorbed variably (25-70%); dietary fat will enhance absorption. The ultramicrosize form of the drug may be nearly 100% absorbed. Generally, the ultramicrosize form is absorbed 1.5 times as well as the microsized form for a given patient.

Griseofulvin is concentrated in skin, hair, nails, fat, skeletal muscle and the liver, and can be found in the stratum corneum within 4 hours of dosing.

Griseofulvin is metabolized by the liver via oxidative demethylation and glucuronidation to 6-desmethylgriseofulvin which is not active. In humans, the half-life is 9-24 hours. A serum half-life of 47 minutes has been reported for dogs. Less than 1% of the drug is excreted unchanged in the urine.

**Contraindications/Precautions/Reproductive Safety** - Griseofulvin is contraindicated in patients hypersensitive to it or with hepatocellular failure.

Because kittens may be overly sensitive to the adverse effects associated with griseofulvin, they should be monitored carefully if treatment is instituted.

Griseofulvin is a known teratogen in cats. Dosages of 35 mg/kg given to cats during the first trimester caused cleft palate, and other skeletal and brain malformations in kittens. Griseofulvin may also inhibit spermatogenesis. Because dermatophytic infections are not generally life-threatening and alternative therapies are available, use of the drug should be considered contraindicated during pregnancy.

To Drug Monograph Index To Ophthalmic Product Index

**Adverse Effects/Warnings** - Griseofulvin can cause anorexia, vomiting, diarrhea, anemia, neutropenia, leukopenia, depression, ataxia, hepatotoxicity or dermatitis/photosensitivity. With the exception of GI symptoms, adverse effects are uncommon at usual doses. Cats, particularly kittens, may be more susceptible to adverse effects than other species. This could be due to this species' propensity to more slowly form glucuronide conjugates and thus metabolize the drug at a slower rate than either dogs or humans.

**Overdosage/Acute Toxicity** - No specifics regarding griseofulvin overdosage or acute toxicity was located. It is suggested that significant overdoses be handled with gut emptying, charcoal and cathartic administration unless contraindicated. Contact a poison control center for more information. Horses have received 100 mg/kg PO for 20 days without apparent ill effect.

**Drug Interactions** - **Phenobarbital** (and other barbiturates) has been implicated in causing decreased griseofulvin blood concentrations, presumably by inducing hepatic microsomal enzymes and/or reducing absorption. If phenobarbital and griseofulvin are given concurrently, griseofulvin dosage adjustment may be necessary. **Coumarin** (*e.g.,* warfarin) **anticoagulants** may have their anticoagulant activity reduced by griseofulvin; anticoagulant adjustment may be required. Griseofulvin may potentiate the effects of **alcohol**.

**Doses** -
Note: all doses are for microsize preparations unless otherwise indicated.
**Horses**:
For susceptible dermatophytic infections:
a) 10 mg/kg PO once daily (Robinson 1987)
b) 10 mg/kg PO (in feed) daily for 7 days (Brumbaugh 1987)

**Monitoring Parameters** -
1) Clinical efficacy; culture
2) Adverse effects
3) CBC q2-3 weeks during therapy
4) Liver enzymes (if indicated)

**Client Information** - Clients should be instructed in procedures used to prevent reinfection (destruction of old bedding, disinfection, periodic reexaminations, hair clipping, etc.) and the importance of compliance with the dosage regimen. Should animal develop adverse effects other than mild GI disturbances, they should contact their veterinarian.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Griseofulvin (Microsize) Powder 2.5 g griseofulvin in 15 g sachets
*Fulvicin-U/F® Powder* (Schering-Plough); (Rx) Approved for use in horses.

Griseofulvin (Microsize) Tablets 250 mg, 500 mg (scored); *Fulvicin-U/F® Tablets* (Schering-Plough); (Rx) Approved for use in dogs and cats.

**Human-Approved Products**:
Griseofulvin (Microsize) Capsules 250 mg; *Grisactin®* (Wyeth-Ayerst); (Rx)

Griseofulvin (Microsize) Tablets 250 mg, 500 mg; *Fulvicin-U/F®* (Schering); *Grifulvin V®* (Ortho); *Grisactin 500®* (Wyeth-Ayerst); (Rx)

Griseofulvin (Microsize) Oral Suspension 125 mg/5 ml in 120 ml; *Grifulvin V®* (Ortho Derm); (Rx)

To Drug Monograph Index To Ophthalmic Product Index

Griseofulvin (Ultramicrosize) Tablets 125 mg, 165 mg, 250 mg, 330 mg; *Fulvicin P/G*® (Schering); *Grisactin Ultra*® (Wyeth-Ayerst); *Gris-PEG*® (Allergan Herbert); generic. (Rx)

## GUAIFENESIN

**Chemistry** - Formerly known as glyceryl guaiacolate, guaifenesin occurs as a white to slightly gray, crystalline powder which may have a characteristic odor. It is nonhygroscopic and melts between 78° - 82°C. One gram is soluble in 15 ml of water and it is soluble in alcohol, propylene glycol and glycerin. Guaifenesin may also be known as glyceryl guaiacolate, GG, or guaiphenesin.

**Storage/Stability/Compatibility** - Guaifenesin is stable in light and heat (less than melting point). It should be stored in well closed containers.

When dissolved into aqueous solutions, guaifenesin may slightly precipitate out of solution when the temperature is less than 22°C (72°F). Slight warming and agitation generally resolubilizes the drug. A microwave oven has been suggested for heating and dissolving the drug. It is recommended that the solution be prepared freshly before use, but a 10% solution (in sterile water) may apparently be stored safely at room temperature for up to one week with only slight precipitation occurring.

Guaifenesin is physically **compatible** with sterile water or $D_5W$. It is also reportedly compatible with ketamine, pentobarbital, thiamylal, thiopental, and xylazine.

**Pharmacology** - While the exact mechanism of action for the muscle relaxant effects are not known, it is believed that guaifenesin acts centrally by depressing or blocking nerve impulse transmission at the internuncial neuron level of the subcortical areas of the brain, brainstem and spinal cord. It relaxes both the laryngeal and pharyngeal muscles, thus allowing easier intubation. Guaifenesin also has mild intrinsic analgesic and sedative qualities.

Guaifenesin causes an excitement-free induction and recovery from anesthesia in horses. It produces relaxation of skeletal muscles, but does not affect diaphragmatic function and has little, if any, effects on respiratory function at usual doses. Possible effects on the cardiovascular system include transient mild decreases in blood pressure and increases in cardiac rate. Gastrointestinal motility may be increased, but generally no adversity is seen with this.

Guaifenesin potentiates the activity of preanesthetic and anesthetic agents.

**Uses/Indications** - In veterinary medicine, guaifenesin is used to induce muscle relaxation and restraint as an adjunct to anesthesia for short procedures (30-60 minutes) in large and small animal species.

In human medicine, guaifenesin has long been touted as an oral expectorant, but definitive proof of its efficacy is lacking.

**Pharmacokinetics** - The pharmacokinetics of guaifenesin have not been thoroughly studied in most species. When administered alone to horses IV, recumbency usually occurs within 2 minutes and light (not surgical level) restraint persists for about 6 minutes. Muscle relaxation reportedly persists for 10-20 minutes after a single dose.

Guaifenesin is conjugated in the liver and excreted into the urine. A gender difference in the elimination half-life of guaifenesin in ponies has been demonstrated, with males having a $t_{1/2}$ of approximately 85 minutes,

and females a $t_{1/2}$ of about 60 minutes. Guaifenesin reportedly crosses the placenta, but adverse effects in newborns of mothers who received guaifenesin have not been described.

**Contraindications/Precautions** - The manufacturer states that the use of physostigmine is contraindicated with guaifenesin (see Drug Interactions).

**Adverse Effects/Warnings** - At usual doses, side effects are transient and generally minor. A mild decrease in blood pressure and increase in cardiac rate can be seen. Thrombophlebitis has been reported after IV injection, and perivascular administration may cause some tissue reaction. Hemolysis may occur in solutions containing greater than a 5% concentration of guaifenesin, but some sources state this is insignificant at even a 15% concentration.

**Overdosage** - The margin of safety is reportedly 3 times the usual dose. Symptoms of apneustic breathing, nystagmus, hypotension, and contradictory muscle rigidity are associated with toxic levels of the drug. No specific antidote is available. It is suggested that treatment be supportive until the drug is cleared to sub-toxic levels.

**Drug Interactions** - Drug interactions with guaifenesin are not well studied. The manufacturer (Robins) states that **physostigmine** is contraindicated in horses receiving guaifenesin, but does not elucidate on the actual interaction. It may be logical to assume that other anticholinesterase agents (neostigmine, pyridostigmine, edrophonium) may also be contraindicated.

**Doses** -
**Horses**:

a) 110 mg/kg IV, give first 1/3-1/2 of dose until horse falls gently, then give remainder unless respiratory or cardiovascular effects are observed. (Package Insert, *Guailaxin*® - Robins)
b) Guaifenesin only: 66 - 132 mg/kg IV; or guaifenesin 44 - 88 mg/kg IV with 2.2 - 6.6 mg/kg thiamylal (Muir )
c) 55 - 110 mg/kg IV (Mandsager 1988)
d) For anesthesia: 100 mg/kg IV combined with barbiturate in 5% dextrose. As an expectorant: 3 mg/kg PO (Robinson 1987)

**Monitoring Parameters** -

1) Level of muscle relaxation
2) Cardiac and respiratory rate

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Guaifenesin Sterile Powder for Injection 50 gram for reconstitution in 4 oz and 32 oz containers; *Guailaxin*® (Fort Dodge), *Gecolate*® (Summit Hill); (Rx) Approved for use in horses.

Guaifenesin Injection 50mg/ml 1000ml; *Gecolate*® (Summit Hill); generic (Phoenix); (Rx) Approved for use in horses.

**Human-Approved Products**: No parenteral preparations are approved. There are many OTC oral expectorant/cough preparations on the market.

## HALOPERIDOL

To Drug Monograph Index To Ophthalmic Product Index

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

a) For the transport of wild African elephants, according to shoulder height: 1.60-1.69 m shoulder height (40 mg haloperidol); 1.70-1.79 m (50 mg); 1.80-1.89 m (60 mg); 1.90-2.09 m (70 mg); 2.10-2.19 m (80 mg); 2.20-2.39 m (100 mg); > 2.40 m (120 mg). Do not give haloperidol to juveniles < 1.6 m. Elephants 1.8 – 2.1 m are profoundly influenced by the drug and difficult to transport. Effective for about 8 hours. du Toit,J.G., 2001. **Veterinary Care of African Elephants**. Novartis, Pretoria, Republic of South Africa, 1-59 pp. www.wildlifedecisionsupport.com

b) Following immobilization for translocation of 670 African elephants in family units in 1993, haloperidol (40 to 120 mg depending on body size) was used as a tranquilizer during transport. In addition, azaperone, (50-200 mg) was often administered to avoid aggression. Coetsee,C. 1996. **Elephant Translocations**. Pachyderm 22:81

c) 40 mg/animal IM or oral for captive Asian elephants. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants** . In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

d) an adult Asian bull was given 100 mg haloperidol orally bid. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1992. **A case of ochlophobia in a tusker**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 176

**Full text:** An adult captive tusker to be used for ceremonial purpose could not tolerate crowd (ochlophobia - fear of the crowd). The animal was put on 2000 mg of chlorpromazine twice daily orally and behaved normally during the entire festival season of 6 months. The animal again showed symptoms of fear of the crowd when the owner withdrew the drug. So the animal was put on 100 mg haloperidol twice daily orally. This relieved the symptoms very well but without sedation compared to chlorpromazine hydrochloride.

**See also:**

Ebedes,H. 1995. **The use of long term neuroleptics in the confinement and transport of wild animals**. Joint Conf AAZV/WDA/AAWV. Pages: 173-176

Raath,J.P., 1993. **Chemical capture of the African elephant**. In: The Capture and care manual : capture, care, accommodation and transportation of wild African animals. Pretoria : Wildlife Decision Support Services : South African Veterinary Foundation, Pretoria pp. 484-511

Blumer,E.S. 1991. **A review of the use of selected neuroleptic drugs in the management of nondomestic hoofstock**. Proc. Am. Assoc. Zoo Vet. Pages: 333-339

To Drug Monograph Index To Ophthalmic Product Index

Lance,W.R. 1991. **New pharmaceutical tools for the 1990's**. Proceedings of the American Association of Zoo Veterinarians 354-359

## HALOTHANE

**Chemistry** - An inhalant general anesthetic agent, halothane occurs as a colorless, nonflammable, heavy liquid. It has a characteristic odor resembling chloroform and sweet, burning taste. Halothane is slightly soluble in water and miscible with alcohol. At 20°C, halothane's specific gravity is 1.872-1.877 and vapor pressure is 243 mm Hg.

**Storage/Stability/Compatibility** - Store halothane below 40°C in a tight, light-resistant container. Halothane stability is maintained by the addition of thymol and ammonia. The thymol does not vaporize so it may accumulate in the vaporizer causing a yellow discoloration. Do not use discolored solutions. Discolored vaporizer and wick may be cleaned with diethyl ether (all ether must be removed before reuse).

In the presence of moisture, halothane vapor can react with aluminum, brass and lead (not copper). Rubber and some plastics are soluble in halothane leading to their rapid deterioration.

**Pharmacology** - While the precise mechanism that inhalent anesthetics exert their general anesthetic effect is not precisely known, they may interfere with functioning of nerve cells in the brain by acting at the lipid matrix of the membrane. Some key pharmacologic effects noted with halothane include: CNS depression, depression of body temperature regulating centers, increased cerebral blood flow, respiratory depression (pronounced in ruminants), hypotension, vasodilatation, and myocardial depression.

Minimal Alveolar Concentration (MAC; %) in oxygen reported for halothane in various species: Dog = 0.76; Cat = 0.82; Horse = 0.88; Human = 0.76. Several factors may alter MAC (acid/base status, temperature, other CNS depressants on board, age, ongoing acute disease, etc.).

**Uses/Indications** - Halothane remains a useful general anesthetic in veterinary medicine due to its relative safety, potency, controllability, non-flammability, and comparative low cost.

**Pharmacokinetics** - Halothane is rapidly absorbed through the lungs. About 12% of absorbed drug is metabolized by the liver to trifluoroacetic acid (only small amounts), chlorine and bromine radicals which are excreted in the urine. The bulk of the absorbed drug is re-excreted by the lungs and eliminated with expired air. Halothane is distributed into milk.

**Contraindications/Precautions/Reproductive Safety** - Halothane is contraindicated in patients with a history or predilection towards malignant hyperthermia or significant hepatotoxicity after previous halothane exposure (see Adverse Reactions below). It should be used with caution (benefits vs. risks) in patients with hepatic function impairment, cardiac arrhythmias, increased CSF or head injury, myasthenia gravis, or pheochromocytoma (cardiac arrhythmias due to catecholamines).

Some animal studies have shown that halothane may be teratogenic; use only when benefits outweigh potential risks.

**Adverse Effects/Warnings** - Hypotension may occur and is considered to be dosage related. A malignant hyperthermia-stress syndrome has been reported in pigs, horses, dogs and cats. Halothane may cause cardiac depression and dysrhythmias. Halothane-induced hypotension may be treated by volume expansion and dobutamine. Lidocaine has been used to treat or prevent halothane-induced cardiac dysrhythmias.

To Drug Monograph Index  To Ophthalmic Product Index

In humans, jaundice and a postanesthetic fatal liver necrosis has been reported rarely. The incidence of this effect in veterinary species is not known. However, halothane should be considered contraindicated for future use if unexplained fever, jaundice or other symptoms associated with hepatotoxicity occur.

**Drug Interactions** - **Acetaminophen** is not recommended to be used for post-operative analgesia in animals who have received halothane anesthesia. Because halothane sensitizes the myocardium to the effects of sympathomimetics, especially catecholamines, severe ventricular arrhythmias may result. Drugs included are: **dopamine, epinephrine, norepinephrine, ephedrine, metaraminol, etc.** If these drugs are needed, they should be used with caution and in significantly reduced dosages with intensive monitoring. **Non-depolarizing neuromuscular blocking agents, systemic aminoglycosides, systemic lincomycins** should be used with caution with halogenated anesthetic agents as additive neuromuscular blockade may occur. Reportedly, **d-tubocurarine** may cause significant hypotension if used with halothane. Concomitant administration of **succinylcholine** with inhalation anesthetics (halothane, cyclopropane, nitrous oxide, diethyl ether) may induce increased incidences of cardiac effects (bradycardia, arrhythmias, sinus arrest and apnea) and in susceptible patients, malignant hyperthermia.

**Laboratory Considerations -** Halothane may transiently increase values of **liver function tests.**

**Doses** -
**Horses**:

a)For draft horses: Following induction, the largest ET tube that will comfortably fit (20 - 40 mm) should be placed and cuff inflated. In an oxygen-enriched semi-closed large animal circle system 4-5% of halothane is administered initially and is reduced as indicated by physical monitoring of neural reflexes and cardiopulmonary parameters. The goal should be the lowest concentration inhalant anesthetic that provides adequate surgical anesthesia and restraint. Most draft horses can be maintained on 2.5 - 3% halothane. (See reference for more information on monitoring and use.) (Geiser 1992)

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

**SPECIAL NOTE CONCERNING THE USE OF HALOTHANE:** several authors recommend that halothane be discontinued for a period of time (10-40 minutes) prior to the administration of narcotic antagonists in elephants immobilized with etorphine or carfentanil. The administration of oxygen (with a high flow rate and frequent emptying of the re-breathing bag) facilitates removal of halothane and can prevent ataxia once the narcotic antagonist is given.

a) Halothane at 1-2% was used to maintain anesthesia in two five-year-old African elephants with estimated weights of 1200 and 1000 kg subsequent to the administration of azaperone and etorphine. Stegmann,G.F. 1999. **Etorphine-halothane anaesthesia in two five-year-old African elephants (Loxodonta africana)**. Journal of the South African Veterinary Medical Association 70:(4):164-166 **Abstract:** Anaesthesia of 2 five-year-old female African elephants (Loxodonta africana) was required for dental surgery. The animals were each premedicated with 120 mg of azaperone 60 min before transportation to the hospital. Before offloading, 1 mg etorphine was administered intramuscularly (i.m.) to each elephant to facilitate walking them to the equine induction/recovery room. For induction, 2 mg etorphine was administered i.m. to each animal. Induction was complete within 6 min. Surgical anaesthesia was induced with halothane-in-oxygen after intubation of the trunk. During surgery the mean heart rate was 61 and 45 beats/min respectively. Systolic blood pressures increased to 27.5 and 25.6 kPa respectively, and were treated with intravenous azaperone. Blood pressure decreased thereafter to a mean

systolic pressure of 18.1 and 19.8 kPa, respectively. Rectal temperature was 35.6 and 33.9 degrees C at the onset of surgery, and decreased to 35.3 and 33.5 degrees C, respectively, at the end of anaesthesia. Etorphine anaesthesia was reversed with 5 mg diprenorphine at the completion of 90 min of surgery. **Additional information:** Case 1 (1200 kg): A narrow oropharynx precluded tracheal intubation. Latex tubing (15mm) was inserted 30 cm into one trunk passage and a 16 mm silicone endotracheal tube was placed in the other trunk passage to administer anesthesia at a flow rate of 15 l/min. Additional etorphine was given 1.5 hours after induction when anesthetic depth suddenly decreased. Azaperone (40 mg) IV reduced blood pressure from systolic/diastolic 27.5/20.5 kPa to 14.4/7.1 kPa within 15 minutes. Total duration of the procedure was 1 hour 45 minutes. Case 2 (1000kg): Trunk passages were intubated with 12 mm cuffed silicon endotracheal tubes and connected to the circle anesthetic machine with a 2nd Y-piece. The flow rate was 15l/min. Azaperone (20 mg IV) reduced blood pressure from systolic/diastolic 29.2/23.2 kPa after instrumentation to 19.3/8 kPa within 5 minutes. Etorphine (0.5 mg) was given IV at 60 and 75 minutes to maintain anesthesia. Duration of procedure was 2 hr.

b) Halothane at 1-2% was used to maintain anesthesia in 6 elephants ( 650-1500 kg) immobilized with etorphine or carfentanil. Flow rates varied from 5ml/kg/min to 10 ml/kg/min. Welsch,B., Jacobson,E.R., Kollias,G.V., Kramer,L., Gardner,H., and Page,C.D. 1989. **Tusk extraction in the African elephant (*Loxodonta africana*)**. Journal of Zoo and Wildlife Medicine 20:(4):446-453 **Abstract:** Unilateral dentoalveolar abscesses and/or tusk fractures were identified and tusk extractions performed in seven 3.5-21-yr-old African elephants (*Loxodonta africana*) of both sexes weighing 650-3,000 kg. Following immobilization with etorphine hydrochloride or carfentanil citrate, six of seven elephants were intubated and maintained on a 1-1.5% halothane in oxygen mixture; one elephant was maintained in lateral recumbency by multiple i.v. injections of etorphine. All elephants were positioned with the affected tusk up. For one elephant, two surgical procedures were required to remove the tusk. In six of seven elephants, the tusks were sectioned transversely and the tusk wall thinned by enlarging the pulp cavity with carbide burs. In those tusks with remaining pulp, the pulp was removed with stainless steel rods and hooks. Next, the tusk was sectioned longitudinally into three or four segments using a wood saw within the pulp chamber. bone gouges, osteotomes, and a mallet were used to free the outer epithelial and alveolar attachments from the tusk. Starting with the smallest segment, the sections were removed using long screwdriver-shaped stainless steel rods. The alveolar chamber was then periodically flushed postsurgically with a dilute organic iodine solution. For six of seven elephants, complete granulation of the alveolar chamber was evident by 4 mo postsurgery; the seventh elephant showed partial healing with granulation tissue at 2 mo following surgery.

c) Halothane was used to maintain anesthesia in 16 juvenile (3-5 yr) African elephants immobilized 1 or more times (27 procedures). Xylazine (0.1 ± 0.04 mg/kg) and ketamine (0.6 ± 0.13 mg/kg) were given IM for a 45-minute transport. Anesthesia was induced with etorphine (1.9 ±0.56 µg/kg). Endotracheal tubes of 18, 22, and 26 mm (I.D.) were used in elephants weighing 150-304 kg, 204-350 kg, and 280-636 kg respectively. Halothane % varied from 0.5 ± 0.78% during the first 30 minutes to 1.0 ± 0.42% which was attributed to the additive effect of the etorphine and/or the xylazine/ketamine combination given for transport. Heard,D.J., Kollias,G.V., Webb,A.I., Jacobson,E.R., and Brock,K.A. 1988. **Use of halothane to maintain anesthesia induced with etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 193:254-256 **Excerpts:** Sixteen 3- to 5-year-old African elephants were anesthetized one or more times for a total of 27 diagnostic and surgical procedures. Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing juvenile elephants during a 45-minute transport period before administration of general anesthesia. After IM or IV administration of etorphine (1.9 ± 0.56 micrograms/kg), the mean time to lateral recumbency was 20 ± 6.6 and 3 ± 0.0 minutes, respectively. The mean heart rate, systolic blood pressure, and respiration rate during all procedures was 50 ± 12 beats/min, 106 ± 19 mm of Hg, and 10 ± 3 breaths/min, respectively.

To Drug Monograph Index To Ophthalmic Product Index

Cardiac arrhythmias were detected during 2 procedures. In one elephant paroxysmal ventricular tachycardia was detected and the procedure terminated when the arrhythmia failed to stabilize after multiple doses of lidocaine (1 mg/kg, IV). In another elephant, second degree atrioventricular block returned to normal sinus rhythm after IV administration of atropine (0.04 mg/kg).

In one elephant, low mean blood pressure (54 mm of Hg) responded to reduction in halothane (vaporizer setting 1 to 0.75%) and slow infusion of dobutamine HCl ((250 mg/1,000 ml) given to effect. The systolic blood pressure increased to 90 mm of Hg and remained high with a continuous infusion of dobutamine (5 µg/kg/min).

Immediately after induction in another elephant, profound respiratory depression (< 1breath/minute) and palpably weak arterial pulse were identified. Intravenous administration of diprenorphine at half the recommended reversal dose resulted in improvement of respiration and palpable arterial pulse, without the elephant developing signs of complete anesthetic reversal.

Alterations in systolic blood pressure, ear flapping, and trunk muscle tone were useful for monitoring depth of anesthesia. Results indicated that halothane in oxygen was effective for maintenance of surgical anesthesia in juvenile African elephants after induction with etorphine. Note: A correction appeared in a later volume 193(6): p.721.

d) Seven young African elephants (1-2 yrs) were maintained on 0.5 % halothane following induction with etorphine and intubated with 22-26 mm (I.D.) endotracheal tubes. Jacobson,E.R., Chen,C.-L., Gronwall,R., and Tiller,A. 1986. **Serum concentrations of etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 189:(9):1079-1081 **Abstract:** Eleven juvenile African elephants were given etorphine hydrochloride (2.19 + 0.11 micrograms/kg body weight, mean +SD) as a single IM injection; 3 elephants were given additional etorphine (0.42+0.09) IV. After immobilization, each elephant was maintained in lateral recumbency by administration of a 0.5% halothane/oxygen mixture or by administration of multiple IV injections of etorphine. At postinjection hours 0.25 and 0.5 and at 30-minute intervals thereafter, blood samples were collected via an auricular artery, and serum concentrations of etorphine were determined by use of radioimmunoassay. The highest mean serum concentration of etorphine in 6 elephants given a single IM injection and subsequently maintained on halothane and oxygen was 1.62+0.97 ng/ml at postinjection hours 0.5; thereafter, the mean serum concentration decreased steadily. In 4 elephants maintained in lateral recumbency with multiple IV administrations of etorphine, a correlation was not found between the time to develop initial signs of arousal and serum concentrations of etorphine before arousal. After administration of the initial immobilizing dose of etorphine, the interval between successive IV administrations of etorphine decreased.

e) A 25-year-old African elephant (estimated weight 3000 kg) was induced with 6 mg etorphine IM. Trunk passages were intubated with 13 mm (I.D.) endotracheal tubes and cuffs partially inflated. Halothane was initially given at 2.5% at a flow rate of 14L/min. A 30-L rebreathing bag was used. At 30 minutes the halothane was decreased to 0.5%. At 45 minutes the elephant showed signs of arousal. Etorphine (1 mg) was given and halothane increased to 2.5%. Total anesthesia time was 150 minutes. Halothane was discontinued and oxygen administered for 10 minutes prior to narcotic reversal. Tamas,P.M. and Geiser,D.R. 1983. **Etorphine analgesia supplemented by halothane anesthesia in an adult African elephant**. Journal of the American Veterinary Medical Association 183:(11):1312-1314

f) Halothane was used to maintain etorphine-acepromazine induced anesthesia in two Asian elephants. Procedure 1: Elephant “Joti” estimated weight 1000 kg. Premedicated with 1.3 etorphine plus acetylpromazine (Immobilon®). Induced with 5% halothane at a flow rate of 1.5L/min for 10 minutes (HR = 64). Maintained for 25 minutes with 2 % halothane at 5L/min. Anesthesia discontinued due to shallow respiration but resumed after 20 minutes with 3% halothane at 5 L/min. A total of 38 ml of halothane was administered in

To Drug Monograph Index To Ophthalmic Product Index

68 min (0.55 ml/min). Procedure 2: same elephant: 80-minute procedure with total consumption of halothane 26 ml (0.43 ml/min). Procedure 3: Elephant : Raima" weight 890 kg premedicated with 1.2 mg Immobilon®). Anesthesia induced with 2% halothane at 2 L/min. Total duration of anesthesia 52 minutes and total halothane consumption 17 ml (0.33 ml/min). Jarofke,D. 1981. **Use of halothane oxygen anesthesia in elephants (*Elephas maximus*)**. Journal of Zoo Animal Medicine 12:(3):93-95

See also:

Lateur,N. and Stolk,P. 1986. **Repeated general anesthesia in a male Indian elephant**. Proc.Am.Assoc.Zoo Vet. Pages: 128-131 (a 4500 kg Asian elephant was immobilized with etorphine, acepromazine and xylazine and maintained on halothane at 30L/min).

**Monitoring Parameters** - 1) Respiratory and ventilatory status; 2) Cardiac rate/rhythm; blood pressure (particularly with "at risk" patients); 3) Level of anesthesia

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Halothane, USP (with thymol 0.01% and ammonia 0.00025%) in 250 ml bottles; (Fort Dodge); (Rx)

**Human-Approved Products**:
Halothane in 125 & 250 ml bottles; *Halothane*® (Abbott) (Rx), *Fluothane*® (Wyeth-Ayerst) (Rx)

**HCG - see Chorionic Gonadotropin**

## HEPARIN

**Chemistry** - Heparin is an anionic, heterogeneous sulfated glycosaminoglycan molecule with an average molecular weight of 12,000 that is found naturally in mast cells. It is available commercially as either sodium or calcium salts and is obtained from either porcine intestinal mucosa (both calcium and sodium salts) or from bovine lung tissue (sodium salt only). Heparin sodium and calcium occur as white or pale-colored, amorphous, hygroscopic powders having a faint odor. Both are soluble in water and practically insoluble in alcohol; the commercial injections have a pH of 5-7.5. Heparin potency is expressed in terms of USP Heparin units and values are obtained by comparing against a standard reference from the USP. The USP requires that potencies be not less than 120 units/mg on a dried basis for heparin derived from lung tissue, and 140 units/mg when derived from all other tissue sources.

**Storage/Stability/Compatibility** - Heparin solutions should be stored at room temperature (15-30°C) and not frozen. Avoid excessive exposure to heat.

Heparin sodium is reportedly **compatible** with the following intravenous solutions and drugs: amino acids 4.25%-dextrose 25%, dextrose-Ringer's combinations, dextrose-lactated Ringer's solutions, fat emulsion 10%, Ringer's injection, Normosol R, aminophylline, amphotericin B w/ or w/o hydrocortisone sodium phosphate, ascorbic acid injection, bleomycin sulfate, calcium gluconate, cephapirin sodium, chloramphenicol sodium succinate, clindamycin phosphate, dimenhydrinate, dopamine HCl, erythromycin gluceptate, isoproterenol HCl, lidocaine HCl, methylprednisolone sodium succinate, metronidazole with sodium succinate, nafcillin sodium, norepinephrine bitartrate, potassium chloride, prednisolone sodium succinate, promazine HCl, sodium bicarbonate, verapamil HCl and vitamin B-complex w/ or w/o vitamin C.

To Drug Monograph Index To Ophthalmic Product Index

Heparin **compatibility information conflicts** or is dependent on diluent or concentration factors with the following drugs or solutions: dextrose-saline combinations, dextrose in water, lactated Ringer's injection, saline solutions, ampicillin sodium, cephalothin sodium, dobutamine HCl, hydrocortisone sodium succinate, methicillin sodium, oxytetracycline HCl, penicillin G sodium/potassium, and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

Heparin sodium is reported **incompatible** with the following solutions or drugs: sodium lactate 1/6 M, amikacin sulfate, chlorpromazine HCl, codeine phosphate, cytarabine, daunorubicin HCl, diazepam, doxorubicin HCl, droperidol HCl w/ & w/o fentanyl citrate, erythromycin lactobionate, gentamicin sulfate, hyaluronidase, kanamycin sulfate, levorphanol bitartrate, meperidine HCl, methadone HCl, morphine sulfate, pentazocine lactate, phenytoin sodium, polymyxin B sulfate, streptomycin sulfate and vancomycin HCl.

**Pharmacology** - Heparin acts on coagulation factors in both the intrinsic and extrinsic coagulation pathways. Low concentrations of heparin when combined with antithrombin III inactivate factor $X_a$ and prevent the conversion of prothrombin to thrombin. In higher doses, heparin inactivates thrombin, blocks the conversion of fibrinogen to fibrin and when combined with antithrombin III inactivates factors IX, X, XI, XII. By inhibiting the activation of factor XIII (fibrin stabilizing factor), heparin also prevents the formation of stable fibrin clots. While heparin will inhibit the reactions that lead to clotting, it does not significantly change the concentrations of clotting factors. Heparin does not lyse clots, but can prevent the growth of existing clots.

Heparin also causes increased release of lipoprotein lipase, thereby increasing the clearance of circulating lipids and increasing plasma levels of free fatty acids.

**Uses/Indications** - Heparin's primary uses in small animal medicine include treatment of Disseminated Intravascular Coagulation (DIC), and treatment of thromboembolic disease. In horses, it has also been used in the treatment of DIC and as prophylactic therapy for laminitis (unproven efficacy).

**Pharmacokinetics** - Heparin is not absorbed by the gut if administered orally and must be given parenterally to be effective. Anticoagulant activity begins immediately after direct IV bolus injection, but may take up to one hour after deep SQ injection. When heparin is given by continuous IV infusion, an initial bolus must be administered for full anticoagulant activity to begin.

Heparin is extensively protein bound, primarily to fibrinogen, low-density lipoproteins and globulins. It does not appreciably cross the placenta or enter milk.

Heparin's metabolic fate is not completely understood. The drug is apparently partially metabolized by the liver and also inactivated by the reticuloendothelial system. Serum half-lives in humans average 1-2 hours.

**Contraindications/Precautions/Reproductive Safety** - Heparin is contraindicated in patients hypersensitive to it, have severe thrombocytopenia or uncontrollable bleeding (caused by something other than DIC). One author (Green 1989) states that with DIC "heparin should not be given to actively bleeding patients that have severe factor depletion and thrombocytopenia, as fatal hemorrhage may result."

Do not administer IM, as heparin may cause hematoma formation. Hematomas, pain, and irritation may also occur after deep SQ dosing.

To Drug Monograph Index To Ophthalmic Product Index

While heparin does not cross the placenta and is generally felt to be the anticoagulant of choice during pregnancy, its safe use in pregnancy has not been firmly established and pregnancy outcomes may be unfavorable. It should be used cautiously and only when clearly necessary.

**Adverse Effects/Warnings** - Bleeding and thrombocytopenia are the most common adverse effects associated with heparin therapy. Because heparin is derived from bovine or porcine tissues, hypersensitivity reactions may be possible. Less commonly encountered adverse effects that have been reported in animals and/or humans include vasospastic reactions (after several days of therapy), osteoporosis and diminished renal function (after long-term, high-dose therapy), rebound hyperlipidemia, hyperkalemia, alopecia, suppressed aldosterone synthesis and priapism.

**Overdosage/Acute Toxicity** - Overdosage of heparin is associated with bleeding. Symptoms that could be seen before frank bleeding occurs may be manifested by hematuria, tarry stools, petechiae, bruising, etc. Protamine can reverse heparin's effects; see the Protamine monograph for more information.

**Drug Interactions** - Use heparin with caution with other drugs that can cause changes in coagulation status or platelet function (*e.g.,* **aspirin, phenylbutazone, dipyridamole, warfarin**, etc.); more intensive monitoring may be indicated. Heparin may antagonize the actions of **corticosteroids, insulin or ACTH**. Heparin may increase plasma levels of **diazepam**.
**Antihistamines, intravenous nitroglycerin, propylene glycol, digoxin,** and **tetracyclines** may partially counteract the actions of heparin.

**Drug/Laboratory Interactions -** Unless heparin is administered by continuous infusion, it can alter **prothrombin time (PT)** which can be misleading in patients also receiving a coumarin or an indandione anticoagulant.

Heparin can interfere with the results of the **BSP** (sulfobromophthaelein, bromosulfophthalein) test by changing the color intensity of the dye and shifting the absorption peak from 580 nm to 595 nm.

Heparin can cause falsely elevated values of **serum thyroxine** if using competitive protein binding methods of determination. Radioimmunoassay (RIA) and protein bound iodine methods are apparently unaffected by heparin.

When heparin is used as an anticoagulant ***in vitro*** (*e.g.,* in blood collection containers), **white cell counts** should be performed within 2 hours of collection. Do not use heparinized blood for **platelet counts, erythrocyte sedimentation rates, erythrocyte fragmentation tests**, or for any tests involving **complement or isoagglutinins**. Errors in **blood gas determinations** for $CO_2$ pressure, bicarbonate concentration or base excess may occur if heparin encompasses 10% or more of the blood sample.

**Doses** - Doses of heparin are controversial; dosage ranges and methods may vary widely depending on the clinician/author. Refer to the actual references for these doses for more complete information.
**Horses**:

For adjunctive treatment of DIC: Note: Heparin therapy may be only one aspect of successful treatment of DIC. Alleviation of the precipitating cause, administration of fluids, blood, aspirin, and diligent monitoring of coagulation tests (APTT, PT), fibrin degradation products, and fibrinogen may all be important factors in the treatment of DIC.

a) 80 - 100 U/kg IV q4-6h (may be added to fluids and given as a slow drip). Low grade DIC may be treated with 25 - 40 U/kg SQ 2-3 times a day. (Byars 1987)

As adjunctive therapy in endotoxic shock:

a) 40 Units/kg IV or SQ 2-3 times a day may prevent the development of microthrombi; additional studies required to confirm positive benefits. (Semrad and Moore 1987)

To Drug Monograph Index To Ophthalmic Product Index

**Monitoring Parameters** - Note: The frequency of monitoring is controversial and is dependent on several factors, including heparin dose, patient's condition, concomitant problems, etc. Because of the high incidence of hemorrhage associated with heparin use, frequent monitoring of APTT is essential early in therapy (particularly using higher dosages) and in critically ill animals.

1) While whole blood clotting time (WBCT), partial thromboplastin time (PTT) and activated partial thromboplastin times (APTT) may all be used to monitor therapy, APTT is most often recommended.
2) Platelet counts and hematocrit (PCV) should be done periodically
3) Occult blood in stool and urine; other observations for bleeding
4) Clinical efficacy

**Client Information** - Because of the intense monitoring necessary with heparin's use and the serious nature of the disease states in which it is used, this drug should be utilized only by professionals familiar with it and, preferably, in an inpatient setting.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None located.

**Human-Approved Products**:

Heparin Sodium Injection 1000 U/ml, 2000 U/ml, 2500 U/ml, 5000 U/ml, 10,000 U/ml, 20,000 U/ml, 40,000 U/ml in 0.5, 1, 2, 4, 5, 10, and 30 ml amps and multi-dose vials (depending on concentration and manufacturer).

Also available for heparin sodium are pre-filled syringes in various concentrations and amounts, and premixed in normal saline and half-normal saline in 250 ml, 500 ml and 1000 ml containers.

## HEXACHLOROPHENE

### Elephants:

a) 10 mg/kg orally for amphistomiasis and cestodiasis. Chandrasekharan,K. 2002. **Specific diseases of Asian elephants**. Journal of Indian Veterinary Association Kerala 7:(3):31-34

## HYALURONATE SODIUM
## SODIUM HYALURONATE

**Chemistry** - Hyaluronate sodium (HS) is the sodium salt of hyaluronic acid which is a naturally occurring high-viscosity mucopolysaccharide.

**Storage/Stability/Compatibility** - Store at room temperature or refrigerate depending on the product used—check label; do not freeze. Protect from light.

**Pharmacology** - Hyaluronate sodium (HS) is found naturally in the connective tissue of both man and animals and is identical chemically regardless of species. Highest concentrations found naturally are in the synovial fluid, vitreous of the eye and umbilical cord. Surfaces of articular cartilage are covered with a thin layer of a protein-hyaluronate complex, hyaluronate is also found in synovial fluid, and the cartilage matrix. The net effects in joints are: a cushioning effect, reduction of protein and cellular influx into the joint and a

lubricating effect. Hyaluronate also has a direct antiinflammatory effect in joints by scavenging free radicals and suppressing prostaglandins.

**Uses/Indications** - HS is useful in the treatment of synovitis not associated with severe degenerative joint disease. It may be helpful to treat secondary synovitis in conditions where full thickness cartilage loss exists.

The choice of a high molecular weigh product (MW >1 x $10^6$) versus a low molecular weight one is quite controversial. One author (Nixon 1992) states that "...low molecular weight products (which tend to be less expensive) can be equally efficacious in ameliorating signs of joint disease. When synovial adhesions and pannus are to be avoided (as in most surgeries for carpal and fetlock fracture fragment removal), higher molecular weight preparations are recommended because they inhibit proliferation of synovial fibroblasts."

**Pharmacokinetics** - No specific information located.

**Contraindications/Precautions/Reproductive Safety** - No contraindications to HS's use are noted on the label. HS should not be used as a substitute for adequate diagnosis; radiographic examinations should be performed to rule out serious fractures. Do not perform intra-articular injections through skin that has been recently fired or blistered, or that has excessive scurf and counterirritants on it.

While HS would unlikely cause problems, safe use in breeding animals has not been established and most manufacturers caution against its use in these animals.

**Adverse Effects/Warnings** - Some patients may develop local reactions manifested by heat, swelling and/or effusion. Effects generally subside within 24-48 hours; some animals may require up to 96 hours for resolution. No treatment for this effect is recommended. When used in combination with other drugs, incidence of flares may actually be higher. No systemic adverse effects have been noted.

**Overdosage/Acute Toxicity** - Acute toxicology studies performed in horses have demonstrated no systemic toxicity associated with overdoses.

**Drug Interactions/Laboratory Considerations** - None noted.

**Doses** -
**Horses**: Because of the differences in the commercially products see each individual product's label for specific dosing information.

**Client Information** - HS should be administered by a veterinarian only using aseptic technique.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Hyaluronate Sodium (average MW of 500,000 - 730,000) 20 mg/ml in 2 ml disposable syringes; *Hyalovet*® (Fort Dodge); (Rx)

Hyaluronate Sodium Injection *Legend*® (Bayer) (Rx); 2 ml vial for IA administration; 4 ml vials for IV administration. Approved for use in horses.
Also available *Hyvisc*® (Boehringer Ingelheim) (Rx)

Hyaluronate Sodium 10 mg/ml (MW 3.5 x $10^6$) in 2 ml disposable syringes; *Hylartin*® (Pharmacia & Upjohn); (Rx)

All the above products are approved for use in horses. Not for use in horses intended for food.

To Drug Monograph Index To Ophthalmic Product Index

## HYALURONIDASE

Hyaluronidase is an enzyme that facilitates drug absorption.

**Elephants:**

a) 3000-7500IU/dart.Raath,J.P., 1999. **Relocation of African elephants**. In: Fowler,M.E. and Miller,R.E. (Editors), Zoo and Wild Animal Medicine: Current Therapy 4. W.B. Saunders, Philadelphia, PA, USA pp. 525-533

b) Thirty-seven wild African elephants were immobilized as follows: Calves (4-6 years; n=4) were immobilized with 1 mg carfentanil and adults with 3 mg carfentanil mixed with 1500 IU of hyaluronidase. All animals were reversed with naltrexone at a rate of 100 mg for every mg of carfentanil used. For 15 elephants, mean minutes elapsed for initial effect of standing still, recumbency, and recovery following reversal were 5.0 ± 1.6, 10.7 ± 3.9, and 5.9 ± 3.9 respectively. Karesh,W.B., Smith,K.H., Smith,F., Atalia,M., Morkel,P., Torres,A., House,C., Braselton,W.E., and Dierenfeld,E.S. 1997. **Elephants, buffalo, kob, and rhinoceros: immobilization, telemetry, and health evaluations.** Proceedings American Association of Zoo Veterinarians. Pages: 296-230

c) Twenty free-ranging adult wild African elephants in northern Botswana were immobilized with a mean (±SD) of 9.5 ± 0.5 mg etorphine hydrochloride and 2000 IU hyaluronidase by i.m. dart.(Osofsky, 1997). Osofsky,S.A. 1997. **A practical anesthesia monitoring protocol for free-ranging adult African elephants (Loxodonta africana)**. Journal of Wildlife Diseases 33:(1):72-77. **Abstract:** Twenty free-ranging adult African elephants in northern Botswana were immobilized with a mean (± SD) of 9.5 ± 0.5 mg etorphine hydrochloride and 2000 IU hyaluronidase by i.m. dart. The mean time to recumbency was 8.7 ± 2.4 min. All animals were maintained in lateral recumbency. The anaesthesia monitoring protocol included cardiothoracic auscultation; palpation of auricular pulse for quality and regularity; checking of rectal temperature, and monitoring of respiratory and heart rates. Results of basic physiological measurements were similar to those of previous field studies of African elephants immobilized with etorphine or etorphine-hyaluronidase. In addition, continuous real-time pulse rate and percent oxygen saturation of haemoglobin ($SpO_2$) readings were obtained on 16 elephants with a portable pulse oxygen meter. Duration of pulse oximetry monitoring ranged from 3 to 24 min (mean ±SD = 8.2 ± 4.8 min). Differences between minimum and maximum $SpO_2$ values for any given elephant ranged from 1 to 6 percentage points, evidence for relatively stable trends. The SpO2 readings ranged from 70% to 96% among the 16 elephants, with a mean of 87.3 ± 2.8%. 15 of 16 elephants monitored with a pulse oximeter had mean $SpO_2$ values ≥ 81 ± 2.4%, with 11 having mean $SpO_2$ values ≥ 85 ± 1.5%. All 20 animals recovered uneventfully following reversal: diprenorphine at 23.3 ± 1.5 mg (IV) with 11.7 ± 0.5 mg IM, or 24 mg diprenorphine given all IV.

Osofsky,S.A. 1995. **Pulse oximetry monitoring of free-ranging African elephants (*Loxodonta africana*) immobilized with an etorphine/hyaluronidase combination antagonized with diprenorphine.** Joint Conference AAZV/WDA/AAWV. Pages: 237-277

d) Azaperone (60-100 mg) was combined with etorphine (7-15 mg) and hyaluronidase 1500-3000 IU) in a translocation operation of 26 elephants in central Kenya. Induction time was 7-15 minutes. Five elephants died from metabolic changes unrelated to drugs administered.
Njumbi,S.T., Waithaka,J., Gachago,S., Sakwa,J., Mwathe,K., Mungai,P., Mulama,M., Mutinda,H., Omondi,P., and Litoroh,M. 1996. **Translocation of elephants: the Kenyan experience**. Pachyderm 22:61-65. Author's (Mikota) note: hyaluronidase (hyalase) is incorrectly described as a tranquilizer in this article.

To Drug Monograph Index To Ophthalmic Product Index

e) 4500 IU. (Kock,M.D., Martin,R.B., and Kock,N. 1993. **Chemical immobilization of free-ranging African elephants (Loxodonta africana) in Zimbabwe, using etorphine (M99) mixed with hyaluronidase, and evaluation of biological data collected soon after immobilization**. Journal of Zoo and Wildlife Medicine 24:(1):1-10 **Abstract:** Sixteen adult female free-ranging elephants were immobilized in July 1990, using a mean (±SE) dose per animal of 11.6 ± 0.3 mg of etorphine (M99) mixed with a standard dose of hyaluronidase (4500 IU), at the Sengwa Wildlife Research Area, Zimbabwe, to attach telemetry and infrasound detection collars. The 16 elephants were reimmobilized in December 1990, using higher doses of etorphine (standardized at 15 mg total dose) with hyaluronidase (4500 IU), to remove the collars. The higher doses of etorphine produced more rapid inductions. Biological data were collected on both occasions. Significant differences in selected measures indicative of stress, including lactic dehydrogenase and aspartate transaminase, were seen between immobilizations. Comparisons were made of selected health measures between samples collected in the early winter and late winter/early spring season. Significant differences were seen with total protein, albumin, urea nitrogen, creatinine, calcium, magnesium, inorganic phosphorus, chloride, and alanine transaminase.

Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants**. In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441

**See also:**

Hoare,R. 1999. **Reducing drug immobilization time in the field immobilization of elephants**. Pachyderm 27:(Jan-Dec):49-54 Note: doses not specified.

Morton,D.J. and Kock,M.D. 1991. **Stability of hyaluronidase in solution with etorphine and xylazine**. J.Zoo and Wildlife Medicine 22:(3):345-347 **Abstract:** During capture of free-living wildlife, stress is potentially the greatest problem encountered. For this reason, reduction in induction time during immobilization is of paramount importance. Hyaluronidase reduces induction times, although no reports have assessed stability of the enzyme in drug mixtures used for chemical capture. This report presents information on the stability of hyaluronidase in combination with etorphine and xylazine, one of the most common drug mixtures used in chemical immobilization of wildlife. Hyaluronidase activity remains high for at least 48 hr, provided storage temperatures can be maintained at less than or equal to 30º C. Storage at greater than or equal to 40ºC is associated with rapid loss of enzyme activity in the mixture.

**Dosage Forms/Preparations**
Hyalase, CP Pharmaceuticals
Hyalase, 1500 IU/ampule, Fisons Pharmaceuticals, 1624 Chloorkop, South Africa
Hyalase, Zimethicals, Harara, Zimbabwe
Hyaluronidase, Sigma, St.Louis, Missouri, 61378, USA
Hyaluronidase, 5000 IU/vial, Kyron Labs, South Africa

**HYDROCORTISONE**
**HYDROCORTISONE ACETATE**
**HYDROCORTISONE CYPIONATE**
**HYDROCORTISONE SODIUM PHOSPHATE**
**HYDROCORTISONE SODIUM SUCCINATE**

Note: For more information refer to the monograph: Glucocorticoids, General Information.

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - Also known as compound F or cortisol, hydrocortisone is secreted by the adrenal gland. Hydrocortisone occurs as an odorless, white to practically white, crystalline powder. It is very slightly soluble in water and sparingly soluble in alcohol. Hydrocortisone is administered orally.

Hydrocortisone acetate occurs as an odorless, white to practically white, crystalline powder. It is insoluble in water and slightly soluble in alcohol. Hydrocortisone acetate is administered via intra-articular, intrabursal, intralesional, intrasynovial or soft tissue injection.

Hydrocortisone cypionate occurs as an odorless or with a slight odor, white to practically white, crystalline powder. It is insoluble in water and soluble in alcohol. It is administered orally.

Hydrocortisone sodium phosphate occurs as an odorless or practically odorless, hygroscopic, white to light yellow powder. It is freely soluble in water and slightly soluble in alcohol.

Hydrocortisone sodium phosphate may be administered via IM, SQ, or IV routes.

Hydrocortisone sodium succinate occurs as an odorless, white to nearly white, hygroscopic, amorphous solid. It is very soluble in both water and alcohol. Hydrocortisone sodium succinate injection is administered via IM or IV routes.

**Storage/Stability/Compatibility** - Hydrocortisone tablets should be stored in well-closed containers. The cypionate oral suspension should be stored in tight, light resistant containers. All products should be stored at room temperature (15-30°C); avoid freezing the suspensions or solutions. After reconstituting solutions, only use products that are clear. Discard unused solutions after 3 days.

Hydrocortisone sodium phosphate solution for injection is reportedly **compatible** with the following solutions and drugs: 10% fat emulsion, amikacin sulfate, amphotericin B (with or without heparin sodium), bleomycin sulfate, cephapirin sodium, metaraminol bitartrate, sodium bicarbonate, and verapamil HCl.

Hydrocortisone sodium succinate is reportedly **compatible** with the following solutions and drugs: dextrose-Ringer's injection combinations, dextrose-Ringer's lactate injection combinations, dextrose-saline combinations, dextrose injections, Ringer's injection, lactated Ringer's injection, sodium chloride injections, amikacin sulfate, aminophylline, amphotericin B (limited quantities), calcium chloride/gluconate, cephalothin sodium (not in combination with aminophylline), cephapirin sodium, chloramphenicol sodium succinate, clindamycin phosphate, corticotropin, daunorubicin HCl, dopamine HCl, erythromycin gluceptate, erythromycin lactobionate, lidocaine HCl, mephentermine sulfate, metronidazole with sodium bicarbonate, netilmicin sodium, penicillin G potassium/sodium, piperacillin sodium, polymyxin B sulfate, potassium chloride, prochlorperazine edisylate, sodium bicarbonate, thiopental sodium, vancomycin HCl, verapamil HCl and vitamin B-complex with C.

Hydrocortisone sodium succinate is reportedly **incompatible** with the following solutions and drugs: ampicillin sodium, bleomycin sulfate, colistemethate sodium, diphenhydrinate, diphenhydramine HCl, doxorubicin HCl, ephedrine sulfate, heparin sodium, hydralazine HCl, metaraminol bitartrate, methicillin sodium, nafcillin sodium, oxytetracycline HCl, pentobarbital sodium, phenobarbital sodium, promethazine HCl, secobarbital sodium and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Doses** -
**Horses**:

As a glucocorticoid:

a) Hydrocortisone sodium succinate: 1 - 4 mg/kg as an IV infusion (Robinson 1987)

To Drug Monograph Index To Ophthalmic Product Index

**Dosage Forms/Preparations/Approval Status/Withdrawal Times**-
There are no known veterinary-approved products containing hydrocortisone (or its salts) for systemic use. There are a variety of hydrocortisone veterinary products for topical use. A 10 ppb tolerance has been established for hydrocortisone (as the succinate or acetate) in milk.

**Human-Approved Products** (all require a prescription):

Hydrocortisone oral tablets 5 mg, 10 mg, 20 mg; *Cortef*® (Upjohn), *Hydrocortone*® (MSD),*Hydrocortisone*® (Major) generic

Hydrocortisone acetate Injection; 25 mg/ml, 50 mg/ml in 5 & 10 ml vials; *Hydrocortone*® *Acetate* (MSD); generic (Rx)

Hydrocortisone cypionate oral suspension 2 mg/ml hydrocortisone in 120 ml;*Cortef*® (Upjohn)

Hydrocortisone sodium phosphate Injection 50 mg/ml in 2 & 10 ml vials; *Hydrocortone*® *Phosphate* (MSD)

Hydrocortisone sodium succinate injection; 100 mg/vial, 250 mg/vial, 500 mg/vial, 1000 mg/vial; *Solu-Cortef*® (Upjohn), *A-hydroCort*® (Abbott)

There are many OTC and Rx topical and anorectal products available in a variety of dosage forms.

## HYDROXYZINEHCL
## HYDROXYZINE PAMOATE

**Chemistry** - A piperazine-derivative antihistamine, hydroxyzine HCl occurs as a white, odorless powder. It is very soluble in water and freely soluble in alcohol. Hydroxyzine pamoate occurs as a light yellow, practically odorless powder. It is practically insoluble in water or alcohol.

**Storage/Stability/Compatibility** - Hydroxyzine oral products should be stored at room temperature in tight, light-resistant containers. Avoid freezing all liquid products.

The HCl injection has been reported to be compatible with the following drugs when mixed in syringes: atropine sulfate, benzquinamide HCl, butorphanol tartrate, chlorpromazine HCl, cimetidine HCl, codeine phosphate, diphenhydramine HCl, doxapram HCl, droperidol, fentanyl citrate, glycopyrrolate, hydromorphone HCl, lidocaine HCl, meperidine HCl, methotrimeprazine, metoclopramide HCl, midazolam HCl, morphine sulfate, oxymorphone HCl, pentazocine lactate, procaine HCl, prochlorperazine edisylate, promazine HCl, promethazine HCl, and scopolamine HBr. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography) for more specific information.

**Pharmacology** - Like other $H_1$-receptor antihistamines, hydroxyzine acts by competing with histamine for sites on $H_1$-receptor sites on effector cells. Antihistamines do not block histamine release, but can antagonize its effects. In addition to its antihistaminic effects, hydroxyzine possesses anticholinergic, sedative, tranquilizing, antispasmodic, local anesthetic, mild bronchodilative, and antiemetic activities.

**Uses/Indications** - Hydroxyzine is used principally for its antihistaminic, antipruritic and sedative/tranquilization qualities, often in atopic patients.

**Pharmacokinetics** - Hydroxyzine is rapidly and well absorbed after oral administration. Effects generally persist for 6-8 hours in dogs and up to 12 hours in cats. Hydroxyzine is apparently metabolized in liver.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions/Reproductive Safety** - Hydroxyzine is contraindicated in patients hypersensitive to it. It should be used with caution in patients with prostatic hypertrophy, bladder neck obstruction, severe cardiac failure, angle-closure glaucoma, or pyeloduodenal obstruction.
At doses substantially greater than used therapeutically, hydroxyzine has been shown to be teratogenic in lab animals. Use during pregnancy (particularly during the first trimester) only when the benefits outweigh the risks. It is unknown if hydroxyzine enters maternal milk.

**Adverse Effects/Warnings** - The most likely adverse effect associated with hydroxyzine is sedation. In dogs, this is usually mild and transient. Occasionally antihistamines can cause a hyperexcitability reaction. Dogs have reportedly developed fine rapid tremors, whole body tremors and rarely, seizures while taking this drug. Safe dosages have not been established for cats.

**Overdosage/Acute Toxicity** - There is limited information available. There are no specific antidotes available. Overdoses would be expected to cause increased sedation and perhaps, hypotension. Gut emptying protocols should be considered with large or unknown quantity overdoses. Supportive and symptomatic treatment is recommended if necessary.

**Drug Interactions** - Additive CNS depression may be seen if combining hydroxyzine with other **CNS depressant medications**, such as barbiturates, tranquilizers, etc. Additive anticholinergic effects may occur when hydroxyzine is used concomitantly with other **anticholinergic agents**. Hydroxyzine may inhibit or reverse the vasopressor effects of **epinephrine**. Use norepinephrine or metaraminol instead.

**Laboratory Considerations -** False increases have been reported in **17-hydroxycorticosteroid urine** values after hydroxyzine use. Because antihistamines can decrease the wheal and flair response to **skin allergen testing**, antihistamines should be discontinued from 3-7 days (depending on the antihistamine used and the reference) before intradermal skin tests.

**Doses** -
**Horses**:

a) 0.5 - 1 mg/kg IM or PO *bid* (Robinson 1992)
b) Using the pamoate salt: 0.67 mg/kg PO twice daily (Duran 1992)

**Monitoring Parameters** - Efficacy and Adverse Effects

**Client Information** - May cause drowsiness and impede working dogs' abilities.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Hydroxyzine HCl Oral Tablets 10 mg, 25 mg, 50 mg, 100 mg; *Atarax*® (Roerig), *Anxanil*® (film coated tabs) (Econo Med), generic; (Rx)

Hydroxyzine HCl Oral Solution 10 mg/5 ml; *Atarax*® (Roerig), generic; (Rx)

Hydroxyzine HCl Injection (for IM use only) 25 mg/ml in 2 ml syringes & 1 and 10 ml vials & 50 mg/ml in 2 ml amps, 1 & 2 ml syringes & 1, 2 and 10 ml vials *Vistaril*® (Roerig) is the most commonly known trade name, there are several others including generically labeled products available; (Rx)

Hydroxyzine Pamoate Oral Capsules (equivalent to hydroxyzine HCl) 25 mg, 50 mg, 100 mg; *Vistaril*® (Pfizer), generic; (Rx)

To Drug Monograph Index To Ophthalmic Product Index

Hydroxyzine Pamoate Oral Suspension (equivalent to hydroxyzine HCl) 25 mg/5 ml; *Vistaril*® (Pfizer); (Rx)

## IBUPROFEN

### Elephants:

a) 6 mg/kg PO BID for Asian elephants; 7 mg/kg PO BID for African elephants (Bechert, 2003).

**PHARMACOKINETICS OF ORALLY ADMINISTERED IBUPROFEN IN AFRICAN AND ASIAN ELEPHANTS (LOXODONTA AFRICANA AND ELEPHAS MAXIMUS).** U. BECHERT AND J. M. CHRISTENSEN, J ZOO WILDL MED 2007 VOL. 38 ISSUE 2 PAGES 258-68. ACCESSION NUMBER: 17679510 DOI: 10.1638/1042-7260(2007)038[0258:POOAII]2.0.CO;2

THE PHARMACOKINETIC PARAMETERS OF S(+) AND R(-) IBUPROFEN WERE DETERMINED IN 20 ELEPHANTS AFTER ORAL ADMINISTRATION OF PRELIMINARY 4-, 5-, AND 6-MG/KG DOSES OF RACEMIC IBUPROFEN. FOLLOWING ADMINISTRATION OF 4 MG/KG IBUPROFEN, SERUM CONCENTRATIONS OF IBUPROFEN PEAKED AT 5 HR AT 3.9 +/- 2.07 MICROG/ML R(-) AND 10.65 +/- 5.64 MICROG/ML S(+) (MEAN +/- SD) IN AFRICAN ELEPHANTS (LOXODONTA AFRICANA) AND AT 3 HR AT 5.14 +/- 1.39 MICROG/ML R(-) AND 13.77 +/- 3.75 MICROG/ML S(+) IN ASIAN ELEPHANTS (ELEPHAS MAXIMUS), RESPECTIVELY. SIX-MILLIGRAM/KILOGRAM DOSAGES RESULTED IN PEAK SERUM CONCENTRATIONS OF 5.91 +/- 2.17 MICROG/ML R(-) AND 14.82 +/- 9.71 MICROG/ML S(+) IN AFRICAN ELEPHANTS, AND 5.72 +/- 1.60 MICROG/ML R(-) AND 18.32 +/- 10.35 MICROG/ML S(+) IN ASIAN ELEPHANTS. IBUPROFEN WAS ELIMINATED WITH FIRST-ORDER KINETICS CHARACTERISTIC OF A SINGLE-COMPARTMENT MODEL WITH A HALF-LIFE OF 2.2-2.4 HR R(-) AND 4.5-5.1 HR S(+) IN AFRICAN ELEPHANTS AND 2.4-2.9 HR R(-) AND 5.9-7.7 HR S(+) IN ASIAN ELEPHANTS. SERUM CONCENTRATIONS OF R(-) IBUPROFEN WERE UNDETECTABLE AT 24 HR, WHEREAS S(+) IBUPROFEN DECREASED TO BELOW 5 MICROG/ML 24 HR POSTADMINISTRATION IN ALL ELEPHANTS. THE VOLUME OF DISTRIBUTION WAS ESTIMATED TO BE BETWEEN 322 AND 356 ML/KG R(-) AND 133 AND 173 ML/KG S(+) IN ASIAN ELEPHANTS AND 360-431 ML/KG R(-) AND 179-207 ML/KG S(+) IN AFRICAN ELEPHANTS. STEADY-STATE SERUM CONCENTRATIONS OF IBUPROFEN RANGED FROM 2.2 TO 10.5 MICROG/ML R(-) AND 5.5 TO 32.0 MICROG/ML S(+) (MEAN: 5.17 +/- 0.7 R(-) AND 13.95 +/- 0.9 S(+) MICROG/ML IN AFRICAN ELEPHANTS AND 5.0 +/- 1.09 MICROG/ML R(-) AND 14.1 +/- 2.8 MICROG/ML S(+) IN ASIAN ELEPHANTS). RACEMIC IBUPROFEN ADMINISTERED AT 6 MG/KG/12 HR FOR ASIAN ELEPHANTS AND AT 7 MG/KG/12 HR FOR AFRICAN ELEPHANTS RESULTS IN THERAPEUTIC SERUM CONCENTRATIONS OF THIS ANTIINFLAMMATORY AGENT.

## IMIPENEM-CILASTATIN SODIUM

**Chemistry** - Imipenem monohydrate is a carbapenem antibiotic that occurs as white or off-white, non-hygroscopic, crystalline compound. At room temperature, 11 mg are soluble in 1 ml of water. Cilastatin sodium, an inhibitor of dehydropeptidase I (DHP I), occurs as an off-white to yellowish, hygroscopic, amorphous compound. More than 2 grams are soluble in 1 ml of water.

The commercially available injections are available in a 1:1 fixed dose ratio. The solutions are clear to yellowish in color. pH after reconstitution ranges from 6.5 to 7.5. These products also have sodium bicarbonate added as a buffer. The suspensions for IM use are white to light tan in color.

**Storage/Stability/Compatibility** - Commercially available sterile powders for injection should be stored at room temperature (<30°C). After reconstitution with 100 ml of sterile normal saline, the solution is stable for 10 hours at room temperature and 48 hours when refrigerated. If other diluents are used, stability times may be reduced (see package insert or *Trissell*). Do not freeze solutions. The manufacturer does not recommend admixing with other drugs.

To Drug Monograph Index To Ophthalmic Product Index

After reconstitution the sterile powder for suspension with 1% lidocaine HCl injection, the suspension should be used within one hour.

**Pharmacology** - This fixed combination of a carbapenem antibiotic (imipenem) and an inhibitor (cilastatin) of dehydropeptidase I (DHP I) has a very broad spectrum of activity. Imipenem is considered to be generally a bactericidal agent, but may be static against some bacteria. It has an affinity and binds to most penicillin-binding protein sites, thereby inhibiting bacterial cell wall synthesis.

Imipenem has activity against a wide variety of bacteria, including Gram-positive aerobic cocci (including some bacteriostatic activity against enterococci), Gram-positive aerobic bacilli (including static activity against *Listeria*), Gram-negative aerobic bacteria (H*aemophilus, Enterobacteriaceae*, many strains of *Pseudomonas aeruginosa*), and anaerobes (including some strains of *Bacteroides*).

Cilastatin inhibits the metabolism of imipenem by DHP 1 on the brush borders of renal tubular cells. This serves two functions: it allows higher urine levels and may also protect against proximal renal tubular necrosis that can occur when imipenem is used alone.

**Uses/Indications** - Imipenem may be useful in equine or small animal medicine to treat serious infections when other less expensive antibiotics are ineffective or have unacceptable adverse effect profiles.

**Pharmacokinetics** - Neither drug is absorbed appreciably from the GI tract and therefore they are given parenterally. Bioavailability after IM injection is approximately 95% for imipenem and 75% for cilastatin. Imipenem is distributed widely throughout the body, with the exception of the CSF. Imipenem crosses the placenta and is distributed into milk. When given with cilastatin, imipenem is eliminated by both renal and non-renal mechanisms. Approximately 75% of a dose is excreted in the urine and about 25% is excreted by unknown non-renal mechanisms. Half lives in patients with normal renal function range from 1-3 hours on average.

**Contraindications/Precautions/Reproductive Safety** - The potential risks versus benefits should be carefully weighed before using imipenem/cilastatin in patients hypersensitive to it or other beta-lactam antibiotics (*e.g.*, penicillins, cephalosporins as partial cross-reactivity may occur), in patients with renal function impairment (dosages may need to be reduced or time between doses lengthened), or in patients with CNS disorders (*e.g.*, seizures, head trauma) as CNS adverse effects may be more likely to occur.

While no teratogenic effects have been noted in animal studies, safe use during pregnancy has not been firmly established. While imipenem enters milk, no adverse effects attributable to it have been noted in nursing offspring.

**Adverse Effects/Warnings** - Potential adverse effects include: GI effects (vomiting, anorexia, diarrhea), CNS toxicity (seizures, tremors), hypersensitivity (pruritus, fever to anaphylaxis) and infusion reactions (thrombophlebitis; too rapid IV infusions may cause GI toxicity or other untoward effects).

Rarely, transient increases in renal (BUN or serum creatinine values) or hepatic (AST/ALT/Alk Phosphatase) function tests may be noted, as well as hypotension or tachycardias.

**Overdosage/Acute Toxicity** - Little information is available. The $LD_{50}$ of imipenem:cilastatin in a1:1 ratio in mice and rats is approximately 1 g/kg/day. Acute overdoses should be handled by halting therapy and treating supportively and symptomatically.

**Drug Interactions** - There apparently is no therapeutic benefit in adding **probenecid** to prolong the half lives of imipenem/cilastatin (does not appreciably affect imipenem excretion).

To Drug Monograph Index To Ophthalmic Product Index

Additive effects or synergy may result when **aminoglycosides** are added to imipenem/cilastatin therapy, particularly against *Enterococcus, Staph. aureus, and Listeria monocytogenes*. There is apparently neither synergy nor antagonism when used in combination against Enterobacteriaceae, including *Pseudomonas aeruginosa*.

Antagonism may occur when used in combination with **other** beta **lactam antibiotics** against several Enterobacteriaceae (including many strains of *Pseudomonas aeruginosa* and some strains of *Klebsiella, Enterobacter, Serratia*, *Enterobacter*, *Citrobacter* and *Morganella*. The clinical importance of this interaction is unclear, but at present it is not recommended to use imipenem in conjunction with other beta lactam antibiotics.

Synergy may occur against *Nocardia asteroides* when used in combination with **trimethoprim/sulfa**. **Chloramphenicol** may antagonize the antibacterial effects of imipenem.

**Laboratory Considerations -** When using Kirby-Bauer disk diffusion procedures for testing susceptibility, a specific 10 micrograms imipenem disk should be used. An inhibition zone of 16 mm or more indicates susceptibility; 14-15 mm, intermediate; and 13 mm or less, resistant.
When using a dilution susceptibility procedure, an organism with a MIC of 4 micrograms/ml or less is considered susceptible; 8 micrograms /ml moderately susceptible; and 16 micrograms/ml or greater, resistant. Imipenem may cause a **false-positive urine glucose determination** when using the cupric sulfate solution test (*e.g.*, *Clinitest*®).

**Doses -**
**Horses**:
For susceptible infections: 15 mg/kg IV (over a 20 minute period) q 4- 6 hours (Walker 1992)

**Monitoring Parameters** - 1) Efficacy; 2) Adverse effects (including renal and hepatic function tests if treatment is prolonged or patient's renal or hepatic function are in question)

**Client Information** - Imipenem/cilastatin should be administered in an inpatient setting. Clients should be informed of the cost of using this medication.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:
Imipenem:Cilastatin Parenteral for Injection for IV infusion: 250 mg:250 mg (with 10 mg sodium bicarbonate), 500 mg:500 mg (with 20 mg sodium bicarbonate); *Primaxin*® *I.V.* (Merck); (Rx)

Imipenem:Cilastatin Suspension for IM Injection: 500 mg:500 mg, 750 mg:750 mg; *Primaxin*® *I.M.* (Merck); (Rx)

**INSULIN INJECTION, REGULAR**
**INSULIN, ISOPHANE SUSPENSION**
**INSULIN, PROTAMINE ZINC SUSPENSION**
**INSULIN, ZINC SUSPENSION, EXTENDED (ULTRALENTE)**

To Drug Monograph Index To Ophthalmic Product Index

Note: Insulin preparations available to the practitioner are in a constant state of change. It is highly recommended to review current references or sources of information pertaining to insulin therapy for dogs and cats, to maximize efficacy of therapy and reduce chances of errors.

**Chemistry** - Insulin is a 2 chained hormone linked by disulfide linkages secreted by the beta cells of the pancreatic islets. It has an approximate molecular weight of 6000 daltons. Insulin is measured in Units/ml; one International Unit (IU) is equivalent to 0.04167 mg of the 4th International Standard (a mixture containing 52% beef insulin and 48% pork insulin). There are species variations of insulin, with different amino acids found at positions 8, 9, & 10 of the A chain and position 30 of the B chain. Dog and cat insulin are thought to more closely resemble porcine insulin, rather than beef insulin. There are two basic purity grades of insulin available from bovine and porcine sources. Single-peak insulins contain not more than 25 parts per million (ppm) of proinsulin. Purified insulins contain not more than 10 parts per million (ppm) of proinsulin.

**Regular insulin**, also known as crystalline zinc insulin or unmodified insulin, is obtained for commercial uses from the pancreases of pigs and/or cattle at slaughter. The insulin is prepared by precipitating the insulin with zinc chloride, forming zinc insulin crystals. The commercially available solutions have a pH of 7 - 7.8.

**Isophane insulin**, more commonly known as **NPH insulin**, occurs as a sterile suspension of zinc insulin crystals and protamine zinc in buffered water for injection. It is a cloudy or milky suspension with a pH of 7.1-7.4. NPH insulin is an abbreviation for neutral protamine Hagedorn insulin.

**Protamine zinc insulin (PZI)** occurs as a sterile suspension of insulin modified by the addition of protamine sulfate and zinc chloride in buffered water for injection. It is cloudy or milky suspension with a pH of 7.1-7.4.

**Storage/Stability/Compatibility** - **Regular insulin** is recommended by the manufacturers to be stored in the original container at refrigerated temperatures (2 - 8°C), but the new neutral formulations have been demonstrated to be stable at room temperature for 24-30 months. Temperature extremes should be avoided; do not freeze. Do not use regular insulin that is turbid, discolored or has an alteration in viscosity. Regular insulin has been shown to adsorb to the surface of IV bottles/bags and tubing. This may be of greater importance when concentrations of less than 100 IU/liter are used intravenously. Flushing the IV set before administering may allow a more consistent delivery of insulin to the patient. Since IV insulin is given to effect and patients are closely monitored, the problem may be overstated. Difficulties in determining subsequent SQ doses using the quantities of insulin required during intravenous therapy may occur, however.

Regular insulin is reportedly **compatible** with following drugs/solutions: normal saline, TPN solutions (4% amino acids, 25% dextrose with electrolytes & vitamins; must occasionally shake bag to prevent separation), bretylium tosylate, cimetidine HCl, lidocaine HCl, oxytetracycline HCl and verapamil HCl. Regular insulin may also be mixed with other insulin products (*e.g.,* NPH, PZI, etc.).

Regular insulin is reportedly **incompatible** with the following drugs/solutions: aminophylline, amobarbital sodium, chlorothiazide sodium, dobutamine HCl, nitrofurantoin sodium, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, secobarbital sodium, sodium bicarbonate, sulfisoxizole sodium, and thiopental sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**NPH insulin** and **Protamine zinc insulin (PZI)** should be stored in a manner similar to that of regular insulin (see above). Freezing may cause improper resuspension of the particles with resultant improper dosing; do not use if solution is clear or if the particles appear clumped or granular.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Insulin is responsible for the proper usage of glucose and other metabolic fuels by cells in the normal metabolic processes. After binding to specific receptors of target cells, the insulin-receptor complex is thought to activate a membrane protease that catalyzes a peptide mediator(s) that affects certain intracellular enzymes.

Insulin affects primarily liver, muscle and adipose tissues. In the liver, insulin decreases glycogenolysis, gluconeogenesis, ketogenesis, and increases glycogen synthesis and fatty acid synthesis. In muscle, insulin decreases protein catabolism and amino acid output, and increases amino acid uptake, protein synthesis and glycogen synthesis. In adipose tissue, insulin decreases lipolysis and increases glycerol and fatty acid synthesis.

**Uses/Indications -** Insulin preparations have been used for the adjunctive treatment of diabetic ketoacidosis, uncomplicated diabetes mellitus and as adjunctive therapy in treating hyperkalemia. Insulin treatment in veterinary species has been primarily in dogs and cats. Experience in using insulin in large animals is rather limited.

**Pharmacokinetics** - In dogs and cats, regular insulin's effects are continuous when infused at low dosages intravenously, but effects tend to cease immediately when the infusion is stopped. After IM or IV bolus injection, the duration of action is only 2-4 hours. After subcutaneous injection, regular insulin's actions may persist for 4-6 hours.

In dogs, PZI insulin may take from 1-4 hours for onset of action to take place. The effects of PZI peak between 5-20 hours after dosing and persist for up to 30 hours. The majority of dogs receiving PZI injections can be adequately controlled with once daily administration. The onset of effect after SQ injection of NPH insulin may be immediate or take up to 3 hours. NPH peaks generally 2-10 hours after injection and its effects may persist for up to 24 hours. Most dogs require twice daily injections for optimal control, however.

In cats, PZI insulin will begin to lower blood glucose in about 1-3 hours and has its peak effects in 4-10 hours after injection. The duration of action of PZI in cats may be from 12-30 hours. Because of the variability of PZI's duration in cats, some animals may require twice daily injections for optimal control. NPH insulin peaks sooner (1.5-6 hours) and has a shorter duration of action (4-10 hours) than PZI. Nearly all cats will require twice daily administration of NPH for good control.

**Contraindications/Precautions** - Because there are no alternatives for insulin when it is used for diabetic indications, there are no absolute contraindications to its use. If animals develop hypersensitivity (local or otherwise) or should insulin resistance develop, a change in type or species of insulin should be tried. Insulin derived from swine is closest in structure to canine insulin and is thought to be closer to feline insulin, than is insulin derived from bovine sources.
Do not inject insulin at the same site day after day or lipodystrophic reactions can occur.

**Adverse Effects/Warnings** - Adverse effects of insulin therapy can include, hypoglycemia (see overdosage below), insulin-induced hyperglycemia ("Somogyi effect"), insulin antagonism/resistance, rapid insulin metabolism, and local reactions to the "foreign" proteins.

**Overdosage** - Overdosage of insulin can lead to various degrees of hypoglycemia. Symptoms may include weakness, shaking, head tilting, lethargy, ataxia, seizures and coma. Prolonged hypoglycemia can result in permanent brain damage or death.

Mild hypoglycemia may be treated by offering the animal its usual food. More serious symptoms should be treated with oral dextrose solutions (*e.g., Karo*® syrup) rubbed on the oral mucosa or by intravenous injections of 50% dextrose solutions. Should the animal be convulsing, fluids should not be forced orally nor

To Drug Monograph Index To Ophthalmic Product Index

fingers placed in the animal's mouth. Once the animal's hypoglycemia is alleviated, it should be closely monitored (both by physical observation and serial blood glucose levels) to prevent a recurrence of hypoglycemia (especially with the slower absorbed products) and also to prevent hyperglycemia from developing. Future insulin dosages or feeding habits should be adjusted to prevent further occurrences of hypoglycemia.

**Drug Interactions** - The following drugs may potentiate the hypoglycemic activity of insulin: **alcohol, anabolic steroids (***e.g.,* **stanozolol, boldenone, etc.),** beta**-adrenergic blockers (e.g propranolol), monoamine oxidase inhibitors, guanethidine, phenylbutazone, sulfinpyrazone, tetracycline, aspirin or other salicylates**. The following drugs may decrease the hypoglycemic activity of insulin: **glucocorticoids, dextrothyroxine, dobutamine, epinephrine, estrogen/progesterone combinations, furosemide and thiazide diuretics**. Thyroid hormones can also elevate blood glucose levels in diabetic patients when **thyroid hormone** therapy is first initiated. Because insulin can alter serum potassium levels, patients receiving concomitant **cardiac glycoside (***e.g.,* **digoxin)** therapy should be closely monitored. This is especially true in patients also receiving concurrent **diuretic therapy**.

**Doses** -
Note: The reader is strongly encouraged to refer to the original referenced materials for the doses below, for more thorough discussions on the treatment of diabetes.
**Horses**:

For diabetes mellitus:

a) True diabetes mellitus rarely occurs in horses. Most cases are a result of pituitary tumors that cause hyperglycemia secondary to excessive ACTH or Growth Hormone. A case is cited where an animal received 0.5 - 1.0 Unit/kg of PZI insulin and the hyperglycemia was controlled. Patients with hyperglycemia secondary to a pituitary tumor are apparently insulin-resistant. (Merritt 1987)
b) PZI insulin 0.15 U/kg IM or SQ *bid* (Robinson 1987)

**Monitoring Parameters** - 1) Blood glucose; 2) Patient weight, appetite, fluid intake/output; 3) Blood, urine ketones (if warranted); 4) Glycosylated hemoglobin (if available and warranted)

**Client Information** - Keep insulin products away from temperature extremes. If stored in the refrigerator, allow to come to room temperature in syringe before injecting.

Clients must be instructed in proper techniques for withdrawing insulin into the syringe, including rolling the vial, not shaking before withdrawing into syringe, and to use the proper syringe size with insulin concentration (*e.g.,* don't use U-40 insulin with U-100 syringes). Proper injection techniques should be taught and practiced with the client before the animal's discharge. The symptoms of hypoglycemia should be thoroughly reviewed with the owner. A written protocol outlining monitoring procedures and treatment steps for hypoglycemia should be also be sent home with the owner.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** - All products except 500 U/ml insulin are available without prescription.

**Veterinary-Approved Products**: None

**Human-Approved Products (partial listing)**:

**Insulin Injection, Regular**

From pork sources; 100 Units/ml
*Regular Insulin* (Novo-Nordisk)
*Regular Purified Pork insulin* (Novo-Nordisk); *Pork Regular Iletin II* (Lilly)

Human (either rDNA or semi-synthetic) insulin:

*Humulin® R* (Lilly); *Novolin® R* (Novo-Nordisk), *Velosulin® Human* (Novo-Nordisk)

**Insulin, Isophane Suspension (NPH)**

From beef sources; 100 Units/ml
*Insulin, NPH* (Novo-Nordisk)

From pork sources (purified); 100 Units/ml
*Iletin® II, NPH Purified Pork* (Lilly), *NPH-N®* (Novo-Nordisk)

Human (either rDNA or semi-synthetic) insulin:
*Humulin® N,* (Lilly); *Novolin® N* (Novo-Nordisk),

**Insulin, Zinc Suspension, Extended (Ultralente)**

From rDNA Human sources; 100 Units/ml
*Humulin® U Ultralente* (Lilly)

Other insulins that are commercially available, but have not been used extensively in veterinary patients, include: Insulin Zinc (Lente), and fixed dose combination products containing regular insulin and isophane insulin (NPH).

## ISOFLURANE

**Chemistry** - An inhalant general anesthetic agent, isoflurane occurs as a colorless, nonflammable, stable liquid. It has a characteristic mildly pungent musty, ethereal odor. At 20°C, isoflurane's specific gravity is 1.496 and vapor pressure is 238 mm Hg.

**Storage/Stability/Compatibility** - Isoflurane should be stored at room temperature; it is relatively unaffected by exposure to light, but should be stored in a tight, light-resistant container. Isoflurane does not attack aluminum, brass, tin, iron or copper.

**Pharmacology** - While the precise mechanism that inhalent anesthetics exert their general anesthetic effects is not precisely known, they may interfere with functioning of nerve cells in the brain by acting at the lipid matrix of the membrane. Some key pharmacologic effects noted with isoflurane include: CNS depression, depression of body temperature regulating centers, increased cerebral blood flow, respiratory depression, hypotension, vasodilatation, and myocardial depression (less so than with halothane) and muscular relaxation.

Minimal Alveolar Concentration (MAC; %) in oxygen reported for isoflurane in various species: Dog = 1.5; Cat = 1.2; Horse = 1.31; Human = 1.2. Several factors may alter MAC (acid/base status, temperature, other CNS depressants on board, age, ongoing acute disease, etc.).

**Uses/Indications** - Isoflurane is an inhalant anesthetic that has some distinct advantages over either halothane or methoxyflurane due to its lessened myocardial depressant and catecholamine sensitizing effects, and the ability to use it safely in patients with either hepatic or renal disease. Isoflurane's higher cost than either methoxyflurane or halothane is a disadvantage.

Horses may recover more rapidly than with halothane, but be more susceptible to anesthetic associated-myopathy.

**Pharmacokinetics** - Isoflurane is rapidly absorbed from the alveoli. It is rapidly distributed into the CNS and crosses the placenta. The vast majority of the drug is eliminated via the lungs; only about 0.17% is metabolized in liver and only very small amounts of inorganic fluoride is formed.

To Drug Monograph Index  To Ophthalmic Product Index

**Contraindications/Precautions/Reproductive Safety** - Isoflurane is contraindicated in patients with a history or predilection towards malignant hyperthermia. It should be used with caution (benefits vs. risks) in patients with increased CSF or head injury, or myasthenia gravis.
Some animal studies have indicated that isoflurane may be fetotoxic. Use during pregnancy with caution.

**Adverse Effects/Warnings** - Hypotension (secondary to vasodilation, not cardiodepression) may occur and is considered to be dose related. Dose-dependent respiratory depression, and GI effects (nausea, vomiting, ileus) have been reported. While cardiodepression generally is minimal at doses causing surgical planes of anesthesia, it may occur. Arrhythmias have also rarely been reported.

**Drug Interactions** - While isoflurane sensitizes the myocardium to the effects of sympathomimetics less so than halothane, arrhythmias may still result. Drugs included are: **dopamine, epinephrine, norepinephrine, ephedrine, metaraminol, etc.** Caution and monitoring is advised. **Non-depolarizing neuromuscular blocking agents, systemic aminoglycosides, systemic lincomycins** should be used with caution with halogenated anesthetic agents as additive neuromuscular blockade may occur. Concomitant administration of **succinylcholine** with inhalation anesthetics may induce increased incidences of cardiac effects (bradycardia, arrhythmias, sinus arrest and apnea) and in susceptible patients, malignant hyperthermia as well.

**Doses** -
**Dogs/Cats**: (Note: Concentrations are dependent upon fresh gas flow rate; the lower the flow rate, the higher the concentration required.)

a) 5% induction; 1.5 - 2.5% maintenance (Papich 1992)
b) 0.5 - 3 %, inhaled (Hubbell 1994)

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

**SPECIAL NOTE CONCERNING THE USE OF ISOFLURANE:** several authors recommend that gas anesthesia be discontinued for a period of time (10-40 minutes) prior to the administration of narcotic antagonists in elephants immobilized with etorphine or carfentanil. The administration of oxygen (with a high flow rate and frequent emptying of the re-breathing bag) facilitates removal of the gas and can prevent ataxia once the narcotic antagonist is given.

a,b) A 2817 kg female Asian elephant was induced with 1.75 mg etorphine IM, followed by 0.75 mg etorphine at 40 minutes. The elephant was intubated with a 30 mm endotracheal tube and maintained with 1.5-2.0% isoflurane. A latex weather balloon was used as a rebreathing bag. Additional etorphine (total additional 1.4 mg) was supplemented IV during the procedure to surgically remove P-3. Thirty minutes prior to the completion of the procedure isoflurane was discontinued, but oxygen continued to flow. Additional etorphine was given intermittently IV (0.4 mg total) during the remaining 45 minutes of recumbency. Naltrexone (250 mg) was given IV and the elephant was standing within 3 minutes. Fowler,M.E., Steffey,E.P., Galuppo,L., and Pascoe,J.R. 2000. **Facilitation of Asian elephant (Elephas maximus) standing immobilization and anesthesia with a sling**. Journal of Zoo and Wildlife Medicine 31:(1):118-123 **Abstract:** An Asian elephant (Elephas maximus) required general anesthesia for orthopedic foot surgery. The elephant was unable to lie down, so it was placed in a custom-made sling, administered i.m. etorphine hydrochloride in the standing position, and lowered to lateral recumbency. General anesthesia was maintained with isoflurane administered through an endotracheal tube. After surgery, the isoflurane anesthesia was terminated, with immobilization maintained with additional i.v. etorphine. The elephant was

To Drug Monograph Index To Ophthalmic Product Index

lifted to the vertical position, and the immobilizing effects of etorphine were reversed with naltrexone. The suspension system and hoist for the sling were designed specifically for the elephant house.

Fowler,M.E., Steffey,E.P., Galuppo,L., and Pascoe,J.R. 1999. **Standing immobilization and anesthesia in an Asian elephant (*Elephas maximus*)**. Proc. Am. Assoc. Zoo Vet. Pages: 107-110

c) Dunlop,C.I., Hodgson,D.S., Cambre,R.C., Kenny,D.E., and Martin,H.D. 1994. **Cardiopulmonary effects of three prolonged periods of isoflurane anesthesia in an adult elephant**. Journal of the American Veterinary Medical Association 205:(10):1439-1444. **Abstract:** An adult 3500-kg female African elephant (Loxodonta africana) was anaesthetized 3 times for treatment of subcutaneous fistulas over the lateral aspect of each cubitus (anaesthesia 1 and 2) and for repair of a fractured tusk (anaesthesia 3). Lateral recumbency and anaesthesia were achieved with etorphine (anaesthesia 1 and 2) or etorphine and azaperone (anaesthesia 3). The trachea was intubated and anaesthesia was maintained by isoflurane and oxygen delivered through 2 standard large animal anaesthesia machines joined in parallel. The range of total recumbency time was 2.4 to 3.3 h. Breathing and heart rates, systemic arterial pressure, rectal temperature, PaO2, pH and end-tidal gases were monitored. After administration of etorphine, measurements were made while the elephant was recumbent and breathing air, then every 5 min (cardiovascular) or 15 min (blood gases) after the start of administration of isoflurane and oxygen. Tachycardia and hypertension were detected after administration of etorphine, but heart rate and systemic arterial pressure decreased to within normal ranges after administration of isoflurane and oxygen. The elephant remained well oxygenated while anaesthetized and breathing a high oxygen mixture. The elephant had an uneventful recovery from each anaesthesia.

d) Following induction with 6 mg etorphine and 150 mg atropine IM, followed by 2-4 mg etorphine IV, a 3500 kg African elephant was intubated with a 40 mm (I.D.) cuffed endotracheal tube using a large stomach tube passed through the larynx as a guide. Anesthesia was maintained for 2.5 hrs during each of two procedures. Details of isoflurane % and flow rate not stated. Isoflurane was discontinued and oxygen administered at 120L/min for 40 minutes prior to reversal with 20 mg diprenorphine IV. Dunlop,C.I., Hodgson,D.S., Cambre,R.C., and Kenney,D. 1988. **Prolonged isoflurane anesthesia of an adult elephant on two occasions**. Veterinary Surgery 17:(3):167-168

**Monitoring Parameters** - 1) Respiratory and ventilatory status; 2) Cardiac rate/rhythm; blood pressure (particularly with “at risk” patients; 3) Level of anesthesia

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Isoflurane in 100 ml bottles; *Aerrane*® (Anaquest; *Isovet*® (Schering) (Rx) Approved for use in dogs and cats.; *IsoFlo*® (Abbott) (Rx); Approved for dogs and horses.

**Human-Approved Products**:

Isoflurane in 100 ml bottles;*Isoflurane*®(Abbott), *Forane*® (Anaquest); (Rx)

## ISONIAZID * PK ADVERSE EFFECT REPORTED

The following section was authored by Joel Maslow MD PhD MBA

**Chemistry** – Isoniazid is a synthetic isonicotinic acid derivative antituberculosis agent. The drug occurs as a colorless or while crystalline powder. It is soluble in water at concentrations ≤125 mg/ml and 20 mg/ml in alcohol.

To Drug Monograph Index To Ophthalmic Product Index

**Storage/Stability/Compatibility** – Isoniazid is stable at room temperature in tablet form. INH powder and liquid concentrate (600 mg/ml) should be stored at 4°C. The stability of an oral concentrate is unknown, but while stable for a period of at least 1 month, there appears to be drug decay resulting in lower serum concentrations (Maslow JN, unpublished observations). In liquid form, the drug crystallizes at low temperature and can be re-solubilized at increased temperatures. INH tablets should be stored in well-closed, light-resistant, containers between 15-30ºC.

**Mechanism of action -** Isonicotinc acid hydrazide (isoniazid or INH) has an unknown mechanism of action to inhibit mycolic acid biosynthesis (a cell wall lipid of mycobacteria).

**Uses/Indications** – INH is indicated for the treatment of *M. tuberculosis* complex (*M. tuberculosis* and *M. bovis*). Non-tuberculous mycobacteria are typically resistant to INH. INH should be administered in conjunction with other anti-mycobacterial to avoid the development of bacterial resistance.

**Pharmacology** – INH is well absorbed both orally and intramuscularly. CSF levels are approximately 20% of the serum. INH is metabolized in the liver through the action of N-acetyltransferase. Diminished acetylation capacity is observed in some individuals and is more common in certain ethnic groups resulting in increased serum concentrations.

INH has been administered successfully orally and rectally to elephants (**Maslow JN et al. submitted**). Achievable Cmax are greatest for oral administration of freshly suspended powder (2.2 mcg/ml/mg of INH). Oral administration of INH concentrate yields serum levels between 0.4-1 mcg/ml/mg of INH, the serum concentration being directly proportional to the level that the animals are trained to accept the drug. Oral administration of INH as a mixture with feeds yields inconsistent serum concentrations and should be avoided. Rectal enema administration yields Cmax of 0.5-0.8 mcg/ml/mg of INH. The Tmax for each form of administration was 2 hrs. In general, the serum half life ranged between 1 and 2 hrs.

In bongo antelope, INH administered orally achieves a Cmax ranging between 0.05-0.1 mcg/ml/mg of INH with a Tmax between 2-4 hrs **Population pharmacokinetics of antituberculous drugs and treatment of *Mycobacterium bovis* infection in Bongo Antelope (*Tragelaphus eurycrus isaaci* ).** B. Auclair, S. Mikota, C. A. Peloquin, R. Aguilar and J. N. Maslow. Journal of Zoo and Wildlife Medicine 2002 Vol. 33 Issue 3 Pages 193-203. Parenterally administered INH given IM achieves a Cmax of 0.3-0.45, Tmax of 2.5 hrs, and serum half life of 2.4 hrs. The volume of distribution is 1.3 L/kg.

**Contraindications/Precautions/Reproductive Safety** – INH has been shown to be embryocidal in rats and rabbits. Teratogenicity has not been demonstrated in any mammalian species. INH has been used to treat TB in pregnant humans. INH can cause the placenta and is distributed in milk of lactating females. INH has been reported to cause pulmonary tumors in animals (McEvoy, 2000).

**Adverse Effects/Warnings** – INH appears to be bitter tasting and oral tolerability may be increased by mixture with various, non glucose containing, sweeteners and/or flavorings.

The major side effects of INH are hepatotoxicity and neuropathy. Hepatotoxicity is observed approximately 4-8 weeks after initiation of treatment in humans and is potentiated by other hepatotoxic agents. While peripheral neuropathy is the most common neurologic manifestation, seizures, psychosis and memory loss are also observed infrequently among humans. INH may also cause a hypersensitivity reaction marked by spiking fevers and skin rash. Other uncommon disorders include arthritis. Neuropathic effects are prevented with the co-administration of pyridoxine (50 mg; ~0.8 mg/kg).

INH administered to bongo antelope appeared to be well tolerated without documented adverse effects (Mikota SK, unpublished observations).

To Drug Monograph Index To Ophthalmic Product Index

In camels, INH administration has resulted in irreversible granulocytopenia.

Elephants: see text below.

**Overdosage/Acute Toxicity** - Symptoms associated with overdosage of INH generally are extensions of the adverse effects outlined above Treatment is with pyridoxine given by parenteral administration at a dose of 0.8 mg/kg.

**Drug Interactions** – Phenytoin toxicity is potentiated by INH and can cause mental status changes, seizures, and ataxia in humans. Theophylline toxicity is also potentiated by INH.

**Doses** – INH should be given concurrently with pyridoxine. The effective dose for animals has not been determined. The human dose of 50 mg daily corresponds to ~0.8 mg/kg/day.

**Human dosing**:
The dose for humans is 300 mg/day (4-5 mg/kg/day) and is not weight based. This dose typically yields a therapeutic serum concentration of 3-5 mcg/ml (Peloquin, 1997). Decreases in dose are occasionally required for slow acetylators.

**Bongo antelope:**
An initial dose of 10 mg/kg given by intramuscular injection is recommended. Serum levels should be determined at 2.5 hrs after administration to document absorption and limit toxicity.

**Elephants:** An initial dose of 4 mg/kg is recommended if INH is administered as a freshly suspended powder via oral bolus and 7.5 mg/kg if given as orally or rectally as a pre-mixed suspension.

**Monitoring –** The efficacy of antituberculosis drug administration should be monitored by measurement of serum concentrations. Ideally, serum concentrations should be ascertained over a range of times to determine both the pharmacokinetics (as a means to monitor total area under the curve (AUC)) and the time (Tmax) of occurrence individual peak serum concentration (Cmax). For elephants administered oral or rectal INH, peak serum concentrations occur at 2 hr. For bongo antelope levels should be determined a 2.5 hrs after intramuscular administration. Based on studies in humans, a serum concentration of 3-5 mcg/ml is associated with therapeutic success (Peloquin, 1997).

Elephants:

a) 5 mg/kg orally. Devine,J.E., Boever,W.J., and Miller,E. 1983. **Isoniazid therapy in an Asiatic elephant (*Elephas maximus*)**. Journal of Zoo Animal Medicine 14:130-133. **Summary:** A single Asian elephant (approx. 2300 kg) was given 10 g of isoniazid with food and blood levels evaluated at 1,2,3,4,6, and 7 hours after dosing. Total INH concentrations ranged from 8.63 µg/ml at 1 hour to 2.63 µg/ml at 7 hours. The authors suggest that a dose of 5 mg/kg in elephants should be adequate to achieve blood levels found to be effective in humans.

b) Adverse effects: In one elephant under treatment for tuberculosis, isoniazid (INH) administered orally together with rifampin (8 mg/kg), pyrazinamide (35mg/kg) and vitamin B6 caused partial anorexia. Rifampin was discontinued after the first 6 months of treatment due to failure to achieve therapeutic levels. Rectally administered INH at a dose of 11.5 mg/kg resulted in anorexia, lethargy, and pica. Yellow brown urine was observed and serum AST, total bilirubin, GGT, and bile acids were elevated. Signs resolved within 2-3 days after treatment was stopped. Daily treatment with INH (3.75 mg/kg per rectum) had no adverse effects but symptoms resumed if the dose was increased to 5 mg/kg or greater. When INH and pyrazinamide were administered rectally 4 times weekly, a low grade anemia was observed. The anemia resolved when the INH dose was decreased from 3.75 to 2.5 mg/kg and the PZA dose was decreased from 35 to 25 mg/kg.

To Drug Monograph Index To Ophthalmic Product Index

- Four elephants receiving daily direct oral administration of isoniazid (7.5 mg/kg) and rifampin (9.9 mg/kg) developed inappetance, lethargy, and pica. Symptoms resolved when the INH dose was reduced to 5.6 mg/kg and the rifampin dose was reduced to 7.5 mg/kg.

- One elephant showed a decreased white blood cell count (from 13,000 / µl to 1,900 / µl) which resolved when INH was discontinued.

- One elephant given INH (10 mg/kg) rectally as the only drug developed lethargy, inappetance and an elevated LDH within 3 weeks. Treatment was discontinued for one month then reinstated at 5 mg/kg. Pyrazinamide (25 mg/kg/day) was added and both drugs were given rectally. Periodic episodes of lethargy on this regimen responded to 1-2 weeks rest (no drugs) then reinstating INH at a half-dose and increasing to a full dose over a period of several weeks. (Mikota, et.al. 2001).

Mikota,S.K., Peddie,L., Peddie,J., Isaza,R., Dunker,F., West,G., Lindsay,W., Larsen,R.S., Salman,M.D., Chatterjee,D., Payeur,J., Whipple,D., Thoen,C., Davis,D.S., Sedgwick,C., Montali,R.J., Ziccardi,M., and Maslow,J. 2001. **Epidemiology and diagnosis of Mycobacterium tuberculosis in captive Asian elephants (Elephas maximus)**. Journal of Zoo and Wildlife Medicine 32:(1):1-16.

c) **Population pharmacokinetics of isoniazid in the treatment of Mycobacterium tuberculosis among Asian and African elephants (Elephas maximus and Loxodonta africana).** 2005. J. N. Maslow, S. K. Mikota, M. Zhu, R. Isaza, L. R. Peddie, F. Dunker, et al.
J. Vet. Pharmacol. Ther Vol. 28 Issue 1 Pages 21-27. DOI: JVP619 [pii];10.1111/j.1365-2885.2004.00619.x [doi]

Request full article here:
https://www.researchgate.net/publication/8011954_Pharmacokinetics_of_isoniazid_INH_in_the_treatment_of_Mycobacterium_tuberculosis_among_Asian_and_African_elephants_Elephas_maximus_and_Loxodonta_africana

We recently described the clinical presentation and treatment of 18 elephants from six herds infected with TB. Treatment protocols and methods varied between herds to include both oral and rectal dosing using multiple drug doses and formulations. In this paper we present information regarding the pharmacokinetics (PK) of isoniazid (INH) in elephants and provide suggestions regarding initial treatment regimens. Forty-one elephants received INH daily by either oral or rectal administration with different formulations. Population PK analysis was performed using Non-linear Mixed Effect Modeling (NONMEM). Results of oral administration indicated that compared with premixed INH solution, the drug exposure was highest with a suspension prepared freshly with INH powder. When INH was concomitantly given as an admixture over food, Tmax was delayed and variability in drug absorption was significantly increased. Compared with oral administration, similar drug exposures were found when INH was dosed rectally. The data generated suggest that a starting dose of 7.5 mg/kg of INH is appropriate for initial TB treatment in elephants when premixed solution is administered directly into the oropharynx or rectal vault and 4 mg/kg are when INH is administered following immediate suspension from powdered form.

d) **The pharmacokinetics of a single oral or rectal dose of concurrently administered isoniazid, rifampin, pyrazinamide, and ethambutol in Asian elephants (Elephas maximus).**
2014. A. P. Brock, R. Isaza, E. F. Egelund, R. P. Hunter and C. A. Peloquin. Journal of Veterinary Pharmacology and Therapeutics Vol. 37 Issue 5 Pages 472-479.
Accession Number: WOS:000342801400007 DOI: 10.1111/jvp.12119

Tuberculosis, caused by Mycobacterium tuberculosis, is a disease of concern in captive Asian elephants (Elephas maximus). Treatment for tuberculosis in elephants utilizes multidrug protocols combining isoniazid, rifampin, pyrazinamide, and/or ethambutol. In this study, a single, coformulated dose of isoniazid 5mg/kg, rifampin 10mg/kg, pyrazinamide 30mg/kg, and ethambutol 30mg/kg was administered orally to six Asian

To Drug Monograph Index To Ophthalmic Product Index

elephants, and rectally to five elephants using a cross-over design. Blood samples were collected serially over 24h. Pyrazinamide and ethambutol concentrations were determined using validated gas chromatography assays. Isoniazid and rifampin concentrations were determined using validated high-performance liquid chromatography assays. Rectal isoniazid produced an earlier T-max compared with oral administration. Oral isoniazid resulted in a comparatively lower C-max, but higher AUC values compared with rectal isoniazid. Oral rifampin and oral ethambutol were well absorbed while rectal rifampin was not. Oral pyrazinamide produced comparatively higher C-max and AUC values compared with rectal pyrazinamide. Results of this study indicate that currently recommended therapeutic monitoring sample collection times for rectal isoniazid and oral rifampin do not provide an accurate assessment of exposure for these drugs. This study demonstrates notable individual variability, indicating that dosing of these medications requires individual monitoring and provides additional information to guide the clinician when treating elephants.

**ISONIAZID AND RIFAMPIN PHARMACOKINETICS IN TWO ASIAN ELEPHANTS (ELEPHAS MAXIMUS) INFECTED WITH MYCOBACTERIUM TUBERCULOSIS.** E. F. Egelund, R. Isaza, A. Alsultan and C. A. Peloquin. Journal of Zoo and Wildlife Medicine 2016 Vol. 47 Issue 3 Pages 868-871. Accession Number: WOS:000385639100021

This report describes the pharmacokinetic profiles of chronically administered oral isoniazid and rifampin in one adult male and one adult female Asian elephant (Elephas maximus) that were asymptomatically infected with Mycobacterium tuberculosis. Rifampin's half-life was reduced when compared to previous single-dose pharmacokinetic profiles of healthy uninfected Asian elephants. Both elephants experienced delayed absorption of isoniazid and rifampin as compared to previous pharmacokinetic studies in this species. The altered pharmacokinetics of both drugs in repeated-dosing clinical situations underscores the need for individual therapeutic drug monitoring for tuberculosis treatment.

Also see:
Using therapeutic drug monitoring to dose the antimycobacterial drugs. C. Peloquin.
Clinics in Chest Medicine 1997 Vol. 18 Pages 79-97

Clinical pharmacology of the anti-tuberculoisis drugs. C. A. Peloquin.In: Clinical Tuberculosis, edited by P. D. O. Davies. Arnold Publishers 2003

Tuberculosis treatment protocols and complications for elephants. G. Dumonceaux and S. Mikota. Proceedings International Elephant Conservation and Research Symposium 2006 Pages 84-85. Request full paper from smikota@elephantcare.org.

## ISOPROTERENOL HCL

**Chemistry** - Also called isoprenaline HCl, isoproterenol HCl is a synthetic beta adrenergic agent that occurs as a white to practically white, crystalline powder that is freely soluble in water and sparingly soluble in alcohol. The pH of the commercially available injection is 3.5 - 4.5.

**Storage/Stability/Compatibility** - Store isoproterenol preparations in tight, light-resistant containers. It is stable indefinitely at room temperature. Isoproterenol salts will darken with time, upon exposure to air, light, or heat. Sulfites or sulfur dioxide may be added to preparations as an antioxidant. Solutions may become pink or brownish-pink if exposed to air, alkalies or metals. Do not use solutions that are discolored or contain a precipitate. If isoproterenol is mixed with other drugs or fluids that results in a solution with a pH greater than 6, it is recommended that it be used immediately.

To Drug Monograph Index  To Ophthalmic Product Index

Isoproterenol for injection is reported to be **compatible** with all commonly used IV solutions (except 5% sodium bicarbonate), and the following drugs: calcium chloride/gluceptate, cephalothin sodium, cimetidine HCl, dobutamine HCl, heparin sodium, magnesium sulfate, multivitamin infusion, netilmicin sulfate, oxytetracycline HCl, potassium chloride, succinylcholine chloride, tetracycline HCl, verapamil HCl, and vitamin B complex w/C.

It is reported to be **incompatible** with: aminophylline or sodium bicarbonate. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** - Isoproterenol is a synthetic beta$_1$ and beta$_2$ adrenergic agonist that has no appreciable alpha activity at therapeutic doses. It is thought that isoproterenol's adrenergic activity is a result of stimulating cyclic-AMP production. Its primary actions are increased inotropism and chronotropism, relaxation of bronchial smooth muscle and peripheral vasodilitation. Isoproterenol may also increase perfusion to skeletal muscle (at the expense of vital organs in shock). Isoproterenol will also inhibit the antigen-mediated release of histamine and slow releasing substance of anaphylaxis (SRS-A).

Hemodynamic effects noted include decreased total peripheral resistance, increased cardiac output, increased venous return to the heart and increased rate of discharge by cardiac pacemakers.

**Uses/Indications** - Isoproterenol is primarily used in veterinary medicine in the treatment of acute bronchial constriction, cardiac arrhythmias (complete AV block) and occasionally as adjunctive therapy in shock or heart failure (limited use because of increases in heart rate and ventricular arrhythmogenicity).

**Pharmacokinetics** - Isoproterenol is rapidly inactivated by the GI tract and metabolized by the liver after oral administration. Sublingual administration is not reliably absorbed and effects may take up to 30 minutes to be seen. Intravenous administration result in immediate effects, but only persist for a few minutes after discontinuation.

It is unknown if isoproterenol is distributed into milk. The pharmacologic actions of isoproterenol are ended primarily through tissue uptake. Isoproterenol is metabolized in the liver and other tissues by catechol-*O*-methyltransferase (COMT) to a weakly active metabolite.

**Contraindications/Precautions** - Isoproterenol is contraindicated in patients that have tachycardias or AV block caused by cardiac glycoside intoxication. It is also contraindicated in ventricular arrhythmias that do not require increased inotropic activity.

Use isoproterenol with caution in patients with coronary insufficiency, hyperthyroidism, renal disease, hypertension or diabetes. Isoproterenol is not a substitute for adequate fluid replacement in shock.

**Adverse Effects/Warnings** - Isoproterenol can cause tachycardia, anxiety, tremors, excitability, headache, weakness and vomiting. Because of isoproterenol's short duration of action, adverse effects are usually transient and do not require cessation of therapy, but may require lowering the dose or infusion rate. Isoproterenol is considered to be more arrhythmogenic than either dopamine or dobutamine, so it is rarely used in the treatment of heart failure.

**Overdosage** - In addition to the symptoms listed in the adverse effects section, high doses may cause an initial hypertension, followed by hypotension as well as tachycardias and other arrhythmias. Besides halting or reducing the drug, treatment is considered to be supportive. Should tachycardias persist, a beta blocker could be considered for treatment (if patient does not have a bronchospastic disease).

To Drug Monograph Index To Ophthalmic Product Index

**Drug Interactions** - Do not use with other **sympathomimetic amines (***e.g.,* **epinephrine)** because of additive effects and toxicity. **Propranolol** (or other beta-blockers) may antagonize isoproterenol's cardiac, bronchodilating, and vasodilating effects by blocking the beta effects of isoproterenol. Beta blockers may be administered to treat the tachycardia associated with isoproterenol use, but should not be given to patients with bronchospastic disease.
When isoproterenol is used with drugs that sensitize the myocardium **(halothane, digoxin**) monitor for signs of arrhythmias. Hypertension may result if isoproterenol is used with **oxytocic agents**. When isoproterenol is used with **potassium depleting diuretics (***e.g.,* **furosemide)** or other drugs that affect cardiac rhythm, there is an increased chance of arrhythmias occurring.
Although not unequivocally established, there is some evidence that isoproterenol used concomitantly with **theophylline** may induce increased cardiotoxic effects.

**Doses** - Note: Because of the cardiostimulatory properties of isoproterenol, its parenteral use in human medicine for the treatment of bronchospasm has been largely supplanted by other more beta$_2$ specific drugs (*e.g.,* terbutaline) and administration methods (nebulization). Use with care.
**Horses**:

For short-term bronchodilitation:

a) Dilute 0.2 mg in 50 ml of saline and administer 0.4 micrograms/kg as an IV infusion, monitor heart rate continuously and discontinue when heart rate doubles. Effects may only last for an hour. (Derksen 1987)

**Monitoring Parameters** -

1) Cardiac rate/rhythm
2) Respiratory rate/auscultation during anaphylaxis
3) Urine flow if possible
4) Blood pressure, and blood gases if indicated and if possible

**Client Information** - Isoproterenol for injection should be used only by trained personnel in a setting where adequate monitoring can be performed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Isoproterenol for Injection 1:5000 solution (0.2 mg/ml) in 1 & 5 ml amps; *Isuprel*® (Winthrop Pharm.); Generic; (Rx)

Isoproterenol sublingual or rectal Glossets 10 mg, 15 mg; *Isuprel*® *Glossets* (Winthrop); (Rx)

Isoproterenol is also available in aerosol or solution form for oral inhalation.

## ISOXSUPRINE HCL

**Chemistry** - A peripheral vasodilating agent, isoxsuprine occurs as an odorless, bitter-tasting, white, crystalline powder with a melting point of about 200°C. It is slightly soluble in water and sparingly soluble in alcohol.

**Storage/Stability/Compatibility** - Tablets should be stored in tight containers at room temperature (15-30°C).

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Isoxsuprine causes direct vascular smooth muscle relaxation primarily in skeletal muscle. While it stimulates beta-adrenergic receptors it is believed that this action is not required for vasodilitation to occur. In horses with navicular disease, it has been demonstrated that isoxsuprine will raise distal limb temperatures significantly. Isoxsuprine will also relax uterine smooth muscle and may have positive inotropic and chronotropic effects on the heart. At high doses, isoxsuprine can decrease blood viscosity and reduce platelet aggregation.

**Uses/Indications** - Isoxsuprine is used in veterinary medicine principally for the treatment of navicular disease in horses. It has been used in humans for the treatment of cerebral vascular insufficiency, dysmenorrhea, and premature labor, but efficacies are unproven for these indications.

**Pharmacokinetics** - In humans, isoxsuprine is almost completely absorbed from the GI tract, but in one study that looked at the cardiovascular and pharmacokinetic effects of isoxsuprine in horses (Mathews and et 1986), bioavailability was low after oral administration, probably due to a high first-pass effect. After oral dosing of 0.6 mg/kg, the drug was non-detectable in the plasma and no cardiac changes were detected. This study did not evaluate cardiovascular effects in horses with navicular disease, nor did it attempt to measure changes in distal limb blood flow. After IV administration in horses, the elimination half-life is between 2.5 - 3 hours.

**Contraindications/Precautions** - Isoxsuprine should not be administered to animals immediately post-partum or in the presence of arterial bleeding.

**Adverse Effects/Warnings** - After parenteral administration, horses may show symptoms of CNS stimulation (uneasiness, hyperexcitability, nose-rubbing) or sweating. Adverse effects are unlikely after oral administration, but hypotension, tachycardia, and GI effects are possible.

**Overdosage** - Serious toxicity is unlikely in horses after an inadvertent oral overdose, but symptoms listed in the Adverse Effects section could be seen. Treat symptoms if necessary. CNS hyperexcitability could be treated with diazepam, and hypotension with fluids.

**Drug Interactions** - No clinically significant drug interactions have been reported for this agent.

**Doses** -
**Horses**:

For treatment of navicular disease:

a) 0.6 - 0.66 mg/kg *bid* PO X 21 days; then once daily for 14 days; then once every other day for 7 days. (Note: 0.66 mg/kg is fifteen 20 mg tabs for a 1000 lb. horse)

For refractory cases: regimen may be repeated at 1.32 mg/kg. If no improvement seen after 6 week course then discontinue. (Forney and Allen 1984)

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects (tachycardia, GI disturbances, CNS stimulation)

**Client Information** - To be maximally effective, doses must be given routinely as directed. Tablets may be crushed and made into a slurry/suspension/paste by adding corn syrup, cherry syrup, etc., just before administration.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Isoxsuprine HCl Tablets 10 mg, 20 mg; *Vasodilan*® (Mead Johnson), *Voxsuprine*® (Major), Generic; (Rx)

## ITRACONAZOLE

**Chemistry** - A synthetic triazole antifungal, itraconazole is structurally related to fluconazole. It has a molecular weight of 706 and a pKa of 3.7.

**Pharmacology** - Itraconazole is a fungistatic triazole compound. Triazole-derivative agents, like the imidazoles (clotrimazole, ketoconazole, etc.), presumably act by altering the cellular membranes of susceptible fungi, thereby increasing membrane permeability and allowing leakage of cellular contents and impaired uptake of purine and pyrimidine precursors. Itraconazole has efficacy against a variety of pathogenic fungi, including yeasts and dermatophytes. *In vivo* studies using laboratory models have shown that itraconazole has fungistatic activity against many strains of *Candida, Aspergillus, Cryptococcus, Histoplasma*, *Blastomyces* and *Trypanosoma cruzi*.

**Uses/Indications** - Itraconazole may have use in veterinary medicine in the treatment of systemic mycoses, including aspergillosis, cryptococcal meningitis, blastomycosis, and histoplasmosis. It may also be useful for superficial candidiasis or dermatophytosis. Itraconazole does not have appreciable effects (unlike ketoconazole) on hormone synthesis and may have fewer side effects than ketoconazole in small animals.

In horses, itraconazole may be useful in the treatment of sporotrichosis and *Coccidioides immitis* osteomyelitis.

**Pharmacokinetics** - Itraconazole absorption is highly dependent on gastric pH and presence of food. When given on an empty stomach bioavailability may only be 50% or less, with food it may approach 100%.

Itraconazole has very high protein binding and is widely distributed throughout the body, particularly to tissues high in lipids (drug is highly lipophilic). Skin, female reproductive tract and pus all have concentrations greater than found in the serum. Only minimal concentration are found in the CSF, aqueous humor and saliva, however.

Itraconazole is metabolized by the liver to many different metabolites, including to hydroxyitraconazole which is active. In humans, itraconazole's serum half life ranges from 21-64 hours. Elimination may be a saturable process.

**Contraindications/Precautions/Reproductive Safety** - Itraconazole should be used in patients hypersensitive to it or other azole antifungal agents, in patients with hepatic impairment, or achlorhydria (or hypochlorhydria) only when the potential benefits outweigh the risks.

In laboratory animals, itraconazole has caused dose-related maternotoxicity, fetotoxicity and teratogenicity at high dosages (5-20 times labeled). As safety has not been established, use only when the benefits outweigh the potential risks. Itraconazole does enter maternal milk, significance is unknown.

**Adverse Effects/Warnings** - In dogs, hepatic toxicity appears to be the most significant adverse effect. Approximately 10% of dogs recieving 10 mg/kg/day and 5% of dogs recieving 5 mg/kg/day develop hepatic toxicosis serious enough to discontinue (at least temporarily) treatment. Hepatic injury is determined by an increased ALT activity. Anorexia is often the symptomatic marker for toxicity and usually occurs in the second moth of treatment. Some dogs given itraconazole at the higher dosage rate (10 mg/kg/day) may develop ulcerative skin lesions/vasculitis and limb edema that may require dosage reduction.

To Drug Monograph Index To Ophthalmic Product Index

In cats, adverse effects appear to be dose related. GI effects (anorexia, weight loss, vomiting), hepatotoxicity (increased ALT, jaundice) and depression and have been noted. Should adverse effects occur and ALT is elevated, the drug should be discontinued. Once ALT levels return to normal and other adverse effects have diminished, and if necessary, the drug may be restarted at a lower dosage or longer dosing interval with intense monitoring.

**Overdosage/Acute Toxicity** - There is very limited information on the acute toxicity of itraconazole. Giving oral antacids may help reduce absorption. If a large overdose occurs, consider gut emptying and give supportive therapy as required. Itraconazole is not removed by dialysis. In chronic toxicity studies, dogs receiving 40 mg/kg PO daily for 3 months demonstrated no overt toxicity.

**Drug Interactions** - Itraconazole requires an acidic environment for maximal absorption, therefore **antacids**, **Histamine$_2$-blockers (cimetidine, ranitidine, etc)** or **didanosine** will cause marked reduction in absorption of itraconazole. Didanosine must not be taken concurrently with itraconazole, the others (noted above), if required, should be given two hours after itraconazole dose. Itraconazole may cause increased prothrombin times in patients receiving **warfarin** or other coumarin anticoagulants. **Rifampin** may enhance the rate of metabolism of itraconazole; itraconazole dosage adjustment may be required. Itraconazole may decrease the metabolism of **phenytoin or cyclosporine**. Veterinary significance is unclear. Itraconazole may increase the risks of cardiovascular effects occurring if used concomitantly with either **terfenadine or astemizole**. If itraconazole is required, it is best to switch to another antihistamine. Itraconazole may increase serum **digoxin** concentrations; monitor serum digoxin levels. Itraconazole may increase the serum levels of **oral antidiabetic agents** (*e.g.,* chlorpropamide, glipizide, etc.) which may result in hypoglycemia. Elevated concentrations of **cisapride** with resultant ventricular arrhythmias may result if coadministered with ketoconazole, itraconazole, IV miconazole or troleandomycin. At present, the manufacturer states that cisapride should not be used with these drugs.

**Laboratory Considerations -** Itraconazole may cause **hypokalemia** or increases in **liver function tests** in a small percentage of patients.

**Doses** -
**Horses**:

For aspergillosis:

a) 3 mg/kg twice a day (Legendre 1993)

A method to prepare an itraconazole suspension has been provided by the manufacturer with the following caveats: 1) No bioavailability data available; 2) Use only if no other alternative.

Empty 24 (twenty four) 100 mg capsules into a glass mortar. Add 4 to 5 ml of 95% ethyl alcohol USP and let stand 3 to 4 minutes to soften. Grind to a heavy paste; this will leave a powder when the alcohol dries. Slowly triturate with 15 ml of simple syrup. Transfer to a 60 ml amber bottle and continue to rinse mortar with simple syrup to get 60 ml. Shake Well and Refrigerate. Discard after 35 days. Janssen Corp.: 1-800-526-7736

**Monitoring Parameters** - 1) Clinical Efficacy; 2) With long-term therapy, routine liver function tests are recommended (monthly ALT) 3) Appetite 4) Physical asssessment for ulcerative skin lesions in dogs

**Client Information** - Compliance with treatment recommendations must be stressed. Have clients report any potential adverse effects. Give with food.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

To Drug Monograph Index To Ophthalmic Product Index

**Human-Approved Products**:

Itraconazole Oral Capsules 100 mg; *Sporanox*® (Janssen); (Rx)

## IVERMECTIN

**Chemistry** - An avermectin anthelmintic, ivermectin occurs as an off-white to yellowish powder. It is very poorly soluble in water (4 micrograms/ml), but is soluble in propylene glycol, polyethylene glycol, and vegetable oils.

**Storage/Stability/Compatibility** - Ivermectin is photolabile in solution; protect from light. Unless otherwise specified by the manufacturer, store ivermectin products at room temperature (15-30°C).

Ivermectin 1% oral solution (equine tube wormer product) is stable at 1:20 and 1:40 dilutions with water for 72 hours when stored in a tight container, at room temperature and protected from light.

**Pharmacology** - Ivermectin enhances the release of gamma amino butyric acid (GABA) at presynaptic neurons. GABA acts as an inhibitory neurotransmitter and blocks the post-synaptic stimulation of the adjacent neuron in nematodes or the muscle fiber in arthropods. By stimulating the release of GABA, ivermectin causes paralysis of the parasite and eventual death. As liver flukes and tapeworms do not use GABA as a peripheral nerve transmitter, ivermectin is ineffective against these parasites.

**Uses/Indications** - Ivermectin is approved in **horses** for the control of: large strongyles (adult) (*Strongylus vulgaris, S. edentatus, S. equinus, Triodontophorus spp.*), small strongyles, pinworms (adults and 4th stage larva), ascarids (adults), hairworms (adults), large-mouth stomach worms (adults), neck threadworms (microfilaria), bots (oral and gastric stages), lungworms (adults and 4th stage larva), intestinal threadworms (adults) and summer sores (cutaneous 3rd stage larva) secondary to *Hebronema* or *Draschia Spp*..

In **cattle**, ivermectin is approved for use in the control of: gastrointestinal roundworms (adults and 4th stage larva), lungworms (adults and 4th stage larva), cattle grubs (parasitic stages), sucking lice, and mites (scabies). For a listing of individual species covered, refer to the product information.

In **swine**, ivermectin is approved for use to treat GI roundworms, lungworms, lice, and mange mites. For a listing of individual species covered, refer to the product information.

In **reindeer**, ivermectin is approved for use in the control of: warbles.

In **American Bison**, ivermectin is approved for use in the control of: grubs.

In **dogs**, ivermectin is approved only for use as a preventative for heartworm. It is also been used as a microfilaricide, ectoparasiticide and endoparasiticide.

**Pharmacokinetics** - In simple-stomached animals, ivermectin is up to 95% absorbed after oral administration. Ruminants only absorb 1/4 - 1/3 of a dose due to inactivation of the drug in the rumen. While there is greater bioavailability after SQ administration, absorption after oral dosing is more rapid than SQ. It has been reported that ivermectin's bioavailability is lower in cats than in dogs, necessitating a higher dosage for prophylaxis of heartworm in this species.

Ivermectin is well distributed to most tissues, but does not readily penetrate into the CSF, thereby minimizing its toxicity. Collie-Breed dogs apparently allow more ivermectin into the CNS than other breeds/species.

To Drug Monograph Index  To Ophthalmic Product Index

| Species | Bioavailability (F) | Volume of Distribution (Vd) (L/kg) | T 1/2 (terminal) (in days) | Total Body Clearance (L/kg/day) |
|---|---|---|---|---|
| **Cattle** | | 0.45 - 2.4 | 2 - 3 | 0.79 |
| **Dogs** | .95 | 2.4 | 2 | |
| **Swine** | | 4 | 0.5 | |
| **Sheep** | 1.0 intra-abomasal<br>.251 intra-ruminal | 4.6 | 2 - 7 | |

Ivermectin has a long terminal half-life in most species (see table below). It is metabolized in the liver via oxidative pathways and is primarily excreted in the feces. Less than 5% of the drug (as parent compound or metabolites) is excreted in the urine.
Pharmacokinetic parameters of ivermectin have been reported for various species:

**Contraindications/Precautions/Reproductive Safety** - The manufacturer recommends that ivermectin not be used in foals less than 4 months old, as safety of the drug in animals this young has not been firmly established. However, foals less than 30 days of age have tolerated doses as high as 1 mg/kg without symptoms of toxicity.

Ivermectin is not recommended for use in puppies less than 6 weeks old. Most clinicians feel that ivermectin should not be used in Collies or Collie-mix breeds at the doses specified for treating microfilaria or other parasites unless alternative therapies are unavailable. After receiving heartworm prophylaxis doses, the manufacturer recommends observing Collie-breeds for at least 8 hours after administration.

Because milk withdrawal times have not been established, the drug is not approved for use in lactating dairy animals or females of breeding age.

The injectable products for use in cattle and swine should be given subcutaneously only; do not give IM or IV.

Ivermectin is considered to be safe to use during pregnancy. Reproductive studies performed in dogs, horses, cattle and swine have not demonstrated adverse effects to fetuses. Reproductive performance in male animals is also apparently unaltered.

**Adverse Effects/Warnings** - In horses, swelling and pruritis at the ventral mid-line can be seen approximately 24 hours after ivermectin administration due to a hypersensitivity reaction to dead *Onchocerca spp.* microfilaria. The reaction is preventable by administering a glucocorticoid just prior to, and for 1-2 days after ivermectin. If untreated, swelling usually subsides within 7 to 10 days and pruritis will resolve within 3 weeks.

Dogs may exhibit a shock-like reaction when ivermectin is used as a microfilaricide, presumably due to a reaction associated with the dying microfilaria.

When used to treat *Hypoderma bovis* larva (Cattle grubs) in cattle, ivermectin can induce serious adverse effects by killing the larva when they are in vital areas. Larva killed in the vertebral canal can cause paralysis and staggering. Larva killed around the gullet can induce salivation and bloat. These effects can be avoided by treating for grubs immediately after the Heal fly (Warble fly) season or after the stages of grub development where these areas would be affected. Cattle may also experience discomfort or transient swelling at the injection site. Using a maximum of 10 ml at any one injection site can help minimize these effects.

To Drug Monograph Index  To Ophthalmic Product Index

In birds, death, lethargy or anorexia may be seen. Orange-cheeked Waxbill Finches and budgerigars may be more sensitive to ivermectin than other species.
For additional information refer to the Overdosage/Acute Toxicity section below.

**Overdosage/Acute Toxicity** - In horses, doses of 1.8 mg/kg (9X recommended dose) PO did not produce symptoms of toxicity, but doses of 2 mg/kg caused symptoms of visual impairment, depression and ataxia.

In cattle, toxic effects generally do not appear until dosages of 30X those recommended are injected. At 8 mg/kg, cattle showed symptoms of ataxia, listless, and occasionally death.

Sheep showed symptoms of ataxia and depression at ivermectin doses of 4 mg/kg.

Swine showed symptoms of toxicosis (lethargy, ataxia, tremors, lateral recumbency, and mydriasis) at doses of 30 mg/kg. Neonatal pigs may be more susceptible to ivermectin overdosages, presumably due to a more permeable blood-brain barrier. Accurate dosing practices are recommended.

In dogs, symptoms of acute toxicity rarely occur at single dosages of 2 mg/kg (2000 micrograms/kg) or less. At 2.5 mg/kg mydriasis occurs, and at 5 mg/kg tremors occur. At doses of 10 mg/kg, severe tremors and ataxia are seen. Deaths occurred when dosages exceeded 40 mg/kg, but the $LD_{50}$ is 80 mg/kg. Dogs (Beagles) receiving 0.5 mg/kg PO for 14 weeks developed no signs of toxicity, but at 1 - 2 mg/kg for the same time period, developed mydriasis and had some weight decreases. Half of the dogs receiving 2 mg/kg/day for 14 weeks developed symptoms of depression, tremors, ataxia, anorexia, and dehydration.

The Collie breed appears to be more sensitive to the toxic effects of ivermectin than other canine breeds. This may be due to a more permeable blood-brain barrier to the drug or drug accumulation in the CNS of this breed. At the dosage recommended for heart worm prophylaxis, it is generally believed that the drug is safe to use in Collies.

Dogs who receive an overdosage of ivermectin or develop signs of acute toxicity (CNS effects, GI, cardiovascular) should receive supportive and symptomatic therapy. Emptying the gut should be considered for recent massive oral ingestions in dogs or cats. For more information on ivermectin toxicity in dogs, refer to the following reference: Paul, A., and W. Tranquilli. 1989. Ivermectin. In Current Veterinary Therapy X: Small Animal Practice. Edited by R. W. Kirk. 140-142. Philadelphia: WB Saunders.

Acute toxic symptoms in cats will appear within 10 hours of ingestion. Symptoms may include agitation, vocalization, anorexia, mydriasis, rear limb paresis, tremors, and disorientation. Blindness, head-pressing, wall-climbing, absence of oculomotor menace reflex, and a slow and incomplete response to pupillary light may also be seen. Neurologic symptoms usually diminish over several days and most animals completely recover within 2-4 weeks. Symptomatic and supportive care are recommended.

**Drug Interactions** - None were located.

**Drug/Laboratory Interactions** - When used at microfilaricide dosages, ivermectin may yield false-negative results in animals with **occult heartworm** infection.

**Doses** -
**Horses**:

For susceptible parasites:

a) 200 micrograms/kg (0.2 mg/kg) PO using oral paste or oral liquid. (Product Information; *Eqvalan*®—MSD)
b) 0.2 mg/kg PO; 0.2 mg/kg PO at 4 day intervals for lice and mange. (Robinson 1987)
c) As a larvacidal for arterial stages of *S. vulgaris*: 0.2 mg/kg once. (Herd 1987)

To Drug Monograph Index To Ophthalmic Product Index

**Elephants:**

For lice infestation:
a) 0.059 – 0.087 mg/kg administered orally using the injectable preparation; may re-treat at 5- 6 weeks. Karesh,W.B. and Robinson,P.T. 1985. **Ivermectin treatment of lice infestations in two elephant species**. Journal of the American Veterinary Medical Association 187:(11):1235-1236 **Summary:** Infestation by the elephant louse, Haematomyzus elephantis was diagnosed in 5 Asian elephants and 4 African elephants. The elephants were treated orally with an injectable ivermectin preparation. Dosages ranged from 0.059 mg/kg to 0.087 mg/kg. Within 48-72 hours the lice became easier to remove manually. Seven days post-treatment lice were not found. Five to six weeks after he first treatment, ivermectin was given again using the same route and same dose. At the time of the second treatment, a few lice were present but no eggs were found. Previously, ivermectin administered by the intramuscularly route was found to be effective against lice, however, it caused local inflammation and soreness at the injection site and use of this route was discontinued.

For helminths:
b) 0.1 mg/kg SQ for strongyles and other helminths. Darunee Tuntasuvan B.Sc., D.V.M., Ph.D. (personal communication) 2003. In an unpublished study, Dr. Tantasuvan found a mixture of 1% ivermectin and 10% Clorsulon (Ivomec – F) administered subcutaneously at a dose of 0.1 mg/kg to be 100 % effective against helminths. Flotation and sedimentation techniques were performed and eggs / gram determined at 0, 1, and 2 days and at weekly intervals for 6 weeks. This dose was not effective against flukes.

c) 0.1 mg/kg PO for strongyles and other helminths.Susan Mikota DVM and Susie Bartlett DVM 2003. In an unpublished study, an ivermectin dose of 0.1 mg/kg administered orally was found to be effective against strongyles in Asian elephants. Egg counts were reduced to zero two weeks post worming (n=10).

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects/toxicity (see Adverse Effects and Overdosage Sections)

**Client Information** - When using large animal products the manufacturer recommends not eating or smoking and to wash hands after use. Avoid contact with eyes. Dispose of unused products and containers by incineration or in approved-landfills. Ivermectin may adversely affect fish or other water-borne organisms if disposed in water.

Contact veterinarian if any treated animal exhibits symptoms of toxicity (see Adverse effects and Overdosage sections above).

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary Approved Products -**

Ivermectin for Injection 10 mg/ml (1%) in 50 ml, 200 ml, 500 ml and 1000 ml bottles

*Ivomec® 1% Injection for Cattle* (MSD-AgVet); (OTC) Approved for use in nonlactating dairy cattle, beef cattle and reindeer. Slaughter withdrawal = 35 days (cattle); 56 days (reindeer and bison)

Ivermectin for Injection 10 mg/ml (1%) & Clorsulon 100 mg/ml; *Ivomec® Plus Injection*(MSD-AgVet); (OTC) Approved for use in cattle.

Ivermectin Oral Paste 0.153% (1.53 mg/gram) in 10.4 oz tubes; *Ivomec® Cattle Paste 0.153%* (MSD-AgVet); (OTC) Approved for use in nonlactating dairy cattle, and beef cattle. Slaughter withdrawal = 24 days

To Drug Monograph Index To Ophthalmic Product Index

Ivermectin for Injection 10 mg/ml (1%) in 50 ml, 200 ml, 500 ml bottles; *Ivomec® 1% Injection for Swine* (MSD-AgVet); (OTC) Approved for use in swine. Slaughter withdrawal = 18 days

Ivermectin for Injection 2.7 mg/ml (0.27%) in 200 ml bottles; *Ivomec® 0.27% Injection for Feeder and Grower Pigs* (MSD-AgVet); (OTC) Approved for use in swine. Slaughter withdrawal = 18 days

Ivermectin Oral Paste 1.87% (18.7 mg/gram) in 6.08 g syringes; *Eqvalan® Paste* 1.87% (MSD-AgVet), *Zimectrin® Paste* (Farnam); (OTC) Approved for use in horses (not intended for food purposes).

Ivermectin Liquid 1% (10 mg/ml) in 50 ml and 100 ml btls (for tube administration; **not** for injection);*Eqvalan® Liquid* for Horses (MSD-AgVet); (Rx) Approved for use in horses (not intended for food purposes).

Ivermectin Oral Tablets 68 micrograms, 136 micrograms, 272 micrograms (Plain or Chewable) in 6 or 9 packs; *Heartgard 30®* (MSD-AgVet) (Rx) Approved for use in dogs.

Ivermectin/Pyrantel Oral Tablets 68 mcg/57 mg, 136 mcg/114mg, 272 mcg/228 mg) in packs; *Heartgard 30® Chewables Plus*(MSD-AgVet) (Rx) Approved for use in dogs.

## KAOLIN/PECTIN

**Chemistry** - Kaolin is a naturally occurring hydrated aluminum silicate which is powdered and refined for pharmaceutical use. Kaolin is a white/light, odorless, almost tasteless powder that is practically insoluble in water.

Pectin is a carbohydrate polymer consisting primarily of partially methoxylated polygalacturonic acids. Pectin is a course or fine, yellowish-white, almost odorless with a mucilagenous flavor. It is obtained from the inner rind of citrus fruits or from apple pomace. One gram of pectin is soluble in 20 ml of water and forms a viscous, colloidal solution.

In the United States, the two compounds generally are used together in an oral suspension formulation in most proprietary products.

**Storage/Stability/Compatibility** - Kaolin/pectin should be stored in airtight containers; protect from freezing. It is incompatible with alkalis, heavy metals, salicylic acid, tannic acid or strong alcohol.

**Pharmacology** - Kaolin/pectin is thought to posses adsorbent and protective qualities. Presumably, bacteria and toxins are adsorbed in the gut and the coating action of the suspension may protect inflamed GI mucosa. The pectin component, by forming galcturonic acid, has been demonstrated to decrease pH in the intestinal lumen.

In one study in children with acute nonspecific diarrhea, stool fluidity was decreased, but stool frequency, water content and weight remained unchanged. No studies documenting the clinical efficacy of this combination in either human or veterinary species were located.

**Uses/Indications -** Although its efficacy is in question, kaolin/pectin is used primarily in veterinary medicine as an oral anti-diarrheal agent. It has also been used as an adsorbent agent following the ingestion of certain toxins. Administration may be difficult due to the large volumes that may be necessary to give orally.

**Pharmacokinetics** - Neither kaolin nor pectin are absorbed after oral administration. Up to 90% of the pectin administered may be decomposed in the gut.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions** - There are no absolute contraindications to kaolin/pectin therapy, but it should not be relied on to control severe diarrheas. Kaolin/pectin should also not replace adequate fluid/electrolyte monitoring or replacement therapy in severe or chronic diarrheas.

**Adverse Effects/Warnings** - At usual doses, kaolin/pectin generally have no adverse effects. Constipation may occur, but is usually transient and associated with high dosages. High doses in debilitated patients or in very old or young patients may rarely cause fecal impaction to occur. In rats, kaolin/pectin has been demonstrated to increase fecal sodium loss in diarrhea.

In humans, kaolin/pectin is only recommended to be used in patients less than 3 years of age or for longer than 48 hours under the direct supervision of a physician.

**Overdosage** - Overdosage is unlikely to cause any serious effects, but constipation requiring treatment may occur.

**Drug Interactions** - Kaolin/pectin may inhibit the oral absorption of **lincomycin**. If both drugs are to be used, administer kaolin/pectin at least 2 hours before or 3-4 hours after the lincomycin dose.

Some evidence exists that kaolin/pectin may impair the oral absorption of **digoxin**. While the clinical significance of this potential interaction is unknown, it is recommended to separate the dosages as outlined above for lincomycin.

**Doses** -
**Horses**:

For diarrhea:

a) 2 - 4 quarts PO per 450 kg body weight *bid* (Robinson 1987)
b) 1 oz. per 8 kg body weight PO 3-4 times a day (Clark and Becht 1987)
c) Foals: 3 - 4 oz PO q6-8h (authors believe that bismuth subsalicylate is superior) (Martens and Scrutchfield 1982)

**Monitoring Parameters** -

1) Clinical efficacy
2) Fluid & electrolyte status in severe diarrhea

**Client Information** - Shake well before using. If diarrhea persists, contact veterinarian. If animal appears listless or develops a high fever, contact veterinarian.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** - There are variety of kaolin/pectin products available without prescription. Several products are labeled for veterinary use; their approval status is not known. Many products that formerly contained kaolin (e.g., Kaopectate®) no longer contain any kaolin, but use attapulgite as the adsorbent.

## KETAMINE HCL * (ADVERSE EFFECT REPORTED)

**Chemistry** - A congener of phencyclidine, ketamine HCl occurs as white, crystalline powder. It has a melting point of 258-261°C., a characteristic odor, and will precipitate as the free base at high pH. One gram is soluble in 5 ml of water, and 14 ml of alcohol. The pH of the commercially available injections are between 3.5-5.5.

To Drug Monograph Index To Ophthalmic Product Index

**Storage/Stability/Compatibility** - Ketamine may be mixed with sterile water for injection, $D_5W$, and normal saline for diluent purposes. Ketamine is compatible with xylazine in the same syringe. Do not mix ketamine with barbiturates or diazepam in the same syringe or IV bag as precipitation may occur.

**Pharmacology** - Ketamine is a rapid acting general anesthetic that also has significant analgesic activity and a lack of cardiopulmonary depressant effects. It is thought to induce both anesthesia and amnesia by functionally disrupting the CNS through over stimulating the CNS or inducing a cataleptic state. Ketamine inhibits GABA, and also may block serotonin, norepinephrine, and dopamine in the CNS. The thalamoneocortical system is depressed while the limbic system is activated. It induces anesthetic stages I & II, but not stage III. In cats, it causes a slight hypothermic effect as body temperatures decrease on average by 1.6°C after therapeutic doses.

Effects on muscle tone are described as being variable, but ketamine generally either causes no changes in muscle tone or increased tone. Ketamine does not abrogate the pinnal and pedal reflexes, nor the photic, corneal, laryngeal or pharyngeal reflexes.

Ketamine's effects on the cardiovascular system include increased cardiac output, heart rate, mean aortic pressure, pulmonary artery pressure, and central venous pressure. Its effects on total peripheral resistance are described as being variable. Cardiovascular effects are secondary to increased sympathetic tone; ketamine has negative inotropic effects if the sympathetic system is blocked,

Ketamine does not cause significant respiratory depression at usual doses, but at higher doses it can cause respiratory rates to decrease. In humans with asthma, ketamine causes decreased airway resistance.

**Uses/Indications** - Ketamine has been approved for use in humans, sub-human primates and cats, although it has been used in many other species (see dosage section). The approved indications for cats include, "for restraint, or as the sole anesthetic agent for diagnostic, or minor, brief, surgical procedures that do not require skeletal muscle relaxation.... and in subhuman primates for restraint." (Package Insert; *Ketaset*® - Bristol).

**Pharmacokinetics** - After IM injection in the cat, peak levels occur in approximately 10 minutes. Ketamine is distributed into all body tissues rapidly, with highest levels found in the brain, liver, lung, and fat. Plasma protein binding is approximately 50% in the horse, 53% in the dogs, and 37-53% in the cat.

The drug is metabolized in the liver principally by demethylation and hydroxylation and these metabolites along with unchanged ketamine are eliminated in the urine. Ketamine will induce hepatic microsomal enzymes, but there appears to be little clinical significance associated with this effect. The elimination half-life in the cat, calf, and horse is approximately 1 hour, in humans it is 2-3 hours. Like the thiobarbiturates, the redistribution of ketamine out of the CNS is more of a factor in determining duration of anesthesia than is the elimination half-life.

By increasing the dose, the duration of anesthesia will increase, but not the intensity.

**Contraindications/Precautions** - Ketamine is contraindicated in patients who have exhibited prior hypersensitivity reactions to it and in animals to be used for human consumption. Its use in patients with significant hypertension, heart failure, and arterial aneurysms could be hazardous. The manufacturer warns against its use in hepatic or renal insufficiency, but in humans with renal insufficiency the duration of action has been demonstrated not to be prolonged. Because ketamine does not give good muscle relaxation, it is contraindicated when used alone for major surgery.

Ketamine can cause increases in CSF pressure and it should not be used in cases with elevated pressures or when head trauma has occurred. Because of its supposed epileptogenic potential, it should generally not

To Drug Monograph Index To Ophthalmic Product Index

be used (unless very cautiously) in animals with preexisting seizure disorders. As myelography can induce seizures, ketamine should be used cautiously in animals undergoing this procedure.

Ketamine is considered to be relatively contraindicated when increased intra-ocular pressure or open globe injuries exist, and for procedures involving the pharynx, larynx, or trachea. Animals who have lost significant amounts of blood, may require significantly reduced ketamine dosages.

While ketamine has been used safely in humans with malignant hyperthermia, its use in animals susceptible to this is controversial. Hyperthyroid human patients (and those receiving exogenous thyroid replacement) may be susceptible to developing severe hypertension and tachycardia when given ketamine. The veterinary significance of this potential problem is unknown.

Cat's eyes remain open after receiving ketamine, and should be protected from injury plus an ophthalmic lubricant (*e.g., Lacrilube*®) should be applied to prevent excessive drying of the cornea.

To minimize the incidences of emergence reactions, it is recommended to minimize exposure to handling or loud noises during the recovery period. The monitoring of vital signs should still be performed during the recovery phase, however.

Because ketamine can increase blood pressure, careful control of hemorrhaging post-surgery (*e.g.,* declawing) should be accomplished. It is not essential to withhold food or water prior to surgery, but in elective procedures it is recommended to withhold food for 6 hours prior to surgery.

**Adverse Effects/Warnings** - In approved species the following adverse reactions are listed by the manufacturer: "respiratory depression....following high doses, emesis, vocalization, erratic and prolonged recovery, dyspnea, spastic jerking movements, convulsions, muscular tremors, hypertonicity, opisthotonos and cardiac arrest. In the cat, myoclonic jerking and/or tonic/clonic convulsions can be controlled by ultrashort-acting barbiturates or acepromazine. These latter drugs must be given intravenously, cautiously, and slowly, to effect (approximately 1/6 to 1/4 the normal dose may be required)." (Package Insert; *Ketaset*® - Bristol)

Seizures have been reported to occur in up to 20% of cats that receive ketamine at therapeutic dosages. Diazepam is suggested to be been used for treatment if necessary. Pain after IM injection may occur.

To reduce the incidence of hypersalivation and other autonomic signs, atropine or glycopyrrolate is often administered.

**Overdosage** - Ketamine is considered to have a wide therapeutic index (approximately 5 times greater when compared to pentobarbital). When given in excessive doses or too rapidly, significant respiratory depression may occur. Treatment using mechanically assisted respiratory support is recommended versus the use of analeptic agents. In cats, yohimbine with 4-aminopyridine has been suggested to be used as a partial antagonist.

**Drug Interactions** - **Narcotics**, **barbiturates**, or **diazepam** may prolong the recovery time after ketamine anesthesia. When used with **halothane**, ketamine recovery rates may be prolonged and the cardiac stimulatory effects of ketamine may be inhibited. Close monitoring of cardiac status is recommended when using ketamine with halothane. **Chloramphenicol** (parenteral) may prolong the anesthetic actions of ketamine. **Thyroid hormones** when given concomitantly with ketamine have induced hypertension and tachycardia in humans. Beta-blockers (*e.g.,* propranolol) may be of benefit in treating these effects. **Neuromuscular blockers** (*e.g.,* succinylcholine and tubocurarine) may cause enhanced or prolonged respiratory depression.

To Drug Monograph Index To Ophthalmic Product Index

**Doses** -

**Horses**: Note: Always used after heavy premedication with a sedative.

a) Initially give xylazine 1.1 mg/kg IV and wait for full sedative effect (4-8 minutes); then give ketamine 2.2 - 2.75 mg/kg IV only (the higher dose may be necessary for ponies, young "high-strung" Arabians, Hackneys, and Thoroughbreds) as a bolus. Do not administer to an "excited" horse. If surgery time requires additional anesthesia, 1/3-1/2 of the original xylazine/ketamine doses may be given IV. For procedures where better muscle relaxation is required, use guaifenesin-thiobarbiturate. Do not disturb horse until fully recovered. (Thurmon and Benson 1987)

b) For foals and ponies: Add 500 mg ketamine and 250 mg xylazine to 500 ml of 5% guaifenesin solution. For induction, give 1.1 ml/kg IV rapidly. Anesthesia may be maintained by constant IV infusion of 2-3 ml/kg/hr. Lower doses for foals, higher doses for ponies. (Thurmon and Benson 1987)

c) For induction of surgical colic patients: Use guaifenesin to effect, than 1.6 - 2.2 mg/kg ketamine (Mandsager 1988)

d) 200 mg bolus (in a 454 kg horse) intra-operatively to reduce movement with light general anesthesia (Mandsager 1988)

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

a,b) **Adverse effect:** A single case of photosensitization (similar to that noted with the use of acepromazine) was seen in an Asian elephant sedated with ketamine-xylazine. The author also reports that "the synergy of ketamine-xylazine combination seen in other animals like carnivores is not noticed in elephants." Cheeran,J. 2002. **Adverse drug experiences in elephants**. Journal of Indian Veterinary Association Kerala 7:(3):61

Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Tranquilization and translocation of elephants**. Journal of Indian Veterinary Association Kerala 7:(3):42-46

c) 5-10 mg/kg ketamine IM; can be combined with xylazine; the dose of individual drugs can be reduced up to 50% when combinations are used. Nayar,K.N.M., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Management of surgical affections in captive elephants**. Journal of Indian Veterinary Association Kerala 7:(3):55-59

d) ketamine:xylazine in a 1.25:1 ratio with xylazine. Sarma,K.K. and Pathak,S.C. 2001. **Cardio vascular response to xylazine and Hellabrunn mixture with Yohimbine as reversal agent in Asian elephants**. Indian Veterinary Journal 78:(5):400-492 **Abstract:** Xylazine (0.1 mg/kg body weight) produced highly significant bradycardia and hypotension in recumbent Asian elephants, with a peak depression observed at the 30th minute for heart rate and 30th minute in the mean arterial pressure (MAP). Ketamine (1.25 : 1 ratio with xylazine) mildly marginalised the bradycardia, but remarkably improved the MAP. Yohimbine, used to reverse the sedation produced by xylazine did not appear to influence these parameters to any appreciable levels.

e) 0.33 mg/kg ketamine combined with 0.12 mg/kg xylazine for immobilization of baby or juvenile Asian elephants; 1.14 mg/kg ketamine combined with 0.14 mg/kg xylazine for immobilization of baby or juvenile African elephants. Fowler,M.E., 1995. **Elephants**. In: Restraint and handling of wild and domestic animals. Iowa State University Press, Ames, Iowa, USA pp. 265-269

To Drug Monograph Index To Ophthalmic Product Index

f) A 3000 kg Asian cow was immobilized with 350 mg ketamine and 350 mg xylazine IM to repair a ventral hernia. Induction took 10 minutes, the cow became recumbent, and the duration of anesthesia was 120 minutes. Sedation was adequate for surgical manipulation. Nayar,K.N.M., Radhakrishnan,K., Chandrasekharan,K., Cheeran,J.V., Ravindran,S., and George,P.O., 1992. **Anaesthesia for surgical manipulations in the elephant**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 156-158 **Abstract:** Anaesthesia using chloral hydrate, thiopentone sodium, xylazine and ketamine was induced in ten elephants. The effects, duration of induction and anaesthesia were recorded. Post anaesthesia complications were not encountered in any of the animals. Surgical manipulations could be carried out under anaesthesia induced with these drugs.

g) A mixture containing 100-150 mg xylazine and 50-100 mg ketamine injected IV in laterally recumbent Asian elephants produces quick, safe and dependable analgesia, anesthesia, and muscular relaxation. Pathak,S.C. 1991. **Xylazine-ketamine anesthesia in Indian elephant (Elephas maximus indicus) - trial on 53 clinical cases**. International Seminar on Veterinary Medicine in Wild and Captive Animals, Nov. 8-10, Bangalore, India. Pages: 21 **Abstract:** Veterinarians are often required to attend and undertake surgery on elephants. Unless the animal is deeply sedated or anesthetized certain works become impractical. Xylazine has proved to be a good sedative and analgesic in elephants. This drug is not freely available in India and is costly. The drug is usually used by intramuscular route but to reduce the dose it has been used intravenously. Intravenous use may be risky for its bradycardia effect and fall in cardiac output. Ketamine, on the other hand, has no depressant effect on the cardiovascular and respiratory system but produces muscular tremor and stiffness of the skeletal muscle. Combination of Xylazine and Ketamine minimizes the undesirable aspects of both the drugs. A mixture containing 100-150 mg xylazine and 50-100 mg ketamine injected intravascularly to the laterally recumbent elephant produced quick, safe and dependable analgesia, anesthesia, and muscular relaxation. Surgical operations like tusk extraction, bullet extraction, umbilical and pleural herniorraphy, trunk injury, extensive wound repair, etc. were performed in 53 elephants. Recovery followed without excitement and untoward effect based on the observations of this trial on clinical cases, combination of Xylazine and Ketamine is recommended in elephant.

h) A 650 kg African elephant was premedicated with 0.27 mg/kg ketamine (175 mg) and 0.23 mg/kg xylazine (150 mg) IM followed 20 minutes later by an IV injection of 0.9 µg/kg etorphine (0.6 mg) then maintained on 1.0-1.5% halothane to perform a tusk extraction. Following a 3- hour surgery, the elephant was reversed with 1.8 µg/kg diprenorphine (1.2 mg) IV and 46 µg yohimbine IV and was standing in 5 minutes. (Welsch,B., Jacobson,E.R., Kollias,G.V., Kramer,L., Gardner,H., and Page,C.D. 1989. **Tusk extraction in the African elephant (*Loxodonta africana*)**. Journal of Zoo and Wildlife Medicine 20:(4):446-453 **Abstract:** Unilateral dentoalveolar abscesses and/or tusk fractures were identified and tusk extractions performed in seven 3.5-21-yr-old African elephants (*Loxodonta africana*) of both sexes weighing 650-3,000 kg. Following immobilization with etorphine hydrochloride or carfentanil citrate, six of seven elephants were intubated and maintained on a 1-1.5% halothane in oxygen mixture; one elephant was maintained in lateral recumbency by multiple i.v. injections of etorphine. All elephants were positioned with the affected tusk up. For one elephant, two surgical procedures were required to remove the tusk. In six of seven elephants, the tusks were sectioned transversely and the tusk wall thinned by enlarging the pulp cavity with carbide burs. In those tusks with remaining pulp, the pulp was removed with stainless steel rods and hooks. Next, the tusk was sectioned longitudinally into three or four segments using a wood saw within the pulp chamber. bone gouges, osteotomes, and a mallet were used to free the outer epithelial and alveolar attachments from the tusk. Starting with the smallest segment, the sections were removed using long screwdriver-shaped stainless steel rods. The alveolar chamber was then periodically flushed postsurgically with a dilute organic iodine solution. For six of seven elephants, complete granulation of the alveolar chamber was evident by 4 mo postsurgery; the seventh elephant showed partial healing with granulation tissue at 2 mo following surgery.

To Drug Monograph Index  To Ophthalmic Product Index

i) Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing juvenile African elephants during a 45-minute transport period before administration of general anesthesia. Heard,D.J., Kollias,G.V., Webb,A.I., Jacobson,E.R., and Brock,K.A. 1988. **Use of halothane to maintain anesthesia induced with etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 193:254-256 **Excerpts:** Sixteen 3- to 5-year-old African elephants were anesthetized one or more times for a total of 27 diagnostic and surgical procedures. Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing juvenile elephants during a 45-minute transport period before administration of general anesthesia. After IM or IV administration of etorphine (1.9 ± 0.56 micrograms/kg), the mean time to lateral recumbency was 20 ± 6.6 and 3 ± 0.0 minutes, respectively. The mean heart rate, systolic blood pressure, and respiration rate during all procedures was 50 ± 12 beats/min, 106 ± 19 mm of Hg, and 10 ± 3 breaths/min, respectively.

Cardiac arrhythmias were detected during 2 procedures. In one elephant paroxysmal ventricular tachycardia was detected and the procedure terminated when the arrhythmia failed to stabilize after multiple doses of lidocaine (1 mg/kg, IV). In another elephant, second degree atrioventricular block returned to normal sinus rhythm after IV administration of atropine (0.04 mg/kg).

In one elephant, low mean blood pressure (54 mm of Hg) responded to reduction in halothane (vaporizer setting 1 to 0.75%) and slow infusion of dobutamine HCl ((250 mg/1,000 ml) given to effect. The systolic blood pressure increased to 90 mm of Hg and remained high with a continuous infusion of dobutamine (5 µg/kg/min).

Immediately after induction in another elephant, profound respiratory depression (< 1 breath / minute) and palpably weak arterial pulse were identified. Intravenous administration of diprenorphine at half the recommended reversal dose resulted in improvement of respiration and palpable arterial pulse, without the elephant developing signs of complete anesthetic reversal.

Alterations in systolic blood pressure, ear flapping, and trunk muscle tone were useful for monitoring depth of anesthesia. Results indicated that halothane in oxygen was effective for maintenance of surgical anesthesia in juvenile African elephants after induction with etorphine. Note: A correction appeared in a later volume 193(6): p.721.

j) For standing sedation of adult Asian elephants: 0.3 to 0.7 mg/kg ketamine and 0.1 mg/kg xylazine IM. For immobilization of Asian elephants: 1.0 to 1.5 mg/kg ketamine and 0.14 mg/kg xylazine IM. In 13 of 14 immobilized elephants, respiratory and heart rates remained stable throughout the duration of immobilization. The mean induction time was 11.6 minutes and the mean duration of immobilization was 27 minutes. Mean respiratory and heart rates were 17 and 45 /minute respectively. (Jacobson, 1988). Jacobson,E.R. 1988. **Chemical restraint and anesthesia of elephants**. Proc.Ann.Elephant Workshop 9. Pages: 112-119

k) A 4000 kg African elephant immobilized with 2.3 µg/kg carfentanil was given 100 mg ketamine IV during a 50 minute duration period. Jacobson,E.R., Kollias,G.V., Heard,D.J., and Caligiuri,R. 1988. **Immobilization of African elephants with carfentanil and antagonism with nalmefene and diprenorphine**. Journal of Zoo Animal Medicine 19:1-7

l) A group of 15 African elephants were immobilized with a combination of xylazine (0.2 mg/kg of body weight, IM) and ketamine (1 to 1.5 mg/kg of body weight, IM). See details in abstract below. Allen,J.L. 1986. **Use of tolazoline as an antagonist to xylazine-ketamine-induced immobilization in African elephants**. American Journal of Veterinary Research 47:(4):781-783 **Abstract:** A group of 15 African elephants (Loxodonta africana) were immobilized with a combination of xylazine (0.2 mg/kg of body weight, IM) and ketamine (1 to 1.5 mg/kg of body weight, IM). Ten of the African elephants were allowed to remain recumbent for 30 minutes and the remaining 5 elephants, for 45 minutes before they were given tolazoline

To Drug Monograph Index To Ophthalmic Product Index

(0.5 mg/kg of body weight, IV). For the group of 15, the mean induction time (the time required from injection of the xylazine-ketamine combination until onset of recumbency) was 14.2 ± 4.35 minutes (mean ± SD), and standing time (the time required from the tolazoline injection until the elephant stood without stimulation or assistance) was 2.8 ± 0.68 minutes. All of the elephants were physically stimulated (by pushing, slapping, shouting) before they were given tolazoline, and none could be aroused. After tolazoline was given and the elephant was aroused, relapses to recumbency did not occur. Recovery was characterized by mild somnolence in an otherwise alert and responsive animal. Failure (no arousal) rates were 0% (95% confidence interval, 0 to 0.3085) for elephants given tolazoline after 30 minutes of recumbency and 100% for elephants that were not given tolazoline. There was no significant (P less than 0.05) difference in standing time 30 or 45 minutes after tolazoline injection.

m) A 1125 kg African elephant was sedated with 100 mg ketamine, 100 mg xylazine and 8 mg butorphanol given IM for a tusk examination. A 423 kg African elephant as given 160 mg ketamine and 35 mg xylazine IM for radiography of tusks. Heard,D.J., Jacobson,E.R., and Brock,K.A. 1986. **Effects of oxygen supplementation on blood gas values in chemically restrained juvenile African elephants**. Journal of the American Veterinary Medical Association 189:(9):1071-1074
**Abstract:** Arterial oxygen and carbon dioxide tensions were determined in sedated immature African elephants and in elephants immobilized with etorphine hydrochloride or with an etorphine-ketamine combination. For manipulative and surgical procedures, the Hudson demand value was used for oxygen supplementation during 6 procedures, and insufflation was used during 2 procedures. The Hudson demand value was more effective than insufflation in sustaining adequate arterial oxygenation.

n) Twenty-two juvenile African elephants were given a combination of xylazine (mean +/- SD = 0.14 +/- 0.03 mg/kg of body weight) and ketamine (1.14 +/- 0.21 mg/kg) as a single IM injection. Jacobson,E.R., Allen,J., Martin,H., and Kollias,G.V. 1985. **Effects of yohimbine on combined xylazine-ketamine-induced sedation and immobilization in juvenile African elephants**. Journal of the American Veterinary Medical Association 187:(11):1195-1198 **Abstract:** Twenty-two juvenile African elephants were given a combination of xylazine (mean +/- SD = 0.14 +/- 0.03 mg/kg of body weight) and ketamine (1.14 +/- 0.21 mg/kg) as a single IM injection; one elephant was immobilized twice, 77 days apart. After injection, 14 elephants were immobilized, 4 were sedated deeply, 2 were sedated moderately, and 2 were sedated minimally. Immobilized elephants had a mean immobilization time of 11.6 +/- 6.9 minutes. At the conclusion of a variety of clinical procedures, 12 of the 14 elephants immobilized with a single dose combination of xylazine and ketamine were given yohimbine (0.13 +/- 0.03 mg/kg) IV, and the remaining 2 elephants were allowed to recover spontaneously; the elephants given yohimbine had a mean standing time of 2.4 +/- 1.1 minutes. Of the 8 sedated elephants, 5 were given an additional dose of combined xylazine (0.08 +/- 0.03 mg/kg), and ketamine (0.61 +/- 0.19 mg/kg) IM, and 1 elephant was given ketamine (0.47 mg/kg) IV. After injection, 4 of the 8 elephants were recumbent laterally within 17 minutes and 2 remained standing, under deep sedation. Seven of the 8 elephants were given yohimbine (0.13 +/- 0.03 mg/kg) IV; all were ambulatory in 2 minutes. Results indicated that yohimbine may be useful in controlling duration of xylazine-ketamine sedation and immobilization in juvenile African elephants.

**Monitoring Parameters** -

1) Level of anesthesia/analgesia
2) Respiratory function; cardiovascular status (rate, rhythm, BP if possible)
3) Monitor eyes to prevent drying or injury
4) Body temperature

**Client Information** - Should only be administered by individuals familiar with its use.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Ketamine HCl for Injection 100 mg/ml in 10 ml vials; *Ketaset*® (Fort Dodge); *Vetalar*® (Fort Dodge);*VetaKet*® (Lloyd) (Rx) Approved for use in cats and sub-human primates.

**Human-Approved Products**:

Ketamine HCl for Injection 10 mg/ml in 20, 25, and 50 ml vials; 50 mg/ml in 10 ml vials; 100 mg/ml in 5 ml vials; *Ketalar*® (Parke-Davis); (Rx)

## KETOCONAZOLE

**Chemistry** - An imidazole antifungal agent, ketoconazole occurs as a white to slightly beige powder with $pK_a$s of 2.9 and 6.5. It is practically insoluble in water.

**Storage/Stability/Compatibility** - Ketoconazole tablets should be stored at room temperature in well-closed containers.

**Pharmacology** - At usual doses and serum concentrations, ketoconazole is fungistatic against susceptible fungi. At higher concentrations for prolonged periods of time or against very susceptible organisms, ketoconazole may be fungicidal. It is believed that ketoconazole increases cellular membrane permeability and causes secondary metabolic effects and growth inhibition. The exact mechanism for these effects have not been determined, but may be due to ketoconazole interfering with ergosterol synthesis. The fungicidal action of ketoconazole may be due to a direct effect on cell membranes.

Ketoconazole has activity against most pathogenic fungi, including Blastomyces, Coccidiodes, Cryptococcus, Histoplasma, Microsporum and Trichophyton. Higher levels are necessary to treat most strains of Aspergillus and Sporothrix. Resistance to ketoconazole has been documented for some strains of *Candida albicans*.

Ketoconazole also has *in vitro* activity against *Staphylococcus aureas* and *epidermidis*, Nocardia, enterococci, and herpes simplex virus types 1 & 2. The clinical implications of this activity are unknown.

Ketoconazole also has endocrine effects as steroid synthesis is directly inhibited by blocking several P-450 enzyme systems. Measurable reductions in testosterone or cortisol synthesis can occur at dosages used for antifungal therapy, but higher dosages are generally required to reduce levels of testosterone or cortisol to be clinically useful in the treatment of prostatic carcinoma or hyperadrenocorticism. Effects on mineralocorticoids are negligible.

**Uses/Indications** - Because of its comparative lack of toxicity when compared to amphotericin B, oral administration and relatively good efficacy, ketoconazole is used to treat several fungal infections in dogs, cats and other small species. See the Dosage section or Pharmacology section for specifics. Although newer antifungal agents (fluconazole, itraconazole) have advantages over ketoconazole–usually less toxicity and/or enhanced efficacy–ketoconazole is significantly less expensive.

Ketoconazole is also used clinically for the medical treatment of hyperadrenocorticism in dogs (and sometimes cats).

**Pharmacokinetics** - Although it is reported that ketoconazole is well absorbed after oral administration, oral bioavailability of ketoconazole tablets in dogs is highly variable. One study (Baxter et al. 1986) in six normal dogs, found bioavailabilities ranging from 0.04-0.89 (4-89%) after 400 mg (19.5 - 25.2 mg/kg) were administered to fasted dogs. Peak serum concentrations occur between 1 and 4.25 hours after dosing and peak serum levels in the 6 dogs studied ranged from 1.1 - 45.6 micrograms/ml. This wide interpatient varia-

tion may have significant clinical implications from both a toxicity and efficacy standpoint, particularly since ketoconazole is often used in life-threatening infections and assays for measuring serum levels are not readily available.

Ketoconazole absorption is enhanced in an acidic environment and should not be administered (at the same time) with $H_2$ blockers or antacids (see Drug Interactions below). Whether to administer ketoconazole with meals or during a fasted state to maximize absorption is controversial. The manufacturer recommends giving with food in human patients. Dogs or cats who develop anorexia/vomiting during therapy may benefit from administration with meals.

After absorption, ketoconazole is distributed into the bile, cerumen, saliva, urine, synovial fluid and CSF. CSF levels are generally less than 10% of those found in the serum, but may be increased if the meninges are inflamed. High levels of the drug are found in the liver, adrenals and pituitary gland, while more moderate levels are found in the kidneys, lungs, bladder, bone marrow and myocardium. At usual doses (10 mg/kg), attained levels are probably inadequate in the brain, testis and eyes to treat most infections; higher dosages are required. Ketoconazole is 84-99% bound to plasma proteins and crosses the placenta (at least in rats). The drug is found in bitch's milk.

Ketoconazole is metabolized extensively by the liver into several inactive metabolites. These metabolites are excreted primarily into the feces via the bile. About 13% of a given dose is excreted into the urine and only 2-4% of the drug is excreted unchanged in the urine. Half-life in dogs is about 1-6 hours (avg. 2.7 hours).

**Contraindications/Precautions/Reproductive Safety** - Ketoconazole is contraindicated in patients with know hypersensitivity to it. It should be used with caution in patients with hepatic disease or thrombocytopenia.

Ketoconazole is a known teratogen and embryotoxin in rats. There have been reports of mummified fetuses and stillbirths in dogs who have been treated. Ketoconazole should not be considered absolutely contraindicated in pregnant animals, however, as it is often used in potentially life-threatening infections. The benefits of therapy should be weighed against the potential risks.

Ketoconazole may cause infertility in male dogs by decreasing testosterone synthesis. Testosterone production rebounds once the drug is discontinued.

**Adverse Effects/Warnings** - Gastrointestinal symptoms of anorexia, vomiting, and/or diarrhea are the most common adverse effects seen with ketoconazole therapy. Anorexia may be minimized by dividing the dose and/or giving with meals. Hepatic toxicity consisting of cholangiohepatitis and increased liver enzymes has been reported with ketoconazole, and may be either idiosyncratic in nature or a dose-related phenomenon. Cats may be more prone to developing hepatoxicity than dogs. Thrombocytopenia has also been reported with ketoconazole therapy, but is rarely encountered. A reversible lightening of haircoat may also occur in patients treated with ketoconazole.

Ketoconazole has a transient dose-related suppressant effect on gonadal and adrenal steroid synthesis. Doses as low as 10 mg/kg depressed serum testosterone levels in dogs within 3-4 hours after dosing, but levels returned to normal within 10 hours. Doses of 30 mg/kg/day have been demonstrated to suppress serum cortisol levels in dogs with hyperadrenocorticism (see Dosages section). Dogs undergoing high dose antifungal therapy may need additional glucocorticoid support during periods of acute stress.

**Overdosage/Acute Toxicity** - No reports of acute toxicity associated with overdosage were located. The oral $LD_{50}$ in dogs after oral administration is >500 mg/kg. Should an acute overdose occur, the

To Drug Monograph Index To Ophthalmic Product Index

manufacturer recommends employing supportive measures, including gastric lavage with sodium bicarbonate.

**Drug Interactions** - **Antacids, anticholinergics (propantheline, etc.) $H_2$ blockers (***e.g.,* **cimetidine, ranitidine)** increase stomach pH and may inhibit the absorption of ketoconazole. If these agents must be used with ketoconazole, they should be given 2 hours after the ketoconazole dose. **Mitotane** and ketoconazole are not recommended to be used together to treat hyperadrenocorticism as the adrenolytic effects of mitotane may be inhibited by ketoconazole's inhibition of cytochrome P450 enzymes. Ketoconazole may increase the anticoagulant effects of **warfarin**. Prothrombin times should be monitored and dosage adjustments made as required. **Phenytoin** and ketoconazole may alter the metabolism of each other. Phenytoin levels and ketoconazole efficacy/toxicity should be monitored. Ketoconazole alters the disposition and extends the duration of activity of **methylprednisolone.**
Elevated concentrations of **cisapride** with resultant ventricular arrhythmias may result if coadministered with ketoconazole, itraconazole, IV miconazole or troleandomycin. At present, the manufacturer states that cisapride should not be used with these drugs.
Ketoconazole may decrease serum **theophylline** concentrations in some patients; theophylline levels should be monitored. **Ethanol** may interact with ketoconazole and produce a disulfiram-like reaction (vomiting). **Rifampin** may decrease the serum levels of ketoconazole if administered together. If these drugs must be used together, ketoconazole dosages may need to be adjusted. Ketoconazole may exhibit synergism with **acyclovir** against herpes simplex viruses. **Cyclosporin** blood levels may be increased by ketoconazole. Because ketoconazole can cause hepatoxicity, it should be used cautiously with **other hepatotoxic agents**.

**Doses** - (Note: Clinical antifungal effects may require 10-14 days of therapy)
**Horses**:
For susceptible fungal infections:
a) 10 mg/kg PO daily (McConnell and Hughey 1987)

**Monitoring Parameters** -
1) Liver enzymes with chronic therapy (at least every 2 months; some clinicians say monthly)
2) CBC with platelets
3) Efficacy and other adverse effects

**Client Information** - If animal develops gastrointestinal symptoms divide dose and administer with meals. Long-term therapy with adequate dosing compliance is usually necessary for successful results; clients must be committed for both the financial and dosing burdens associated with therapy.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:
Ketoconazole 200 mg Tablets (scored); *Nizoral*® (Janssen); (Rx)

## KETOPROFEN

**Chemistry** - A propionic acid derivative nonsteroidal anti-inflammatory agent, ketoprofen occurs as an off white to white, fine to granular powder. It is practically insoluble in water, but freely soluble in alcohol at 20°C. Ketoprofen has a $pK_a$ of 5.9 in a 3:1 methanol:water solution.

**Storage/Stability/Compatibility** - Ketoprofen oral capsules should be stored at room temperature in tight, light resistant containers. The veterinary injection should be stored at room temperature. Compatibility studies with injectable ketoprofen and other compounds have apparently not been published.

**Pharmacology** - Ketoprofen exhibits actions similar to that of other nonsteroidal antiinflammatory agents in that it possesses antipyretic, analgesic and antiinflammatory activity. Its purported mechanism of action is the inhibition of cyclooxygenase catalysis of arachidonic acid to prostaglandin precursors (endoperoxides), thereby inhibiting the synthesis of prostaglandins in tissues. Ketoprofen purportedly has inhibitory activity on lipoxygenase, whereas flunixin reportedly does not at therapeutic doses.

**Uses/Indications** - Ketoprofen is labeled for use in horses for the alleviation of inflammation and pain associated with musculoskeletal disorders. Like flunixin (and other NSAIDs), ketoprofen potentially has many other uses in a variety of species and conditions; however well controlled studies for these uses are generally unavailable.

**Pharmacokinetics** - In species studied (rats, dog, man), ketoprofen is rapidly and nearly completely absorbed after oral administration. The presence of food or milk decreases oral absorption. Oral absorption characteristics in horses was not located. It has been reported that when comparing IV vs. IM injections in horses, the areas under the curve are relatively equivalent.

While distribution characteristics are not well described, the drug does enter synovial fluid and is highly bound to plasma proteins (99% in humans, and approximately 93% in horses). In horses, the manufacturer reports that the onset of activity is within 2 hours and peak effects 12 hours post dose.

Ketoprofen is eliminated via the kidneys both as a conjugated metabolite and unchanged drug. The elimination half life in horses is approximately 1.5 hours.

**Contraindications/Precautions/Reproductive Safety** - While the manufacturer states that there are no contraindications to the drug's use (other than previous hypersensitivity to ketoprofen), it should be used only when the potential benefits outweigh the risks in cases where GI ulceration or bleeding is evident or in patients with significant renal or hepatic impairment. Ketoprofen may mask the signs and symptoms (inflammation, hyperpyrexia) of infection. Because ketoprofen is highly protein bound, patients with hypoproteinemia may have increased levels of free drug, thereby increasing the risks for toxicity.

The manufacturer cautions against ketoprofen's use in breeding animals, because effects on fertility, pregnancy or fetal health have not been established in horses. However, rat and mice studies have not demonstrated increased teratogenicity or embryotoxicity. Rabbits receiving twice the human dose exhibited increased embryotoxicity, but not teratogenicity. Because non-steroidal antiinflammatory agents inhibit prostaglandin synthesis, adversely affecting neonatal cardiovascular systems (premature closure of patent ductus), ketoprofen should not be used late in pregnancy. Studies in male rats demonstrated no changes in fertility.

It is presently unknown whether ketoprofen enters equine milk. Ketoprofen does enter canine milk.

**Adverse Effects/Warnings** - Because ketoprofen is a relatively new agent, its adverse effect profile in horses has not been clearly elucidated. Preliminary studies and reports indicate that ketoprofen appears relatively safe to use in horses and may have a lower incidence of adverse effects than either phenylbutazone or flunixin. Potentially, gastric mucosal damage and GI ulceration, renal crest necrosis, and mild hepatitis may occur.

Do not administer intra-arterially and avoid SubQ injections. While not labeled for IM use in horses, it reportedly is effective and may only cause occasional inflammation at the injection site.

To Drug Monograph Index  To Ophthalmic Product Index

**Overdosage/Acute Toxicity** - Horses given ketoprofen at doses up to 11 mg/kg administered IV once daily for 15 days exhibited no signs of toxicity. Severe laminitis was observed in a horse given 33 mg/kg/day (15X over labeled dosage) for 5 days. Anorexia, depression, icterus, and abdominal swelling was noted in horses given 55 mg/kg/day (25X labeled dose) for 5 days. Upon necropsy, gastritis, nephritis and hepatitis were diagnosed in this group.

Humans have survived oral ingestions of up to 5 grams. The $LD_{50}$ in dogs after oral ingestion has been reported to be 2000 mg/kg. General drug removal and supportive measures have been recommended in cases of oral overdosage.

**Drug Interactions** - Because ketoprofen is highly bound to plasma proteins, it can displace or be displaced by other highly protein bound drugs, including **warfarin, phenylbutazone, etc**.
Because ketoprofen may inhibit platelet aggregation and also cause gastrointestinal ulceration, when used with other drugs that alter hemostasis (*e.g.*, **heparin, warfarin, etc**.) and/or cause gastrointestinal erosion (*e.g.*, **aspirin, flunixin, phenylbutazone, corticosteroids, etc**.), increased likelihood of bleeding or ulceration may occur. Ketoprofen and **probenecid** are not recommended to be used together. Probenecid reduces renal clearance of ketoprofen and also reduces its protein binding; thereby increasing the risk of toxicity. NSAIDs (including ketoprofen) may potentially significantly reduce the excretion of **methotrexate** and cause toxicity.

**Laboratory Considerations -** Ketoprofen may cause falsely elevated **blood glucose values** when using the glucose oxidase and peroxidase method using ABTS as a chromogen; falsely elevated **serum bilirubin** values when using DMSO as a reagent; falsely elevated **serum iron** concentrations using the Ramsey method, or falsely decreased **serum iron** concentrations when using bathophenanthroline disulfonate as a reagent.

**Doses** -
**Horses**:

For labeled indications: 2.2 mg/kg (1 ml/100 lbs) IV once daily for up to 5 days. (Package insert - *Ketofen*®)

**Elephants:**
a) 1 mg/kg every 48 hours to 2 mg/kg every 24 hours in Asian elephants.
Hunter,R.P., Isaza,R., and Koch,D.E. 2003. **Oral bioavailability and pharmacokinetic characteristics of ketoprofen enantiomers after oral and intravenous administration in Asian elephants (Elephas maximus)**. Am J Vet Res 64:(1):109-114 **Abstract:** OBJECTIVE: To assess oral bioavailability (F) and pharmacokinetic characteristics of the R- and S-enantiomers of ketoprofen administered IV and orally to captive Asian elephants (Elephas maximus). ANIMALS: 5 adult Asian elephants. PROCEDURE: Elephants received single treatments of racemic ketoprofen at a dose of 2.2 mg/kg, administered IV and orally, in a complete crossover design. Blood samples were collected at intervals during the 24 hours following treatment. At least 4 weeks elapsed between drug administrations. Samples were analyzed for R- and S-ketoprofen with a validated liquid chromatography-mass spectroscopic assay. Pharmacokinetic parameters were determined by use of noncompartmental analysis. RESULTS: The enantiomers of ketoprofen were absorbed well after oral administration, with median F of 101% for R-ketoprofen and 85% for S-ketoprofen. Harmonic mean half-life ranged from 3.8 to 5.5 hours, depending on route of administration and enantiomer. The area under the concentration-time curve, mean residence time, apparent volume of distribution, plasma clearance, and maximum plasma concentration values were all significantly different between the 2 enantiomers for both routes of administration. CONCLUSIONS AND CLINICAL RELEVANCE: Ketoprofen has a long terminal half-life and complete absorption in this species. Based on the pharmacokinetic data, a dosage of ketoprofen of 1 mg/kg every 48 hours to 2 mg/kg every 24 hours, PO or IV, is recommended for use in Asian elephants, although the safety and efficacy of ketoprofen during long-term administration in elephants have not been determined.

To Drug Monograph Index To Ophthalmic Product Index

**Monitoring Parameters** - 1) Efficacy; 2) Adverse Effects (in humans, occasional liver function tests are recommended with long term therapy)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Ketoprofen Injection 100 mg/ml in 50 ml and 100 ml multi-dose vials; *Ketofen*® (Fort Dodge); (Rx) Approved for use in horses not intended for food.

**Human-Approved Products**:

Ketoprofen Oral Capsules 25 mg, 50 mg, 75 mg;*Orudis*® (Wyeth-Ayerst), generic; (Rx)

Ketoprofen 12.5 mg Tablets *Orudis KT*® (Whitehall-Robins) (OTC);Actron Caplets® (Bayer) (OTC)

Ketoprofen Extended Release 100 mg, 150 mg, 200 mg Capsules *Oruvail*® (Wyeth-Ayerst) (Rx)

**L-Thyroxine - see Levothyroxine**

**Lactated Ringer's—see the appendix section on intravenous fluids**

## LEVAMISOLE * (ADVERSE EFFECT REPORTED TO TETRAMISOLE)

**Chemistry** - The *levo*-isomer of *dl*-tetramisole, levamisole has a greater safety margin than does the racemic mixture. It is available commercially in two salts, a phosphate and a hydrochloride. Levamisole hydrochloride occurs as a white to pale cream colored, odorless or nearly odorless, crystalline powder. One gram is soluble in 2 ml of water.

**Storage/Stability/Compatibility** - Levamisole hydrochloride products should be stored at room temperature (15-30°C), unless otherwise instructed by the manufacturer; avoid temperatures greater than 40°C. Levamisole phosphate injection should be stored at temperatures at or below 21°C (70°F); refrigeration is recommended and freezing should be avoided.
Levamisole tablets should not be crushed nor suspensions made from them.

**Pharmacology** - Levamisole stimulates the parasympathetic and sympathetic ganglia in susceptible worms. At higher levels, levamisole interferes with nematode carbohydrate metabolism by blocking fumarate reduction and succinate oxidation. The net effect is a paralyzing effect on the worm which is then expelled alive. Levamisole's effects are considered to be nicotine-like in action.

Levamisole's mechanism of action for its immunostimulating effects are not well understood. It is believed it restores cell-mediated immune function in peripheral T-lymphocytes and stimulates phagocytosis by monocytes. Its immune stimulating effects appear to be more pronounced in animals that are immune-compromised.

**Uses/Indications** - Depending on the product licensed, levamisole is indicated for the treatment of many nematodes in cattle, sheep & goats, swine, poultry. In sheep and cattle, levamisole has relatively good activity against abomasal nematodes, small intestinal nematodes (not particularly good against *Strongyloides spp.*), large intestinal nematodes (not *Trichuris spp*.), and lungworms. Adult forms of species that are usually covered by levamisole, include: *Haemonchus spp., Trichostrongylus spp., Osteragia spp., Cooperia spp., Nematodirus spp., Bunostomum spp., Oesophagostomum spp., Chabertia spp.,* and *Dictyocaulus vivapurus*. Levamisole is less effective against the immature forms of these parasites and is generally ineffective in cattle (but not sheep) against arrested larval forms. Resistance of parasites to levamisole is a growing concern.

To Drug Monograph Index To Ophthalmic Product Index

In swine, levamisole is indicated for the treatment of *Ascaris suum*, *Oesophagostomum spp., Strongyloides, Stephanurus,* and *Metastrongylus*.

Levamisole has been used in dogs as a microfilaricide to treat *Dirofilaria immitis* infection. It has also garnered much interest as an immunostimulant in the adjunctive therapy of various neoplasms.

**Because of its narrow margin for safety and limited efficacy against many equine parasites, levamisole is not generally used in horses.**

**Pharmacokinetics** - Levamisole is absorbed from the gut after oral dosing and through the skin after dermal application, although bioavailabilities are variable. It is reportedly distributed throughout the body. Levamisole is primarily metabolized with less than 6% excreted unchanged in the urine. Plasma elimination half-lives have been determined for several veterinary species: Cattle 4-6 hours; Dogs 1.8-4 hours; and Swine 3.5-6.8 hours. Metabolites are excreted in both the urine (primarily) and feces.

**Contraindications/Precautions** - Levamisole is contraindicated in lactating animals (not approved). It should be used cautiously, if at all, in animals that are severely debilitated, or have significant renal or hepatic impairment. Use cautiously or, preferably, delay use in cattle that are stressed due to vaccination, dehorning or castration.

There is no information regarding the safety of this drug in pregnant animals. Although levamisole is considered relatively safe to use in large animals that are pregnant, use only if the potential benefits outweigh the risks.

**Adverse Effects/Warnings** - Adverse effects that may seen in cattle can include muzzle-foaming or hypersalivation, excitement or trembling, lip-licking and head shaking. These effects are generally noted with higher than recommended doses or if levamisole is used concomitantly with organophosphates. Symptoms generally subside within 2 hours. When injecting into cattle, swelling may occur at the injection site. This will usually abate in 7-14 days, but may be objectionable in animals that are close to slaughter.

In sheep, levamisole may cause a transient excitability in some animals after dosing. In goats, levamisole may cause depression, hyperesthesia and salivation. Injecting levamisole SQ in goats apparently causes a stinging sensation.

In swine, levamisole may cause salivation or muzzle foaming. Swine infected with lungworms may develop coughing or vomiting.

Adverse effects that may seen in dogs include GI disturbances (usually vomiting, diarrhea), neurotoxicity (panting, shaking, agitation or other behavioral changes), agranulocytosis, dyspnea, pulmonary edema, immune-mediated skin eruptions (erythroedema, erythema multiforme, toxic epidermal necrolysis) and lethargy.

Adverse effects seen in cats include hypersalivation, excitement, mydriasis and vomiting.

**Overdosage/Toxicity** - Symptoms of levamisole toxicity often mimic those of organophosphate toxicity. Symptoms may include hypersalivation, hyperesthesias and irritability, clonic seizures, CNS depression, dyspnea, defecation, urination, and collapse. These effects are best treated by supportive means, as animals generally recover within hours of dosing. Acute levamisole overdosage can result in death due to respiratory failure. Should respiratory failure occur, artificial ventilation with oxygen should be instituted until recovery takes place. Cardiac arrhythmias may also be seen. If the ingestion was oral, emptying the gut and/or administering charcoal with cathartics may be indicated.

To Drug Monograph Index  To Ophthalmic Product Index

Levamisole is considered to be more dangerous when administered parenterally than when given orally or topically. Intravenous administration is particularly hazardous, and is never recommended.

In pet birds (cockatoos, budgerigars, Mynah birds, parrots, etc.), 40 mg/kg has been reported as a toxic dose when administered SQ. IM injections may cause more severe toxicity. Depression, ataxia, leg and wing paralysis, mydriasis, regurgitation, and death may be seen after a toxic dose in birds.

**Drug Interactions** - Other **nicotine-like compounds (***e.g.,* **pyrantel, morantel, diethylcarbamazine), or cholinesterase-inhibitor drugs (***e.g.,* **organophosphates, neostigmine)** could theoretically enhance the toxic effects of levamisole; use together with caution.
Levamisole may enhance the immune-reaction and efficacy to **Brucella vaccines**.
Fatalities have been reported after concomitant levamisole and **chloramphenicol** administration; avoid using these agents together.

**Doses** -
**Cattle**:

For treatment of susceptible nematodes (also refer to specific label directions for approved products):

a) For removal of mature and immature *Dictyocaulus vivapurus*: 5.5 - 11 mg/kg PO, either given in feed or as a drench or oral bolus. May also be administered SQ at 3.3 - 8 mg/kg. (Bennett 1986)
b) 7.5 mg/kg PO (Brander, Pugh, and Bywater 1982)

**Elephants:**

a) 2.5-3 mg/kg orally as a single dose. Chandrasekharan,K. 2002. **Specific diseases of Asian elephants**. Journal of Indian Veterinary Association Kerala 7:(3):31-34

Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T., 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference to Kerala**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-44

Chandrasekharan,K., 1992. **Prevalence of infectious diseases in elephants in Kerala and their treatment**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 148-155
b) 3 mg/kg orally for strongylosis (Chandrasekharan, et.al., 1982).

**Adverse effects:**
c) a case of toxicity in a baby elephant treated with **Tetramisole**, has been reported. Gnanaprakasam,V. and Mahalingam,P., 1992. **Tetramisole toxicity in a baby elephant.** In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 166-167 **Summary:** A case of toxicity in a 2 year old elephant treated with 1 liter of Nilverm (300 g of Tetramisole) is presented. Clinical symptoms included muscular tremors, salivation, initially diarrhoea followed by constipation and bradycardia. Treatment with dextrose, B complex, atropine sulfate and liquid paraffin resulted in alleviation of symptoms and slow improvement. The authors comment that: “tetramisole itself has a safety margin variously estimated to be 2-6 times the therapeutic dose of 15 mg/kg and the safety factor of levamisole is about twice that of the parent compound since levamisole is equally active against parasites in half the dosage.”

**Monitoring Parameters** -

To Drug Monograph Index  To Ophthalmic Product Index

1) Clinical efficacy
2) Adverse effects/toxicity observation

**Client Information** - Levamisole is not approved to be used in dairy animals of breeding age. Follow directions on the product label unless otherwise directed by veterinarian. Animals that are severely parasitized or in conditions with constant helminth exposure should be retreated 2-4 weeks after initial treatment. Do not administer injectable products IV. Report serious adverse effects to veterinarian.

**Dosage Forms/Preparations/FDA Approval Status/Withdrawal Times** -
In cattle, sheep, and swine a level of 0.1 ppm has been established for negligible residues in edible tissues.

**Veterinary-Approved Products**:

**Dosage Forms/Preparations/FDA Approval Status/Withdrawal Times** -
In cattle, sheep, and swine a level of 0.1 ppm has been established for negligible residues in edible tissues.

**Veterinary-Approved Products**:

Levamisole Phosphate Injection 136.5 mg/ml (13.65%)

*Levasole® Injectable Solution* (Schering Plough); *Tramisol® Injectable* (Cyanamid). (OTC) Approved for use in beef cattle and non-lactating dairy cattle. Slaughter withdrawal=7 days.

Levamisole HCl Soluble Powder for Oral Use

*Levasole® Soluble Drench Powder* 11.7 grams/packet (Schering Plough); (OTC) Approved for use in sheep. Slaughter withdrawal=3 days.

*Levasole® Soluble Pig Wormer* 18.15 grams/packet (Schering Plough); (OTC) Approved for use in swine. Slaughter withdrawal=9 days.

*Levasole® Soluble Drench Powder* 46.8 grams/packet (Schering Plough); (OTC) Approved for use in beef cattle, non-lactating dairy cattle, and sheep. Slaughter withdrawal=2 days (cattle); 3 days (sheep).

*Tramisol® Soluble Drench Powder, Tramisol Drench* 46.8 grams/packet (American Cyanamid). (OTC) Approved for use in beef cattle, non-lactating dairy cattle, and sheep. Slaughter withdrawal=2 days (cattle); 3 days (sheep).

*Ripercol® L* 9.075 grams (American Cyanamid). (OTC) Approved for use in swine. Slaughter withdrawal=3 days.

Levamisole Oral Feed Mixes

*Tramisol® Hog Wormer* (American Cyanamid) Each 2.05 oz packet contains levamisole resinate equivalent to 45.5 grams levamisole. (OTC) Approved for use in swine. Slaughter withdrawal=3 days.

Medicated Feed Premix 50% (American Cyanamid) 227 g levamisole HCl/lb. (OTC) Approved for use in non-lactating dairy and beef cattle and swine. Slaughter withdrawal=2 days (cattle); 3 days (swine).

Levamisole HCl Oral Pastes/Gels

*Levasole® Gel* 11.5% (115 mg/gram) (Schering Plough) 237.4 g cartridge. Each cartridge will deliver 27.3 g of levamisole HCl. (OTC) Approved for use in beef cattle, and non-lactating dairy cattle. Slaughter withdrawal=6 days.

*Tramisol® Gel* 11.5% (115 mg/gram) (American Cyanamid). (OTC) Approved for use in beef cattle, and non-lactating dairy cattle, and swine. Slaughter withdrawal=6 days (cattle); 11 days (swine).

To Drug Monograph Index To Ophthalmic Product Index

Levamisole HCl Oral Tablets/Boluses; 184 mg bolus: *Levasole*® *Sheep Wormer Bolus* (Schering Plough); *Tramisole*® *Sheep Wormer* (Cyanamid); *Ripercol*® *L Wormer Oblets* (American Cyanamid). (OTC) Approved for use in sheep. Slaughter withdrawal=3 days.

2.19 gram bolus: *Levasole*® *Cattle Wormer Bolus* (Schering Plough); *Ripercol*® *L Bolus* (Cyanamid); (OTC) Approved for use in beef and non-lactating dairy cattle. Slaughter withdrawal=2 days.

Levamisole Topical (Pour-On) 200 mg/ml; *Totalon*® (Schering); *Tramisol*® *Pour On* (American Cyanamid). (OTC) Approved for use on beef and non-lactating dairy cattle. Slaughter withdrawal=9 days.

**Human-Approved Products**:

Levamisol HCl Tablets: 50 mg levamisole base; *Ergamisol*® (Janssen) (Rx)

## LEVOFLOXACIN PK

The fluoroquinolones as a group have activity against the *M. tuberculosis* complex and the *M. avium* complex. Of the fluoroquinolones, levofloxacin is considered as one of the most active drugs. Administration of levofloxacin to bongo antelope did not yield measurable serum concentrations. **Population pharmacokinetics of antituberculous drugs and treatment of *Mycobacterium bovis* infection in Bongo Antelope (*Tragelaphus eurycrus isaaci* ).** B. Auclair, S. Mikota, C. A. Peloquin, R. Aguilar and J. N. Maslow. Journal of Zoo and Wildlife Medicine 2002 Vol. 33 Issue 3 Pages 193-203

Elephants:

**PHARMACOKINETICS OF RECTALLY AND ORALLY ADMINISTERED LEVOFLOXACIN IN ASIAN ELEPHANTS (ELEPHAS MAXIMUS). 2023.** J. J. Kilburn, D. Schmitt, W. Kiso, M. G. Papich and K. A. Backues. J Zoo Wildl Med Vol. 53 Issue 4 Pages 670-678. Accession Number: 36640068 DOI: 10.1638/2022-0011

Appropriate and effective antibiotic use is a critical component of veterinary medicine, but there are variations across species regarding dosage and administration of these drugs. Oral or rectal routes of administration are typically used in elephants, but not all medications can achieve adequate concentrations rectally. The fluoroquinolone antimicrobials are used in elephants because of their favorable antimicrobial spectrum and pharmacokinetics compared with other oral agents. They are commonly used as part of multiple antibiotic regimens for the treatment of tuberculosis (Mycobacterium tuberculosis). The objective of this study was to determine the pharmacokinetic profile of levofloxacin after oral and rectal administration in Asian elephants (Elephas maximus). Dosages of 5 mg/kg orally and 15 mg/kg rectally were evaluated in 13 Asian elephants. Blood was collected at various time points from 0 to 72 h for pharmacokinetic analysis. Pharmacokinetic parameters were determined and reached concentrations above minimum inhibitory concentrations of various bacterial organisms via both routes. A pharmacokinetic-pharmacodynamic assessment was used to estimate appropriate minimal inhibitory concentrations for bacteria that could be potentially treated with this antimicrobial. Based on these findings, levofloxacin may be a consideration for administration orally (5 mg/kg) and rectally (15 mg/kg) in Asian elephants. Antimicrobial stewardship principles, culture and susceptibility of suspected pathogens, and blood level monitoring should be used to tailor administration of levofloxacin in this species.

## LEVOTHYROXINE SODIUM

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - Prepared synthetically for commercial use, levothyroxine sodium is the *levo* isomer of thyroxine which is the primary secretion of the thyroid gland. It occurs as an odorless, light yellow to buff-colored, tasteless, hygroscopic powder that is very slightly soluble in water and slightly soluble in alcohol. The commercially available powders for injection also contain mannitol.

Levothyroxine sodium may also be known as sodium levothyroxine, thyroxine sodium, L-thyroxine sodium, $T_4$, or $T_4$ thyroxine sodium. 100 micrograms of levothyroxine is approximately equivalent to 65 mg (1 grain) of dessicated thyroid.

**Storage/Stability/Compatibility** - Levothyroxine sodium preparations should be stored at room temperature in tight, light-resistant containers. The injectable product should be reconstituted immediately before use; unused injection should be discarded after reconstituting. Do not mix levothyroxine sodium injection with other drugs or IV fluids.

**Pharmacology** - Thyroid hormones affect the rate of many physiologic processes including: fat, protein and carbohydrate metabolism, increasing protein synthesis, increasing gluconeogenesis and promoting mobilization and utilization of glycogen stores. Thyroid hormones also increase oxygen consumption, body temperature, heart rate and cardiac output, blood volume, enzyme system activity, and growth and maturity. Thyroid hormone is particularly important for adequate development of the central nervous system. While the exact mechanisms how thyroid hormones exert their effects are not well understood, it is known that thyroid hormones (primarily triiodothyronine) act at the cellular level.

In humans, triiodothyronine ($T_3$) is the primary hormone responsible for activity. Approximately 80% of $T_3$ found in the peripheral tissues is derived from thyroxine ($T_4$) which is the principle hormone released by the thyroid.

**Uses/Indications -** Levothyroxine sodium is indicated for the treatment of hypothyroidism in all species.

**Pharmacokinetics** - In dogs, peak plasma concentrations after oral dosing reportedly occur 4-12 hours after administration and the serum half-life is approximately 12-16 hours. There is wide variability from animal to animal, however.

**Contraindications/Precautions** - Levothyroxine (and other replacement thyroid hormones) are contraindicated in patients with acute myocardial infarction, thyrotoxicosis or untreated adrenal insufficiency. It should be used with caution, and at a lower initial dosage, in patients with concurrent hypoadrenocorticism (treated), cardiac disease, diabetes, or in those who are aged.

**Adverse Effects/Warnings** - When administered at an appropriate dose to patients requiring thyroid hormone replacement, there should not be any adverse effects associated with therapy. For adverse effects associated with overdosage, see below.

**Overdosage** - Chronic overdosage will produce symptoms of hyperthyroidism, including tachycardia, polyphagia, PU/PD, excitability, nervousness and excessive panting. Dosage should be reduced and/or temporarily withheld until symptoms subside. Some (10%?) cats may exhibit symptoms of “apathetic” (listlessness, anorexia, etc.) hyperthyroidism.

Acute massive overdosage can produce symptoms resembling thyroid storm. After oral ingestion, treatment to reduce absorption of drug should be accomplished using standard protocols (emetics or gastric lavage, cathartics, charcoal) unless contraindicated by the patient’s condition. Treatment is supportive and symptomatic. Oxygen, artificial ventilation, cardiac glycosides, beta blockers (*e.g.,* propranolol), fluids, dextrose and antipyrexic agents have all been suggested for use if necessary.

To Drug Monograph Index  To Ophthalmic Product Index

**Drug Interactions** - Levothyroxine increases the actions of **epinephrine, norepinephrine** and other catecholamines and sympathomimetics. Thyroid hormones increase the catabolism of vitamin K-dependent clotting factors which may increase the anticoagulation effects in patients on **warfarin**. In diabetic patients, the addition of thyroid hormones may alter **insulin** requirements; monitor carefully during initiation of therapy. **Estrogens** may increase thyroid requirements by increasing TBg. Therapeutic effects of **digoxin or digitoxin** may be decreased by thyroid hormones. **Ketamine** may cause tachycardia and hypertension when used in patients receiving thyroid hormones.

**Drug/Laboratory Interactions -** The following drugs (in humans) that may be used in veterinary species may have effects on thyroid function tests; evaluate results accordingly:
Effects on serum **$T_4$**: aminoglutethimide↓, anabolic steroids/androgens↓, antithyroid drugs (PTU, methimazole)↓, asparaginase↓, barbiturates↓, corticosteroids ↓, danazol↓, diazepam↓, estrogens↑ (Note: estrogens may have no effect on canine $T_3$ or $T_4$ concentrations), fluorouracil↑, heparin↓, insulin↑, lithium carbonate↓, mitotane (*o,p*-DDD)↓, nitroprusside↓, phenylbutazone↓, phenytoin↓, propranolol↑, salicylates (large doses)↓, & sulfonylureas↓.

Effects on serum **$T_3$**: antithyroid drugs (PTU, methimazole)↓, barbiturates↓, corticosteroids↓, estrogens↑, fluorouracil↑, heparin↓, lithium carbonate↓, phenytoin↓, propranolol↓, salicylates (large doses)↓, & thiazides↑

Effects on **$T_3$ uptake resin**: anabolic steroids/androgens↑, antithyroid drugs (PTU, methimazole)↓, asparaginase↑, corticosteroids↑, danazol↑, estrogens↓, fluorouracil↓, heparin↑, lithium carbonate↓, phenylbutazone↑, & salicylates (large doses) ↑.

Effects on serum **TSH**: aminoglutethimide↑, antithyroid drugs (PTU, methimazole)↑, corticosteroids↓, danazol↓, & lithium carbonate↑.

Effects on **Free Thyroxine Index (FTI)**: antithyroid drugs (PTU, methimazole)↓, barbiturates↓□ corticosteroids↓, heparin↑, lithium carbonate↓, & phenylbutazone↓□

**Doses** -
**Horses**:
For hypothyroidism:
a) 10 mg in 70 ml of corn syrup once daily. Monitor $T_4$ levels one week after initiation of therapy. Obtain one blood sample just before administration and on sample 2-3 hours after dosing. (Chen and Li 1987)

**Monitoring Parameters** -
1) Serum thyroid hormone concentrations ($T_4$/$T_3$). Monitoring before therapy is begun can help confirm diagnosis. After therapy is started wait at least 5-10 days before measuring $T_4$, one month may be better, especially if dosage is ineffective or symptoms of thyrotoxicosis develop. Serum levels should be drawn before the dose and 6-8 hours after. Dosage should be reduced if serum thyroxine levels exceed 100 ng/ml or symptoms of thyrotoxicosis develop.

**Client Information** - Clients should be instructed in the importance of compliance with therapy as prescribed. Also, review the symptoms that can be seen with too much thyroid supplementation (see Overdosage section above).

**Dosage Forms/Preparations/FDA Approval Status** - All levothyroxine products require a prescription. There have been bioavailability differences between products reported. It is recommended to use a reputable product and not to change brands indiscriminately.

**Veterinary-Approved Products -**

To Drug Monograph Index To Ophthalmic Product Index

Levothyroxine Sodium Tablets 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg; *Soloxine*® (Daniels), *Thyro-Tabs* ® (Vet-A-Mix); *Thyrozine Tablets*® (Anthony) (Rx) Approved for use in dogs.

Levothyroxine Sodium Tablets Chewable (Veterinary) 0.2 mg, 0.5 mg, 0.8 mg; *Thyro-Form*® (Vet-A-Mix) (Rx) — Approved for use in dogs.

Levothyroxine Sodium Tablets Chewable (Veterinary) 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg; *HESKA Chewable Thyroid Supplement for Dogs* (Heska); Approved for use in dogs (Rx)

Levothyroxine Sodium Powder (Veterinary) 0.22% (1 gram of $T_4$ in 454 grams of powder): One level teaspoonful contains 12 mg of $T_4$. Available in 1 lb. and 10 lb. containers.; *Thyro-L*® (Vet-A-Mix) (Rx) — Approved for use in horses.

**Human-Approved Products -**

Levothyroxine Sodium Tablets 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.1 mg, 0.112 mg, 0.125 mg, 0.137 mg, 0.15 mg, 0.175 mg, 0.2 mg, 0.3 mg; *Synthroid*® (Knoll), *Levothroid*® (Forest); *Levo-T*® (Lederle); Levoxyl® (Daniels); *Eltroxin*® (Roberts); generic, (Rx)

Levothyroxine Powder for Injection 200 micrograms per vial, 500 micrograms/vial in 6 ml and 10 ml vials; *Synthroid*® (Knoll), *Levothroid*® (Forest); *Levoxine*® (Daniels), generic (Rx)

## LIDOCAINE HCL

**Chemistry** - A potent local anesthetic and antiarrhythmic agent, lidocaine HCl occurs as a white, odorless, slightly bitter tasting, crystalline powder with a melting point between 74° - 79°C and a $pK_a$ of 7.86. It is very soluble in water and alcohol. The pH of the commercial injection is adjusted to 5 - 7, and the pH of the commercially available infusion in dextrose 5% is adjusted to 3.5 - 6. Lidocaine is also known as lignocaine HCl.

**Storage/Stability/Compatibility** - Lidocaine for injection should be stored at temperatures less than 40°C and preferably between 15-30°C; avoid freezing.

Lidocaine is **compatible** with most commonly used IV infusion solutions, including D5W, lactated Ringer's, saline, and combinations of these. It is also reportedly physically compatible with: aminophylline, bretylium tosylate, calcium chloride/gluceptate/gluconate, carbenicillin disodium, chloramphenicol sodium succinate, chlorothiazide sodium, cimetidine HCl, dexamethasone sodium phosphate, digoxin, diphenhydramine HCl, dobutamine HCl, ephedrine sulfate, erythromycin lactobionate, glycopyrrolate, heparin sodium, hydrocortisone sodium succinate, hydroxyzine HCl, insulin (regular), mephentermine sulfate, metaraminol bitartrate, methicillin sodium, metoclopramide HCl, nitrofurantoin sodium, oxytetracycline HCl, penicillin G potassium, pentobarbital sodium, phenylephrine HCl, potassium chloride, procainamide HCl, prochlor-perazine edisylate, promazine HCl, sodium bicarbonate, sodium lactate, tetracycline HCl, verapamil HCl, and Vitamin B-Complex w/C.

Lidocaine **may not be compatible** with dopamine, epinephrine, isoproterenol or norepinephrine as these require low pH's for stability. Lidocaine is reportedly **incompatible** with: ampicillin sodium, cefazolin sodium, methohexital sodium, or phenytoin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Lidocaine is considered to be a class IB (membrane-stabilizing) antidysrhythmic agent. It is thought that lidocaine acts by combining with fast sodium channels when inactive which inhibits recovery after repolarization. Class IB agents demonstrate rapid rates of attachment and dissociation to sodium channels. At therapeutic levels, lidocaine causes phase 4 diastolic depolarization attenuation, decreased automaticity, and either a decrease or no change in membrane responsiveness and excitability. These effects will occur at serum levels that will not inhibit the automaticity of the SA node, and will have little effect on AV node conduction or His-Purkinje conduction.

**Uses/Indications** - Besides its use as a local and topical anesthetic agent, lidocaine is used to treat ventricular arrhythmias, principally ventricular tachycardia and ventricular premature complexes in all species. Cats tend to be rather sensitive to the drug and some clinicans feel that it should not be used in this species as an antiarrhythmic.

**Pharmacokinetics** - Lidocaine is not effective orally as it has a high first-pass effect. If very high oral doses are given, toxic symptoms occur (due to active metabolites?) before therapeutic levels can be reached. Following a therapeutic IV bolus dose, the onset of action is generally within 2 minutes and has a duration of action of 10-20 minutes. If a constant infusion is begun without an initial IV bolus it may take up to an hour for therapeutic levels to be reached. IM injections may be given every 1.5 hours in the dog, but because monitoring and adjusting dosages are difficult, it should be reserved for cases where IV infusions are not possible.

After injection, the drug is rapidly redistributed from the plasma into highly perfused organs (kidney, liver, lungs, heart) and is distributed widely throughout body tissues. It has a high affinity for fat and adipose tissue and is bound to plasma proteins, primarily alpha$_1$-acid glycoprotein. It has been reported that lidocaine binding to this protein is highly variable and concentration dependent in the dog and may be higher in dogs with inflammatory disease. Lidocaine is distributed into milk. The apparent volume of distribution ($V_d$) has been reported to be 4.5 L/kg in the dog.

Lidocaine is rapidly metabolized in the liver to active metabolites (MEGX and GX). The terminal half-life of lidocaine in humans is 1.5-2 hours and has been reported to be 0.9 hours in the dog. The half-lives of lidocaine and MEGX may be prolonged in patients with cardiac failure or hepatic disease. Less than 10% of a parenteral dose is excreted unchanged in the urine.

**Contraindications/Precautions** - Cats tend to be more sensitive to the CNS effects of lidocaine; use with caution. Lidocaine is contraindicated in patients with known hypersensitivity to the amide-class local anesthetics, a severe degree of SA, AV or intraventricular heart block (if not being artificially paced), or Adams-Stokes syndrome. The use of lidocaine in patients with Wolff-Parkinson-White (WPW) syndrome is controversial. Some manufacturers state its use is contraindicated, but several physicians have used the drug in people.

Lidocaine should be used with caution in patients with liver disease, congestive heart failure, shock, hypovolemia, severe respiratory depression, or marked hypoxia. It should be also be used with caution in patients with bradycardia or incomplete heart block having VPC's, unless the heart rate is first accelerated. Patients susceptible to developing malignant hyperthermia should receive lidocaine with intensified monitoring.

**Adverse Effects/Warnings** - At usual doses and if the serum level remains within the proposed therapeutic range (1 - 5 micrograms/ml), serious adverse reactions are quite rare. The most common adverse effects reported are dose related (serum level) and mild. CNS signs include drowsiness, depression, ataxia, muscle tremors, etc. Nausea and vomiting may occur, but are usually transient. Adverse cardiac effects generally only occur at high plasma concentrations and are usually associated with PR and QRS interval

To Drug Monograph Index To Ophthalmic Product Index

prolongation and QT interval shortening. Lidocaine may increase ventricular rates if used in patients with atrial fibrillation. If an IV bolus is given too rapidly, hypotension may occur.

Be certain **not** to use the product which contains **epinephrine** intravenously.

**Overdosage** - In dogs, if serum levels of >8 micrograms/ml are attained, toxicity may result. Symptoms may include ataxia, nystagmus, depression, seizures, bradycardia, hypotension and, at very high levels, circulatory collapse. Because lidocaine is rapidly metabolized, cessation of therapy or reduction in infusion rates with monitoring may be all that is required for minor symptoms. Seizures or excitement may be treated with diazepam, or a short or ultrashort acting barbiturate. Longer acting barbiturates (e.g., pentobarbital) should be avoided. Should circulatory depression occur, treat with fluids, pressor agents and if necessary, begin CPR.

**Drug Interactions** - Lidocaine levels or effects may be increased by concomitant administration of **cimetidine** or **propranolol**. Other antiarrhythmics such as **procainamide, quinidine, propranolol, phenytoin** administered with lidocaine may cause additive or antagonistic cardiac effects and toxicity may be enhanced. **Phenytoin** when given IV with lidocaine may cause increased cardiac depression. Large doses of lidocaine may prolong **succinylcholine**-induced apnea.

**Laboratory Interactions** - Lidocaine may cause increased **creatine kinase levels (CK)**.

**Doses** -
**Horses**:

a) Initially IV bolus of 1 - 1.5 mg/kg. Will generally distinguish between ventricular tachyarrhythmias (effective) and supraventricular tachyarrhythmias (no effect). To maintain effect, a constant IV infusion will be required. (Hilwig 1987)

**Elephants:**

a) Local anesthesia with infiltration is rarely attempted in elephants because of the difficulty in administration and the large volumes required. Moreover, local anesthesia does not aid in controlling the animals. Nayar,K.N.M., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Management of surgical affections in captive elephants**. Journal of Indian Veterinary Association Kerala 7:(3):55-59

b) Lidocaine blocks were used in addition to sedation with azaperone but the number of procedures performed and the doses used are not specified. Ramsay,E. 2000. **Standing sedation and tranquilization in captive African elephants (*Loxodonta africana*)**. Proc. Am. Assoc. Zoo Vet. Pages: 111-114

c) To facilitate a vaginal vestibulotomy in an Asian elephant, local anesthesia was administered with 5 injections of 20 ml lidocaine 2% + noradrenaline intra- and subcutaneously in the midline of the perineum, starting 5 cm ventrally of the anus, with an interval of 10 cm. The cow had been previously sedated with zuclopentixol. Schaftenaar,W. 1996. **Vaginal vestibulotomy in an Asian elephant (*Elephas maximus*)**. Proceedings American Association of Zoo Veterinarians. Pages: 434-439 **Abstract:** Due to its dimensions, dystocia in elephants presents a difficult problem. This paper describes the delivery of a dead calf by surgical intervention. A vestibulotomy was performed under local anesthesia. Complications in wound healing resulted in a permanent fistula of the vestibulum. The difficulties in decision making and the interpretation of clinical signs are discussed.

d) In one African elephant under general anesthesia, paroxysmal ventricular tachycardia was detected and the procedure terminated when the arrhythmia failed to stabilize after multiple doses of lidocaine (1 mg/kg, IV). Heard,D.J., Kollias,G.V., Webb,A.I., Jacobson,E.R., and Brock,K.A. 1988. **Use of halothane to**

To Drug Monograph Index To Ophthalmic Product Index

**maintain anesthesia induced with etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 193:254-256 **Excerpts:** Sixteen 3- to 5-year-old African elephants were anesthetized one or more times for a total of 27 diagnostic and surgical procedures. Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing juvenile elephants during a 45-minute transport period before administration of general anesthesia. After IM or IV administration of etorphine (1.9 ± 0.56 micrograms/kg), the mean time to lateral recumbency was 20 ± 6.6 and 3 ± 0.0 minutes, respectively. The mean heart rate, systolic blood pressure, and respiration rate during all procedures was 50 ± 12 beats/min, 106 ± 19 mm of Hg, and 10 ± 3 breaths/min, respectively.

Cardiac arrhythmias were detected during 2 procedures. In one elephant paroxysmal ventricular tachycardia was detected and the procedure terminated when the arrhythmia failed to stabilize after multiple doses of lidocaine (1 mg/kg, IV). In another elephant, second degree atrioventricular block returned to normal sinus rhythm after IV administration of atropine (0.04 mg/kg).

In one elephant, low mean blood pressure (54 mm of Hg) responded to reduction in halothane (vaporizer setting 1 to 0.75%) and slow infusion of dobutamine HCl ((250 mg/1,000 ml) given to effect. The systolic blood pressure increased to 90 mm of Hg and remained high with a continuous infusion of dobutamine (5 µg/kg/min).

Immediately after induction in another elephant, profound respiratory depression (< 1 breath /minute) and palpably weak arterial pulse were identified. Intravenous administration of diprenorphine at half the recommended reversal dose resulted in improvement of respiration and palpable arterial pulse, without the elephant developing signs of complete anesthetic reversal.

Alterations in systolic blood pressure, ear flapping, and trunk muscle tone were useful for monitoring depth of anesthesia. Results indicated that halothane in oxygen was effective for maintenance of surgical anesthesia in juvenile African elephants after induction with etorphine. Note: A correction appeared in a later volume 193(6): p.721.

**Monitoring Parameters** -

1) ECG
2) Symptoms of toxicity (see Adverse Effects and Overdosage)
3) If available and indicated, serum levels may be monitored. Therapeutic levels are considered to range from 1 - 6 micrograms/ml.

**Client Information** - This drug should only be used by professionals familiar with its use and in a setting where adequate patient monitoring can be performed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -Lidocaine is approved for use in veterinary medicine (dogs, cats, horses, and cattle) as an injectable anesthetic, but it is not approved for use as an antiarrhythmic agent. Information regarding its use in food-producing species is conflicting. It is a prescription (Rx) drug.

Lidocaine HCl for Injection
1% (10 mg/ml) in 5 ml (50mg) and 10 ml (100 mg) syringes
2% (20 mg/ml) in 5 ml single use vials and syringes (preservative free)
2% (20 mg/ml) in 100 ml multi-use vials; Veterinary (contains preservatives)

To prepare IV infusion solution using the veterinary 2% solution add 1 gram (50 ml of 2% solution to 1 liter of $D_5W$ or other compatible solution, this will give an approximate concentration of 1 mg/ml (1000 micrograms/ml). When using a mini-drip (60 drops/ml) IV set, each drop will contain approximately 17 micrograms. In small dogs and cats, a less concentrated solution may be used for greater dosage accuracy.

To Drug Monograph Index To Ophthalmic Product Index

When preparing solution be certain that you are **not using** the lidocaine product that also contains **epinephrine**.

Lidocaine (human approved) is also available in 4%, 10%, and 20% preservative free solutions for IV admixture, for direct IM administration, and premixed with $D_5W$ for IV infusion in concentrations of 2 mg/ml, 4 mg/ml, and 5 mg/ml.

Also known as lignocaine HCl. A common trade name is *Xylocaine*® (Astra).

## MAGNESIUM
## MAGNESIUM SULFATE

For information on the use of oral magnesium hydroxide, refer to the monograph for Oral Antacids in the GI section. Magnesium oxide and oral magnesium sulfate are also detailed in the monograph for Saline/Hyperosmotic laxatives in the GI section.

**Chemistry** - Magnesium sulfate occurs as small, usually needle-like, colorless crystals with a cool, saline, bitter taste. It is freely soluble in water and sparingly soluble in alcohol. Magnesium sulfate injection has a pH of 5.5-7. One gram of magnesium sulfate hexahydrate contains 8.1 mEq of magnesium. Magnesium sulfate is also known as Epsom salts.

**Storage/Stability/Compatibility** - Magnesium sulfate for injection should be stored at room temperature (15-30°C); avoid freezing. Refrigeration may result in precipitation or crystallization.

Magnesium sulfate is reportedly **compatible** with the following intravenous solutions and drugs: dextrose 5%, calcium gluconate, cephalothin sodium, chloramphenicol sodium succinate, cisplatin, hydrocortisone sodium succinate, isoproterenol HCl, methyldopate HCl, metoclopramide HCl (in syringes), norepinephrine bitartrate, penicillin G potassium, potassium phosphate, and verapamil HCl. Additionally, at Y-sites: acyclovir sodium, amikacin sulfate, ampicillin sodium, carbenicillin disodium, cefamandole naftate, cefazolin sodium, cefoperazone sodium, ceforanide, cefotaxime sodium, cefoxitin sodium, cephalothin sodium, cephapirin sodium, clindamycin phosphate, doxycycline phosphate, erythromycin lactobionate, esmolol HCl, gentamicin sulfate, heparin sodium, kanamycin sulfate, labetolol HCl, metronidazole (RTU), moxalactam disodium, nafcillin sodium, oxacillin sodium, piperacillin sodium, potassium chloride, tetracycline HCl, ticarcillin disodium, tobramycin sulfate, trimethoprim/sulfamethoxasole, vancomycin HCl, and vitamin B-complex with C.

Magnesium sulfate is reportedly **incompatible** with alkali hydroxides, alkali carbonates, salicylates and many metals, including the following solutions or drugs: fat emulsion 10 %, calcium gluceptate, dobutamine HCl, polymyxin B sulfate, procaine HCl, and sodium bicarbonate. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Magnesium is used as a cofactor in a variety of enzyme systems and plays a role in muscular excitement and neurochemical transmission.

**Uses/Indications** - Parenteral magnesium sulfate is used as a source of magnesium in magnesium deficient states (hypomagnesemia), for adjunctive therapy of malignant hyperthermia in swine, and also as an anticonvulsant.

**Pharmacokinetics** - IV magnesium results in immediate effects, IM administration may require about 1 hour for effect. Magnesium is about 30-35% bound to proteins and the remainder exists as free ions. It is excreted by the kidneys at a rate proportional to the serum concentration and glomerular filtration.

To Drug Monograph Index  To Ophthalmic Product Index

**Contraindications/Precautions** - Parenteral magnesium is contraindicated in patients with myocardial damage or heart block. Magnesium should be given with caution to patients with impaired renal function. Patients receiving parenteral magnesium should be observed and monitored carefully to avoid hypermagnesemia.

**Adverse Effects/Warnings** - Magnesium sulfate (parenteral) adverse effects are generally the result of magnesium overdosage and may include drowsiness or other CNS depressant effects, muscular weakness, bradycardia, hypotension, respiratory depression and increased Q-T intervals on ECG. Very high magnesium levels may cause neuromuscular blocking activity and eventually cardiac arrest.

**Overdosage/Acute Toxicity** - See Adverse Effects above. Treatment of hypermagnesemia is dependent on the serum magnesium level and any associated clinical effects. Ventilatory support and administration of intravenous calcium may be required for severe hypermagnesemia.

**Drug Interactions** - When parenteral magnesium sulfate is used with **other CNS depressant agents (***e.g.,* **barbiturates, general anesthetics)** additive CNS depression may occur.
Parenteral magnesium sulfate with **nondepolarizing neuromuscular blocking agents** has caused excessive neuromuscular blockade. Because serious conduction disturbances can occur, parenteral magnesium should be used with extreme caution with **digitalis cardioglycosides**. Concurrent use of **calcium salts** may negate the effects of parenteral magnesium.

**Doses** -
**Ruminants**:

For hypomagnesemia (grass and other magnesium-related tetanies):

a) Cattle: Magnesium sulfate 20-50%: 200 ml SQ, followed by a slow IV infusion of 500 ml of a calcium/magnesium solution (Calcium borogluconate 23%; $MgCl_2$ 6%). (Phillips 1988a)
b) Cattle: 350 ml (250 ml of 25% calcium borogluconate and 100 ml of 10% of magnesium sulfate) by slow IV. If not a proprietary mixture, give calcium first. Relapses occur frequently after IV therapy, and 350 ml SQ of magnesium sulfate 20% may give more sustained magnesium levels. Alternating calcium and magnesium may prevent adverse effects. Continue control measures for 4-7 days to prevent relapse.

Sheep and Goats: 50 - 100 ml of above solution (calcium/magnesium).

For whole milk tetany in calves 2-4 months of age: Magnesium sulfate 10% 100 ml; followed by oral magnesium oxide at daily doses of 1 gram PO (0-5 weeks old), 2 gram PO (5-10 weeks old), and 3 grams PO (10-15 weeks old). (Merrall and West 1986)

**Monitoring Parameters** -

1) Serum magnesium
2) Physical signs and symptoms associated with hypomagnesemia
3) Serum calcium if indicated

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: There are no parenteral magnesium-only products approved for veterinary medicine. There are, however, several proprietary magnesium-containing products available that may also include calcium, phosphorus, potassium and/or dextrose; refer to the individual product's labeling for specific dosage information. Trade names for these products include: *Norcalciphos*®—Pfizer, *Cal-Dextro*® *Special, & #2,*—Fort Dodge, and *CMPK*®, & *Cal-Phos*® *#2*—(TechAmerica). They are legend (Rx) drugs.

**Human-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Magnesium Sulfate Injection 10% (0.8 mEq/ml), 12.5% (1 mEq/ml), & 50% (4 mEq/ml) in 2, 5, 10, 20 & 50 ml amps, vials and/or syringes; Generic; (Rx)

## MANNITOL

**Chemistry** - An osmotic diuretic, mannitol occurs as an odorless, sweet-tasting, white, crystalline powder with a melting range of 165° - 168° and a $pK_a$ of 3.4. One gram is soluble in about 5.5 ml of water (at 25°) and it is very slightly soluble in alcohol. The commercially available injectable products have approximate pH's of 4.5 - 7.

**Storage/Stability/Compatibility** - Mannitol solutions are stable but are recommended to be stored at room temperature; avoid freezing.

Crystallization may occur at low temperatures in concentrations greater than 15% (see procedure for resolubolization in Dosage Forms/Preparations section). Alternatively, heated storage chambers (35° - 50°C) have been suggested to assure that soluble product is available at all times. Microwaving glass ampules/vials has been suggested, but explosions have been documented and this procedure cannot be recommended. Supersaturated solutions of mannitol in PVC bags may show a white flocullant precipitate that will tend to reoccur even after heating.

Drugs reported to be **compatible** with mannitol include: amikacin sulfate, bretylium tosylate, cefamandole naftate, cefoxitin sodium, cimetidine HCl, dopamine HCl, gentamicin sulfate, metoclopramide HCl, netilmicin sulfate, tobramycin sulfate, and verapamil HCl. Mannitol should not be added to whole blood products to be used for transfusion. Sodium or potassium chloride can cause mannitol to precipitate out of solution when mannitol concentrations are 20% or greater. Mannitol may be incompatible with strongly acidic or alkaline solutions.

Mannitol is reportedly stable when mixed with cisplatin for a short period of time, but advanced premixing of the drugs should be avoided because of a complex that may form between the two drugs.

**Pharmacology** - After intravenous administration, mannitol is freely filtered at the glomerulus and poorly reabsorbed in the tubule. The increased osmotic pressure prevents water from being reabsorbed at the tubule. To be effective, there must be sufficient renal blood flow and filtration for mannitol to reach the tubules. Although water is proportionately excreted at a higher rate, sodium, other electrolytes, uric acid and urea excretions are also enhanced.
Mannitol may have a nephro-protective effect by preventing the concentration of nephrotoxins from accumulating in the tubular fluid. Additionally, it may increase renal blood flow and glomerular filtration by causing renal arteriole dilatation, decreased vascular resistance and decreased blood viscosity.

Mannitol does not appreciably enter the eye or the CNS, but can decrease intraocular and CSF pressure through its osmotic effects. Rebound increases in CSF pressures may occur after the drug is discontinued.

**Uses/Indications -** Mannitol is used to promote diuresis in acute oliguric renal failure, reduce intraocular and intracerebral pressures, enhance urinary excretion of some toxins (*e.g.,* aspirin, some barbiturates, bromides, ethylene glycol) and, in conjunction with other diuretics to rapidly reduce edema or ascites when appropriate (see Contraindications-/Precautions below). In humans, it is also used as an irrigating solution during transurethral prostatic resections.

**Pharmacokinetics** - Although long believed to be unabsorbed from the GI, up to 17% of an oral dose is excreted unchanged in the urine after oral dosing in humans. After intravenous dosing, mannitol is

distributed to the extracellular compartment and does not penetrate the eye. Unless the patient has received very high doses, is acidotic, or there is loss of integrity of the blood-brain barrier, it does not cross into the CNS.

Only 7-10% of mannitol is metabolized, the remainder is excreted unchanged in the urine. The elimination half-life of mannitol is approximately 100 minutes in adult humans. Half-lives in cattle and sheep are reported to be between 40-60 minutes.

**Contraindications/Precautions** - Mannitol is contraindicated in patients with anuria secondary to renal disease, severe dehydration, intracranial bleeding (unless during craniotomy), severe pulmonary congestion or pulmonary edema.

Mannitol therapy should be stopped if progressive heart failure, pulmonary congestion, progressive renal failure or damage (including increasing oliguria and azotemia) develop after mannitol therapy is instituted.

Do not administer more than a test dose of mannitol until determining whether the patient has some renal function and urine output. Adequate fluid replacement must be administered to dehydrated animals before mannitol therapy is begun. Do not give mannitol with whole blood products, unless at least 20 mEq/l of sodium chloride is added to the solution or pseudo-agglutination may result.

**Adverse Effects/Warnings** - Fluid and electrolyte imbalances are the most severe adverse effects generally encountered during mannitol therapy. Adequate monitoring and support are imperative.

Other adverse effects that may be encountered include GI (nausea, vomiting), cardiovascular (pulmonary edema, CHF, tachycardia), and CNS effects (dizziness, headache, etc.).

**Overdosage** - Inadvertent overdosage can cause excessive excretion of sodium, potassium and chloride. If urine output is inadequate, water intoxication or pulmonary edema may occur. Treat by halting mannitol administration and monitoring and correcting electrolyte and fluid imbalances. Hemodialysis is effective in clearing mannitol.

**Drug Interactions** - Mannitol can increase the renal elimination of **lithium**.

**Drug/Laboratory Interactions** - Mannitol can interfere with blood inorganic **phosphorus** concentrations and blood **ethylene glycol** determinations.

**Doses** -
**Horses**:

a) 0.25 - 2.0 gm/kg as a 20% solution by slow IV infusion (Schultz 1986)

**Monitoring Parameters** -

a) Serum electrolytes, osmolality
b) BUN, serum creatinine
c) Urine output
d) Central venous pressure, if possible
e) Lung auscultation

**Client Information** - Mannitol should be administered by professional staff in a setting where adequate monitoring can occur.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

To Drug Monograph Index To Ophthalmic Product Index

**Veterinary-Approved Products**:

Mannitol for Injection 180 mg/ml in 100 ml vials; *Mannitol Injection*® (Anthony) (Rx); Approved for use in dogs

**Human-Approved Products**:

Mannitol for Injection

5% (50 mg/ml; 275 mOsm/l) in 1000 ml
10% (100 mg/ml; 550 mOsm/l) in 500 and 1000 ml
15% (150 mg/ml; 825 mOsm/l) in 500 ml
20% (200 mg/ml; 1100 mOsm/l) in 250 and 500 ml
25% (250 mg/ml; 1375 mOsm/l) in 50 ml vials & syringes (12.5 grams/vial)

Note: Mannitol may tend to crystallize in concentrations of 15% or more when exposed to low temperatures. Resolubolization of the crystals can be accomplished by heating the bottle in hot (up to 80°C) water. Cool to body temperature before administering. An in-line IV filter is recommended when administering concentrated mannitol solutions.

## MEBENDAZOLE

### Elephants:

a) 6-7 mg/kg po Carreno,R.A., Neimanis,A.S., Lindsjo,J., Thongnoppakun,P., Barta,J.R., and Peregrine,A.S. 2001. **Parasites found in faeces of Indian elephants (Elephas maximus) in Thailand following treatment with mebendazole, with observations on Pfenderius papillatus (Cobbold, 1882) Stiles and Goldberger, 1910 by scanning electron microscopy**. Helminthologia 38:(2):75-79 **Abstract:** Three Indian elephants (Elephas maximus) in Thailand were treated with mebendazole at a dose of 6-7 mg/kg body weight. Four days following treatment, faecal examinations were negative for nematode eggs in all elephants and negative for fluke eggs in two of the animals. However, adult parasites were recovered from faeces from each of the animals 36-72 hours after deworming. These included Murshidia falcifera, M. neveulemairei, a Quilonia species, and the amphistome Pfenderius papillatus, 1910. The finding of P. papillatus constitutes the first record of this species in Thailand. Specimens of P. papillatus were examined by scanning electron microscopy. In contrast to earlier descriptions of this species, no prominent papillae were found at the anterior end. Structures on the acetabulum that had previously been described as papillae were actually elevated pores that were spread over the acetabulum. These pores differ from all previous descriptions of P. papillatus and indicate a highly modified acetabulum in P. papillatus relative to other Pfenderius species.

b) 2.5 – 4.0 mg/kg orally as a single dose. Chandrasekharan,K. 2002. **Specific diseases of Asian elephants**. Journal of Indian Veterinary Association Kerala 7:(3):31-34

b) Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T., 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference to Kerala**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-449

b) Chandrasekharan,K., 1992. **Prevalence of infectious diseases in elephants in Kerala and their treatment**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant

To Drug Monograph Index To Ophthalmic Product Index

held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 148-155

c) 3-4 mg/kg orally for strongylosis, Chandrasekharan,K., Cheeran,J.V., Nair,K.N.M., Ramanujam,K.N., and Radhakrishnan,K. 1982. **Comparative efficacy of 6 anti-helminthics against strongylosis in elephants**. Kerala Journal of Veterinary Science 13:15-20 **Summary:** Anthelmintic efficacy of six drugs was compared under field conditions against strongylosis in elephants. Mebendazole at 3 and 4 mg/kg, Levamisole 3 mg/kg and Morantel tartrate 5 mg/kg were proved to be 100% effective. Mebendazole at 2 mg/kg and 2.5 mg/kg, Thiabendazole at 32 mg/kg. Bephenium hydroxynaphthoate at 25 mg/kg and Disophenol at 3 mg/kg were found to be effective only in 79.1 to 92.2 %, 88.1 to 100%, 84.6 to 95.3 %, 85.9 to 100% and 68.3 to 84 % cases respectively.

## MECLOFENAMIC ACID

**Chemistry** - An anthranilic acid derivative (fenamate), meclofenamic acid is a white, crystalline powder that is practically insoluble in water. The sodium salt of meclofenamic acid is available commercially for human use. It is freely soluble in water.

**Storage/Stability/Compatibility** - Should be stored in tight, light-resistant packaging at temperatures below 30°C (86°F).

**Pharmacology** - Meclofenamic acid exhibits pharmacologic actions similar to those of aspirin. It is a potent inhibitor of cyclooxygenase, thereby inhibiting the release of prostaglandins. Like aspirin, meclofenamic acid (sodium salt administered IV) has been demonstrated to reduce the cardiovascular and respiratory effects of experimentally induced anaphylaxis in ponies and calves by its antagonistic effects at high concentrations on histamine, kinins, and prostaglandins.

It also has a transient effect on platelet aggregation, but unlike aspirin, does not appear to affect bleeding times.

**Pharmacokinetics** - Meclofenamic acid is reported to be well absorbed following oral administration, with measurable plasma levels being reached in 30 minutes and peak levels in 1-4 hours.

In studies done with monkeys, highest meclofenamic acid levels were detected in the plasma, liver, and kidneys. Lower levels were detected in skeletal muscle, fat, spleen, heart, and brain.
At plasma levels of 1 micrograms/ml, the drug was 99.8% bound to albumin. It rapidly crosses the placenta, but it is unknown whether it is distributed into milk.

The plasma half-life has been reported to range from 1-8 hours in horses. Therapeutic efficacy does not seem to be closely related with blood levels, however, as the onset of action may take 36-96 hours and significant efficacy may be seen for days following a dose.

Meclofenamic acid is metabolized in the liver primarily by oxidation to an active hydroxymethyl metabolite which may be further oxidized to an inactive metabolite (carboxyl). In humans, meclofenamic acid and its metabolites are then excreted by the kidneys (approx. 70% within 7 days) or eliminated with the feces (20-30%). In horses, meclofenamic acid can be detected in the urine for at least 96 hours following the final dose.

**Uses/Indications** - Meclofenamic acid is used clinically in dogs for the symptomatic relief of symptoms associated with chronic inflammatory disease of the musculoskeletal system; often in an attempt to improve mobility in animals with hip dysplasia or chronic osteoarthritis.

To Drug Monograph Index To Ophthalmic Product Index

In horses, it is indicated for the “oral treatment of acute or chronic inflammatory diseases involving the musculoskeletal system...” (Package Insert; *Arquel*®—Parke-Davis). Meclofenamic acid has also been used for the treatment of laminitis, with varying degrees of success.

**Contraindications/Precautions** - The manufacturer states that meclofenamic acid is contraindicated in animals with “active gastrointestinal, hepatic or renal diseases” (Package Insert; *Arquel*®—Parke-Davis). Additionally, meclofenamic acid is contraindicated in patients demonstrating previous hypersensitivity reactions to it or salicylates. It is relatively contraindicated in patients with active or historical hemorrhagic disorders, or bronchospastic disease. Because meclofenamic acid is highly bound to plasma proteins, patients with hypoproteinemia may require lower dosages to prevent symptoms of toxicity.

Meclofenamic acid has been shown to delay parturition in some species and therefore should be avoided during the last stages of pregnancy. It has caused teratogenic effects (minor skeletal abnormalities, delayed ossification) in rodents. Some preliminary studies have shown no effects with regard to either mare or stallion reproductive performance and no gross defects were seen in foals born to mares who received meclofenamic acid during pregnancy. It should, nevertheless, be used in pregnancy only when the potential benefits outweigh the potential risks of therapy.

**Adverse Effects/Warnings** - Adverse reactions are reported to be fairly uncommon in horses. However, hematologic changes (decreased hematocrit/PCV) and GI effects (buccal erosions, diarrhea, colic, anorexia, changes in stool consistency) have been reported. The diarrheal and colic reactions may be more likely in horses that have a heavy infestation of bots (*Gasterophilus* sp.) With chronic therapy, decreases in plasma protein concentrations may occur.

In dogs, vomiting, decreased hemoglobin, leukocytosis, tarry stools, and small intestinal ulcers have all been reported following therapy at usual effective doses. Clients should be counseled with regard to these potential adverse effects and instructed to monitor their animal carefully for symptoms associated with them.

In humans, NSAIDs have caused hepatotoxicity and it is recommended that human patients receiving chronic meclofenamate sodium therapy undergo occasional liver function tests. Although it does not appear that this adverse reaction is of major concern in either dogs or horses, the potential for hepatotoxicity does exist.

**Overdosage** - There is very limited information regarding acute overdoses of this drug in humans and no information was located regarding overdoses in domestic animals. Following an acute, massive overdose in humans, generalized CNS stimulation initially occurs, with seizures possible. After this initial phase, acute renal failure may occur with secondary azotemia and anuria.

Treatment should follow standard overdose procedures (empty gut following oral ingestion, etc.). Supportive treatment should be instituted as necessary and IV diazepam used to help control seizures. Because meclofenamic acid may cause renal effects, monitor electrolyte and fluid balance carefully and manage renal failure using established guidelines.

**Drug Interactions** - Because meclofenamic acid is highly bound to plasma proteins and may displace other highly bound drugs, increased serum levels and duration of actions of **phenytoin, valproic acid, oral anticoagulants**, other **anti-inflammatory agents, salicylates, sulfonamides**, and the **sulfonylurea antidiabetic agents** can occur. If meclofenamic acid is used concurrently with **warfarin**, enhanced hypoprothrombinemic effects may transpire.
When **aspirin** is used concurrently with meclofenamic acid, plasma levels of meclofenamic acid may decrease as well as a likelihood of increased GI adverse effects (blood loss) developing. Concomitant administration of aspirin with meclofenamic acid is not recommended.

To Drug Monograph Index  To Ophthalmic Product Index

**Doses** -
**Horses**:

a) 2.2 mg/kg PO once daily for 5-7 days, this equates to two 500 mg packets per 454 kg (1000 lb.) animal daily. If treatment is desired past the 7 days recommended, decrease the dosage and increase the dosing interval to obtain the lowest effective dose. The package contents may be added to the daily grain feed ration, a moist feed with molasses added will help to prevent separation of the granules from the feed. (Package Insert; *Arquel*®, Parke-Davis, 1981)
b) 2.2 mg/kg PO q12h (Jenkins 1987)

**Monitoring Parameters** -

1) Analgesic/anti-inflammatory efficacy
2) GI: appetite, feces (occult blood, diarrhea)
3) PCV (packed cell volume), hematocrit if indicated or on chronic therapy
4) WBC's if indicated or on chronic therapy

**Client Information/FDA Approval Status** - Notify veterinarian if symptoms of GI distress (anorexia, vomiting in dogs, diarrhea, black feces or blood in stool) occur or if the animal becomes depressed. Meclofenamic acid is approved for use in dogs (see note below regarding available dosage forms) and horses (not intended for food). Meclofenamic acid is a veterinary prescription (legend) drug.

**Dosage Forms/Preparations** -

**Veterinary-Approved Products:**

Meclofenamic acid 5% granules in 10 gram packets (500 mg meclofenamic acid/10 gram packet) & scored 10 mg & 20 mg tablets; *Arquel*® (Fort Dodge)

## MEDETOMIDINE HCL

**Chemistry/Storage/Stability/Compatibility** - An alpha2-adrenergic agonist, medetomidine occurs as a white or almost white crystalline substance. It is soluble in water. While the compound exists as two stereoisomers, only the D-isomer is active.
The commercially available injection should be stored at room temperature (15-30°C) and protected from freezing.

**Pharmacology** - An alpha adrenergic receptor, medetomidine has an $alpha_2$:$alpha_1$ selectivity factor of 1620, and when compared to xylazine is reportedly 10X more specific for $alpha_2$ receptors versus $alpha_1$ receptors. The pharmacologic effects of medetomidine include: depression of CNS (sedation), GI (decreased secretions, varying affects on intestinal muscle tone) and endocrine functions, peripheral and cardiac vasoconstriction, bradycardia, respiratory depression, diuresis, hypothermia, analgesia, muscle relaxation, blanched or cyanotic mucous membranes and anxiolytic effects. Effects on blood pressure are variable.

**Uses/Indications** - Medetomidine is labeled for use as a sedative and analgesic in dogs over 12 weeks of age to facilitate clinical examinations and procedures, minor surgical procedures not requiring muscle relaxation, and minor dental procedures not requiring intubation. The manufacturer recommends the IV route of administration for dental procedures.
Medetomidine has also been used in cats, primarily in Europe. But there is apparently much less data available to evaluate its use; caution is advised.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacokinetics** - After IV or IM injection, onset of effect is rapid (5 mins. for IV; 10-15 mins. for IM). After subQ injection, responses are unreliable and this method of administration cannot be recommended. The drug is absorbed via the oral mucosa when administered sublingually in dogs, but efficacy at a given dose may be less than IM dosing.

**Contraindications/Precautions/Reproductive Safety -** The label states that medetomidine is contraindicated in dogs having the following conditions: cardiac disease, respiratory disorders, liver or kidney diseases, shock, severe debilitation, or dogs stressed due to heat, cold or fatigue.
Dogs that are extremely agitated or excited may have a decreased response to medetomidine, the manufacturer suggests allowing these dogs to rest quietly before administration of the drug.
Dogs not responding to medetomidine should not be re-dosed. Use in very young or older dogs should be done with caution.

The drug is not recommended to be used in pregnant dogs or those used for breeding purposes as safety data for use during pregnancy is insufficient; therefore use only when the benefits clearly outweigh the drug's benefits.

**Adverse Effects/Warnings** - The adverse effects reported with medetomidine are basically an extension of its pharmacologic effects including bradycardia, occasional AV blocks, decreased respiration, hypothermia, urination, vomiting, hyperglycemia, and pain on injection (IM). Rare effects have also been reported, including prolonged sedation, paradoxical excitation, hypersensitivity, apnea and death from circulatory failure.

**Overdosage** - Single doses of up to 5X (IV) and 10X (IM) were tolerated in dogs, but adverse effects can occur (see above). Death has occurred rarely in dogs (1 in 40,000) receiving 2X doses.

Because of the potential of additional adverse effects occurring (heart block, PVC's or tachycardia), treatment of medetomidine-induced bradycardia with anticholinergic agents (atropine or glycopyrrolate) is often not recommended. Atipamezole is probably a safer choice to treat any medetomidine-induced effect.

**Drug Interactions** - Note: Before attempting combination therapy with medetomidine, it is strongly advised to access references from veterinary anesthesiologists familiar with the use of this product.

When **propofol** is used after medetomidine, hypoxemia may occur. Dosage adjustments may be required along with adequate monitoring. Enhancement of sedation and analgesia may occur when medetomidine is used concurrently with **fentanyl**, **butorphanol** or **meperidine**, but adverse effects may be pronounced as well. Reduced dosages and monitoring is advised if contemplating combination therapy. The use of **atropine** or **glycopyrrolate** to prevent or treat
medetomidine-caused bradycardia is controversial as tachycardia and hypertension may result.

**Doses -**

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

a) 3-5 µg/kg IM. Sarma,B., Pathak,S.C., and Sarma,K.K. 2002. **Medetomidine a novel immobilizing agent for the elephant (Elephas maximus)**. Res Vet Sci 73:(3):315-317

To Drug Monograph Index To Ophthalmic Product Index

**Abstract:** Medetomidine was injected by the intramuscular route at the rates of 3 and 5 micrograms/kg body weight into two groups of Indian elephants (Elephas maximus). Sedation was induced at 6.20 (0.81) and 5.90 (0.60) min respectively after injection. The duration of anaesthesia was 66.20 (10.4) and 134.20 (24.12) min, respectively and recovery occurred at 125.80 (25.23) and 205.89 (29.3) min. The notable signs of sedation exhibited by the elephants were protrusion of penis, complete relaxation of trunk, flaccidity of tail and drooping of the ears with a head down position. During sedation, physiological parameters recorded were bradycardia, decreased respiration and hypothermia.

**Monitoring Parameters** - Level of sedation and analgesia; heart rate; body temperature. Additionally, heart rhythm, blood pressure, respiration rate and pulse oximetry should be considered, particularly in higher risk patients if the drug is to be used.

**Client Information -** This drug should be administered and monitored by veterinary professionals only. Clients should be made aware of the potential adverse effects associated with its use, particularly in dogs at risk (older, preexisting conditions).

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products**:

Medetomidine HCl for Injection 1 mg/ml in 10 ml multidose vials; *Domitor*® (Pfizer); (Rx) Approved for use in dogs.

## MEPERIDINE HCL

**Chemistry** - A synthetic opiate analgesic, meperidine HCl is a fine, white, crystalline, odorless powder that is very soluble in water, sparingly soluble in ether and soluble in alcohol. It has a $pK_a$ of 7.7 - 8.15 and a melting range of 186 - 189°. The pH of the commercially available injectable preparation is between 3.5 and 6. Meperidine may also be known as: Pethidine HCl; Dolantin, Dolantol, Eudolat, or Isonipecaine.

**Storage/Stability/Compatibility** - Meperidine is stable at room temperature. Avoid freezing the injectable solution and protect from light during storage. Meperidine has not exhibited significant sorption to PVC IV bags or tubing in studies to date.

Meperidine is reported to be physically **compatible** with the following fluids and drugs: sodium chloride 0.45 & 0.9%, Ringer's injection, lactated Ringers injection, dextrose 2.5, 5 & 10% for injection, dextrose/ saline combinations, dextrose/Ringers lactated solutions, atropine, benzquinamide, butorphanol, chlorpromazine, dimenhydrinate, diphenhydramine HCl, dobutamine, droperidol, fentanyl citrate, glycopyrrolate, metoclopramide, pentazocine lactate, promazine HCl, succinylcholine and verpamil HCl.

Meperidine is reported to be physically **incompatible** with the following agents: aminophylline, amobarbital sodium, heparin sodium, hydrocortisone sodium succinate, methicillin, methylprednisolone sodium succinate, morphine sulfate, nitrofurantoin sodium, oxytetracycline HCl, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, sodium iodide, tetracycline HCl, thiopental sodium and thiamylal sodium.

**Pharmacology** - Refer to the monograph: Narcotic (opiate) Analgesic Agonists, Pharmacology of, for more information.

Meperidine is primarily a *Mu* agonist. It is approximately 1/8th as potent as morphine, but produces equivalent respiratory depression at equi-analgesic doses as morphine. Like morphine, it can cause histamine release. It does not have antitussive activity at doses lower than those causing analgesia. Meperidine is the only used opioid that has vagolytic and negative inotropic properties at clinically used

doses. One study in ponies demonstrated changes in jejunal activity after meperidine administration, but no effects on transit time or colonic electrical activity were noted.

**Pharmacokinetics** - Although generally well absorbed orally, a marked first-pass effect limits the oral effectiveness of these agents (codeine and oxycodone are exceptions). After injection by IM or subcutaneous routes the peak analgesic effects occur between 30 minutes and one hour, with the IM route having a slightly faster onset. Duration of action is variable with effects generally lasting from 1-6 hours in most species. In dogs and cats a duration of action of only 1-2 hours is generally seen at clinically used doses. The drug is metabolized primarily in the liver (mostly hydrolysis with some conjugation) and approximately 5% is excreted unchanged in the urine.

**Uses/Indications** - Although no product is licensed in the United States for veterinary use, this agent has been used as an analgesic in several different species. It has been used as sedative/analgesic in small animals for both post-operative pain and for medical conditions such as acute pancreatitis and thermal burns. It is occasionally used in equine medicine in the treatment of colic and in other large animal species for pain control.

**Contraindications/Precautions** - All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's disease), and in geriatric or severely debilitated patients. Meperidine is contraindicated in cases where the patient is hypersensitive to narcotic analgesics, or in patients taking monamine oxidase inhibitors (MAOIs). It is also contraindicated in patients with diarrhea caused by a toxic ingestion until the toxin is eliminated from the GI tract.

Meperidine should be used with caution in patients with head injuries or increased intracranial pressure and acute abdominal conditions (*e.g.,* colic) as it may obscure the diagnosis or clinical course of these conditions. It should be used with extreme caution in patients suffering from respiratory disease or from acute respiratory dysfunction (*e.g.,* pulmonary edema secondary to smoke inhalation).

Opiate analgesics are also contraindicated in patients who have been stung by the scorpion species *Centruroides sculpturatus* Ewing and *C. gertschi* Stahnke as they may potentiate these venoms.

**Adverse Effects/Warnings** - Meperidine may be irritating when administered subcutaneously and must be given very slowly IV or it may cause severe hypotension. At usual doses, the primary concern is the effect the opioids have on respiratory function. Decreased tidal volume, depressed cough reflex and the drying of respiratory secretions may all have a detrimental effect on a susceptible patient. Bronchoconstriction following IV doses has been noted in dogs. The CNS depressant effects of the these drugs may encumber the abilities of working animals. Gastrointestinal effects may include: nausea, vomiting, and decreased intestinal persitalsis. In dogs, meperidine causes mydriasis (unlike morphine). If given orally, the drug may be irritating to the buccal mucosa and cause salivation; this is of particular concern in cats. Chronic administration can lead to physical dependence.

In horses undergoing general anesthesia, meperidine has been associated with a reaction that manifests as tachycardia with PVC's, profuse sweating, and hyperpnea.

**Overdosage** - Overdosage may produce profound respiratory and/or CNS depression in most species. Other effects can include cardiovascular collapse, hypothermia, and skeletal muscle hypotonia. Some species (especially cats) may demonstrate CNS excitability (hyperreflexia, tremors) and seizures at doses greater than 20 mg/kg. Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated, and animals should be closely observed as naloxone's effects may diminish before subtoxic levels of meperidine are attained. Mechanical respiratory support should also be considered in cases of severe respiratory depression.

To Drug Monograph Index To Ophthalmic Product Index

Pentobarbital has been suggested as a treatment for CNS excitement and seizures in cats. Caution must be used as barbiturates and narcotics can have additive effects on respiratory depression.

**Drug Interactions** - Other **CNS depressants** (*e.g.,* anesthetic agents, antihis tamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with meperidine. Meperidine is contraindicated in patients receiving **monamine oxidase (MOA) inhibitors** (rarely used in veterinary medicine) for at least 14 days after receiving MOA inhibitors in humans. Some human patients have exhibited signs of opiate overdose after receiving therapeutic doses of meperidine while on these agents.

**Laboratory Interactions**- Plasma **amylase** and **lipase** values may be increased for up to 24 hours following administration of opiate analgesics as they may increase biliary tract pressure.

**Doses** -
**Horses**:

As an analgesic:

a) 2.2 - 4 mg/kg IM or 0.2-0.4 mg/kg IV (may cause excitement) (Robinson 1987)
b) 2 - 4 mg/kg IM or IV (may cause excitement and hypotension with IV use) (Jenkins 1987)
c) 500 mg IV (slowly, CNS excitement may occur) or 1000 mg IM (Booth 1988a)
d) 0.2 - 0.4 mg/kg IV (Muir 1987)

Note: Narcotics (meperidine included) may cause CNS excitement in the horse. Some recommend pretreatment with acepromazine (0.02 - 0.04 mg/kg IV), or xylazine (0.3 - 0.5 mg/kg IV) to reduce the behavioral changes these drugs can cause.
Warning: Narcotic analgesics can mask the behavioral and cardiovascular symptoms associated with mild colic.

**Elephants:**

a) For analgesia and sedation: 75-150 mg/100 kg body weight four times a day. Schmidt,M.J., 1986. **Proboscidea (Elephants)**. In: Fowler,M.E. (Editor), Zoo and wild animal medicine. W.B. Saunders, Philadelphia,PA, USA pp. 884-923

**Monitoring Parameters** -1) Respiratory rate/depth; 2) CNS level of depression/excitation;
3) Blood pressure if possible and indicated (especially with IV use); 4) Analgesic activity

**Client Information** - Oral dosage forms may cause mouth irritation. When given parenterally, this agent should be used in an inpatient setting or with direct professional supervision.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Meperidine HCl for Injection: 50 mg/ml in 30 ml multi-dose vials (MDV); 100 mg/ml in 20 ml MDV; 10 mg/ml in 5 & 10 ml single-dose vial & 30 ml vials for IV infusion only; 25 mg, 50 mg, 75 mg & 100 mg in 1 ml amps and vials, 1 ml fill in 2 ml Tubex, 0.5 ml Uni-Nest amps, 0.5 ml Uni-Amps and 2 ml Carpuject

Meperidine HCl for oral use: 50 mg, 100 mg tablets, 10 mg/ml oral syrup in 500 ml and pt.

A common trade name is: *Demerol HCl*® (Winthrop-Breon)

**Note:** Meperidine is listed as a **Class-II** controlled substance and all products require a prescription. Very accurate record keeping is required as to use and disposition of stock.

To Drug Monograph Index To Ophthalmic Product Index

## METHOCARBAMOL

**Chemistry** - A centrally acting muscle relaxant related structurally to guaifenesin, methocarbamol occurs as a fine, white powder with a characteristic odor. In water, it has a solubility 25 mg/ml. The pH of commercial injection is approximately 4-5.

**Storage/Stability/Compatibility** - Methocarbamol tablets should be stored at room temperature in tight containers; the injection should be stored at room temperature and not frozen. Solutions prepared for IV infusion should not be refrigerated as a precipitate may form. Because a haze or precipitate may form, all diluted intravenous solutions should be physically inspected before administration.

**Pharmacology** - Methocarbamol's exact mechanism of causing skeletal muscle relaxation is unknown. It is thought to work centrally, perhaps by general depressant effects. It has no direct relaxant effects on striated muscle, nerve fibers, or the motor endplate. It will not directly relax contracted skeletal muscles. The drug has a secondary sedative effect.

**Uses/Indications** - In dogs and cats, methocarbamol is indicated (FDA approved) "as adjunctive therapy of acute inflammatory and traumatic conditions of the skeletal muscle and to reduce muscular spasms." In horses, intravenous use is indicated (FDA approved) "as adjunctive therapy of acute inflammatory and traumatic conditions of the skeletal muscle to reduce muscular spasms, and effect striated muscle relaxation." (Package insert; *Robaxin*® *-V* - Robins)

**Pharmacokinetics** - Limited pharmacokinetic data is available in veterinary species. In humans, methocarbamol ha an onset of action of about 30 minutes after oral administration. Peak levels occur approximately 2 hours after dosing. Serum half-life is about 1-2 hours. The drug is metabolized and the inactive metabolites are excreted into the urine and the feces (small amounts).

In horses, plasma clearances appear to be dose dependent after IV administration (Muir, Sams, and Ashcraft 1984), lower clearances were measured after higher doses were given. The serum half-life of methocarbamol in the horse is approximately 60-70 minutes. Guaifenesin is a minor metabolite of methocarbamol, but because of very low concentrations, it probably has no clinical effect in the horse.

**Contraindications/Precautions** - Because the injectable product contains polyethylene glycol 300, the manufacturer lists known or suspected renal pathology as a contraindication to injectable methocarbamol therapy. Polyethylene glycol 300 has been noted to increase preexisting acidosis and urea retention in humans with renal impairment.

Methocarbamol should be used with caution during pregnancy as studies demonstrating its safety during pregnancy are lacking. Methocarbamol should not be used in patients hypersensitive to it or in animals to be used for food purposes.
Do not administer subcutaneously and avoid extravasation. Do not exceed 2 ml per minute when injecting IV in dogs and cats.

**Adverse Effects/Warnings** - Side effects can include sedation, salivation, emesis, lethargy, weakness and ataxia in dogs and cats. Sedation and ataxia are possible in horses. Because of its CNS depressant effects, methocarbamol may impair the abilities of working animals.

**Overdosage** - Overdosage is generally characterized by CNS depressant effects (loss of righting reflex, prostration). Excessive doses in dogs and cats may be represented by emesis, salivation, weakness and ataxia. If the overdose is after oral administration, emptying the gut may be indicated if the overdose was

To Drug Monograph Index To Ophthalmic Product Index

recent. Do not induce emesis if the patient's continued consciousness is not assured. Other symptoms should be treated if severe and in a supportive manner.

**Drug Interactions** - Because methocarbamol is a CNS depressant, additive depression may occur when given with other **CNS depressant agents**.
One patient (human) with myasthenia gravis and taking **pyridostigmine**, developed severe weakness after receiving methocarbamol.

**Doses** -
**Horses**:

a) For moderate conditions: 4.4 - 22 mg/kg IV to effect; for severe conditions: 22 - 55 mg/kg IV (Package insert, *Robaxin®-V* — Robins)
b) 15 - 25 mg/kg IV by slow infusion (Robinson 1987)
c) To give orally: Use 2-3 times the recommended IV dose. (Cunningham, Fisher et al. 1992)

**Monitoring Parameters** -

1) Level of muscle relaxation/sedation

**Client Information** - Animal's urine color may darken, but need not be of concern.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Methocarbamol Tablets 500 mg; *Robaxin®-V* (Fort Dodge); (Rx) Approved for use in dogs and cats.

Methocarbamol Injection 100 mg/ml in vials of 20 ml and 100 ml; *Robaxin®-V* (Fort Dodge); (Rx) Approved for use in dogs, cats, and horses not intended for food.

**Human-Approved Products**:

Methocarbamol Tablets 500 mg, 750 mg; *Robaxin®* (Robins); *Robaxin-750®* (Robins); Generic (Rx)

Methocarbamol Injection 100 mg/ml in 10 ml vials; *Robaxin®* (Robins); generic (Rx)

## METHYLPREDNISOLONE
## METHYLPREDNISOLONE ACETATE
## METHYLPREDNISOLONE SODIUM SUCCINATE

Note: For more information refer to the monograph: Glucocorticoids, General Information or to the manufacturer's product information.

**Chemistry** - Also known as 6-alpha-methylprednislone, methylprednisolone is a synthetically produced glucocorticoid. Both the free alcohol and the acetate ester occur as odorless, white or practically white, crystalline powder. They are practically insoluble in water and sparingly soluble in alcohol.

Methylprednisolone sodium succinate occurs as an odorless, white or nearly white, hygroscopic, amorphous solid. It is very soluble in both water and alcohol.

**Storage/Stability/Compatibility** - Commercially available products of methylprednisolone should be stored at room temperature (15-30°C); avoid freezing the acetate injection. After reconstituting the sodium succinate injection, store at room temperature and use within 48 hours; only use solutions that are clear.

To Drug Monograph Index To Ophthalmic Product Index

Methylprednisolone sodium succinate injection is reportedly **compatible** with the following fluids and drugs: amino acids 4.25%/dextrose 25%, amphotericin B (limited amounts), chloramphenicol sodium succinate, cimetidine HCl, clindamycin phosphate, dopamine HCl, heparin sodium, metoclopramide, norepinephrine bitartrate, penicillin G potassium, sodium iodide/aminophylline, and verapamil.

The following drugs and fluids have either been reported to be **incompatible** with methylprednisolone sodium succinate, **compatible dependent upon concentration, or data conflicts**: $D_5$/half normal saline, $D_5$ normal saline (80 mg/l reported compatible), $D_5W$ (up to 5 grams/L reported compatible), Lactated Ringer's (up to 80 mg/L reported compatible), normal saline (data conflicts; some reports of up to 60 grams/liter compatible), calcium gluconate, cephalothin sodium (up to 500 mg/L in D5W or NS compatible), glycopyrrolate, insulin, metaraminol bitartrate, nafcillin sodium, penicillin G sodium and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Contraindications/Precautions** - The manufacturer (Upjohn Veterinary) states that the drug (tablets) should not be used in dogs or cats "in viral infections, ...animals with arrested tuberculosis, peptic ulcer, acute psychoses, corneal ulcer, and Cushinoid syndrome. The presence of diabetes, osteoporosis, chronic psychotic reactions, predisposition to thrombophlebitis, hypertension, CHF, renal insufficiency, and active tuberculosis necessitates carefully controlled use."

The injectable acetate product is contraindicated as outlined above when used systemically. When injected intrasynovially, intratendinously, or by other local means, it is contraindicated in the "presence of acute local infections."

**Doses -**
**Horses**:

As an antiinflammatory (glucocorticoid effects):

a) Methylprednisolone: 0.5 mg/kg PO; Methylprednisolone sodium succinate: 0.5 mg/kg IV or IM (Robinson 1987)
b) For labeled uses: Methylprednisolone acetate 200 mg IM repeated as necessary (Package insert; *Depo-Medrol*®—Upjohn) The manufacturer has specific directions for use of the drug intrasynovially. It is recommended to refer directly to the package insert for more information.

For shock:

a) Methylprednisolone sodium succinate: 10 - 20 mg/kg IV (Robinson 1987)

**Dosage Forms/Preparations/Approval Status/Withdrawal Times**-

**Veterinary-Approved Products**: A 10 ppb tolerance has been established for methylprednisolone in milk.

Methylprednisolone Tablets 1 mg, 2 mg

*Medrol*® (Upjohn), generic; (Rx) Approved for use in dogs and cats.

Methylprednisolone Acetate Injection 20 mg/ml, 40 mg/ml

*Depo-Medrol*® (Upjohn), generic; (Rx) Approved for use in dogs, cats and horses.

**Human-Approved Products**:

Methylprednisolone Tablets 2 mg, 4 mg, 8 mg, 16 mg, 24 mg, 32 mg; *Medrol*® (Upjohn), generic; (Rx)

Methylprednisolone Acetate for Injection 20 mg/ml, 40 mg/ml, 80 mg/ml in 1, 5 & 10 ml vials; *Depo-Medrol*® (Upjohn) many other trade names and generically-labeled products are available; (Rx)

To Drug Monograph Index To Ophthalmic Product Index

Methylprednisolone Sodium Succinate Powder for Injection: 40 mg/vial; 125 mg/vial; 500 mg/vial; 1000 mg/vial (62.5 mg/ml after reconstitution), 2000 mg/vial; *Solu-Medrol*® (Upjohn), *A-methaPred*® (Abbott), generic; (Rx)

## METOCLOPRAMIDE HCL

**Chemistry** - A derivative of para-aminobenzoic acid, metoclopramide HCl occurs as an odorless, white, crystalline powder with $pK_a$s of 0.6 and 9.3. One gram is approximately soluble in 0.7 ml of water or 3 ml of alcohol. The injectable product has a pH of 3-6.5.

**Storage/Stability/Compatibility** - Metoclopramide is photosensitive and must be stored in light resistant containers. All metoclopramide products should be stored at room temperature. Metoclopramide tablets should be kept in tight containers.
The injection is reportedly **stable** in solutions of a pH range of 2-9 and with the following IV solutions: $D_5W$, 0.9% sodium chloride, $D_5$-1/2 normal saline, Ringer's, and lactated Ringer's injection.

The following drugs have been stated to be **compatible** with metoclopramide for at least 24 hours: aminophylline, ascorbic acid, atropine sulfate, benztropine mesylate, chlorpromazine HCl, cimetidine HCl, clindamycin phosphate, cyclophosphamide, cytarabine, dexamethasone sodium phosphate, dimenhydrinate, diphenhydramine HCl, doxorubicin HCl, droperidol, fentanyl citrate, heparin sodium, hydrocortisone sodium phosphate, hydroxyzine HCl, insulin (regular), lidocaine HCl, magnesium sulfate, mannitol, meperidine HCl, methylprednisolone sodium succinate, morphine sulfate, multivitamin infusion (MVI), pentazocine lactate, potassium acetate/chloride/phosphate, prochlorperazine edisylate, TPN solution (25% dextrose w/4.25% *Travasol*® w/ or w/o electrolytes), verapamil and vitamin B-complex w/vitamin C.

Metoclopramide is reported to be **incompatible** with the following drugs: ampicillin sodium, calcium gluconate, cephalothin sodium, chloramphenicol sodium succinate, cisplatin, erythromycin lactobionate, methotrexate sodium, penicillin G potassium, sodium bicarbonate, and tetracycline. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - The primary pharmacologic effects of metoclopramide are associated with the GI tract and the CNS. In the GI tract, metoclopramide stimulates motility of the upper GI without stimulating gastric, pancreatic or biliary secretions. While the exact mechanisms for these actions are unknown, it appears that metoclopramide sensitizes upper GI smooth muscle to the effects of acetylcholine. Intact vagal innervation is not necessary for enhanced motility, but anticholinergic drugs will negate metoclopramide's effects. Gastrointestinal effects seen include increased tone and amplitude of gastric contractions, relaxed pyloric sphincter, and increased duodenal and jejunal peristalsis. Gastric emptying and intestinal transit times can be significantly reduced. There is little or no effect on colon motility. Additionally, metoclopramide will increase lower esophageal sphincter pressure and prevent or reduce gastroesophageal reflux. The above actions evidently give metoclopramide its local antiemetic effects.

In the CNS, metoclopramide apparently antagonizes dopamine at the receptor sites. This action can explain its sedative, central anti-emetic (blocks dopamine in the chemo-receptor trigger zone), extrapyrimidal, and prolactin secretion stimulation effects.

**Uses/Indications -** Metoclopramide has been used in veterinary species for both its GI stimulatory and antiemetic properties. It has been used clinically for gastric stasis disorders, gastroesophageal reflux, to allow intubation of the small intestine, as a general antiemetic (for parvovirus, uremic gastritis, etc.) and as an antiemetic to prevent or treat chemotherapy induced vomiting.

To Drug Monograph Index  To Ophthalmic Product Index

**Pharmacokinetics** - Metoclopramide is absorbed well after oral administration, but a significant first-pass effect in some human patients may reduce systemic bioavailability to 30%. There apparently is a great deal of interpatient variation with this effect. Bioavailability after intramuscular administration has been measured to be 74-96%. After oral dosing, peak plasma levels generally occur within 2 hours.

The drug is well distributed in the body and enters the CNS. Metoclopramide is only weakly bound to 13-22% of plasma proteins. The drug also crosses the placenta and enters the milk in concentrations approximately twice those of the plasma.

Metoclopramide is primarily excreted in the urine in humans. Approximately 20-25% of the drug is excreted unchanged in the urine. The majority of the rest of the drug is metabolized to glucuronidated or sulfated conjugate forms and then excreted in the urine. Approximately 5% is excreted in the feces. The half-life of metoclopramide in the dog has been reported to be approximately 90 minutes.

**Contraindications/Precautions** - Metoclopramide is contraindicated in patients with GI hemorrhage, obstruction or perforation and in those hypersensitive to it. It is relatively contraindicated in patients with seizure disorders. In patients with pheochromocytoma, metoclopramide may induce a hypertensive crisis.

**Adverse Effects/Warnings** - In dogs, the most common (although infrequent) adverse reactions seen are changes in mentition and behavior. Cats may exhibit signs of frenzied behavior or disorientation. Both species can develop constipation while taking this medication.

In adult horses, IV metoclopramide administration has been associated with the development of severe CNS effects. Alternating periods of sedation and excitement, behavioral changes and abdominal pain have been noted. These effects are less common in foals. Because of the incidence of adverse effects one group of authors (Clark and Becht 1987) does not at the present time recommend its use in adult horses.

Other adverse effects that have been reported in humans and are potentially plausible in animals include extrapyrimidal effects, nausea, diarrhea, transient hypertension and elevated prolactin levels.

**Overdosage** - The oral $LD_{50}$ doses of metoclopramide in mice, rats, and rabbits are 465 mg/kg, 760 mg/kg and 870 mg/kg, respectively. Because of the high dosages required for lethality, it is unlikely an oral overdose will cause death in a veterinary patient. Likely symptoms of overdosage include sedation, ataxia, agitation, extrapyramidal effects, nausea, vomiting and constipation.

There is no specific antidotal therapy for metoclopramide intoxication. If an oral ingestion was recent, the stomach should be emptied using standard protocols. Anticholinergic agents (diphenhydramine, benztropine, etc.) that enter the CNS may be helpful in controlling extrapyrimidal effects. Peritoneal dialysis or hemodialysis is thought not to be effective in enhancing the removal of the drug.

**Drug Interactions** - **Atropine** (and related anticholinergic compounds) and **narcotic analgesics** may negate the GI motility effects of metoclopramide. The GI stimulatory effects of metoclopramide may affect the absorption of many drugs. Drugs that dissolve, disintegrate and/or are absorbed in the stomach (*e.g.,* **digoxin**) may be absorbed less. Due to its small particle size, *Lanoxin*® brand of digoxin is apparently unaffected by metoclopramide administration. Metoclopramide may enhance absorption of drugs that are absorbed primarily in the small intestine (*e.g.,* **cimetidine, tetracycline**, **aspirin, & diazepam**). Metoclopramide may accelerate **food absorption** and thereby alter **insulin** doses and/or timing of insulin effects.
**Phenothiazines** (*e.g.,* acepromazine, chlorpromazine, etc.) and **butyrephenones** (*e.g.,* droperidol, azaperone) may potentiate the extrapyramidal effects of metoclopramide. The CNS effects of metoclopramide may be enhanced by other **sedatives, tranquilizers** and **narcotics.**

To Drug Monograph Index To Ophthalmic Product Index

**Doses -**
**Horses**:

To stimulate the gastrointestinal tract in foals:

a) 0.02 - 0.1 mg/kg IM or IV 3 - 4 times a day (Clark and Becht 1987)

**Elephants:**
a) 250-400 mg/elephant IV as an antiemetic; author's clinical experience.
Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

**Monitoring Parameters** -

1) Clinical efficacy and adverse effects

**Client Information** - Contact veterinarian if animal develops symptoms of involuntary movement of eyes, face, or limbs, or develops a rigid posture.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**: All doses expressed in terms of metoclopramide base.

Metoclopramide HCl Tablets 5 mg, 10 mg; *Reglan*® (Robins); *Clopra*® (Quantum); *Maxolon*® (Beecham); *Octamide*® (Adria); *Reclomide*® (Major); Generic; (Rx)

Metoclopramide HCl Oral Solution (syrup) 1 mg/ml in pints, unit-dose (10 ml); *Reglan*® (Robins), Generic; (Rx)

Metoclopramide HCl Injection 5 mg/ml in 2 & 10 ml amps, and 2, 10, 30, 50 & 100 ml vials (some contain preservatives, some are preservative free and labeled for single-use only); *Reglan*® (Robins); *Metoclopramide HCl*® (Quad); Generic; (Rx)

## METRONIDAZOLE PK

**Chemistry** - A synthetic, nitroimidazole antibacterial and antiprotozoal agent, metronidazole occurs as white to pale yellow crystalline powder or crystals with a $pK_a$ of 2.6. It is sparingly soluble in water or alcohol. Metronidazole base is commercially available as tablets or solution for IV injection and metronidazole HCl is available as injectable powder for reconstitution. The hydrochloride is very soluble in water.

**Storage/Stability/Compatibility** - Metronidazole tablets and HCl powder for injection should be stored at temperatures less than 30°C and protected from light. The injection should be protected from light and freezing and stored at room temperature.

Specific recommendations on the reconstitution, dilution, and neutralization of metronidazole HCl powder for injection are detailed in the package insert of the drug and should be referred to if this product is used. Do not use aluminum hub needles to reconstitute or transfer this drug as a reddish-brown discoloration may result in the solution.

To Drug Monograph Index To Ophthalmic Product Index

The following drugs and solutions are reportedly **compatible** with metronidazole ready-to-use solutions for injection: amikacin sulfate, aminophylline, carbenicillin disodium, cefazolin sodium, cefotaxime sodium, cefoxitin sodium, cefuroxime sodium, cephalothin sodium, chloramphenicol sodium succinate, clindamycin phosphate, disopyramide phosphate, gentamicin sulfate, heparin sodium, hydrocortisone sodium succinate, hydromorphone HCl, magnesium sulfate, meperidine HCl, morphine sulfate, moxalactam disodium, multielectrolyte concentrate, multivitamins, netilmicin sulfate, penicillin G sodium, and tobramycin sulfate.

The following drugs and solutions are reportedly **incompatible** (or compatibility data conflicts) with metronidazole ready-to-use solutions for injection: aztreonam, cefamandole naftate and dopamine HCl.

**Pharmacology** - Metronidazole is bactericidal against susceptible bacteria. Its exact mechanism of action is not completely understood, but it is taken up by anaerobic organisms where it is reduced to an unidentified polar compound. It is believed that this compound is responsible for the drug's antimicrobial activity by disrupting DNA and nucleic acid synthesis in the bacteria.

Metronidazole has activity against most obligate anaerobes including *Bacteroides sp*. (including *B. fragilis*), *Fusobacterium*, *Veillonella*, *Clostridium sp.*, peptococcus, and peptostreptococcus. *Actinomyces* is frequently resistant to metronidazole.

Metronidazole is also trichomonacidal and amebicidal in action and acts as a direct amebicide. Its mechanism of action for its antiprotozoal activity is not understood. It has therapeutic activity against *Entamoeba histolytica*, *Trichomonas*, *Giardia*, and *Balantidium coli*. It acts primarily against the trophozoite forms of *Entamoeba* rather than encysted forms.

**Uses/Indications** - Although there are no veterinary-approved metronidazole products, the drug has been used extensively in the treatment of *Giardia* in both dogs and cats. It is also used clinically in small animals for the treatment of other parasites (*Trichomonas* and *Balantidium coli*) as well as treating both enteric and systemic anaerobic infections.
In horses, metronidazole has been used clinically for the treatment of anaerobic infections.

**Pharmacokinetics** - Metronidazole is relatively well absorbed after oral administration. The oral bioavailability in dogs is high, but interpatient variable with ranges from 50-100% reported. The oral bioavailability of the drug in horses averages about 80% (range 57-100%). If given with food, absorption is enhanced in dogs, but delayed in humans. Peak levels occur about one hour after dosing.

Metronidazole is rather lipophilic and is rapidly and widely distributed after absorption. It is distributed to most body tissues and fluids, including to bone, abscesses, the CNS, and seminal fluid. It is less than 20% bound to plasma proteins in humans.

Metronidazole is primarily metabolized in the liver via several pathways. Both the metabolites and unchanged drug are eliminated in the urine and feces. Elimination half-lives of metronidazole in patients with normal renal and hepatic function in various species are reported as: humans 6-8 hours, dogs 4-5 hours, and horses 2.9-4.3 hours.

**Contraindications/Precautions/Reproductive Safety** - Metronidazole is contraindicated in animals hypersensitive to the drug or nitroimidazole derivatives. It has also been recommended not to use the drug in severely debilitated, pregnant or nursing animals. Metronidazole should be used with caution in animals with hepatic dysfunction.

Metronidazole has been implicated as being a teratogen in some laboratory animal studies, but no information is available for dogs and cats. Unless the benefits to the mother outweigh the risks to the fetuses, it should not be used during pregnancy, particularly during the first 3 weeks of gestation.

To Drug Monograph Index  To Ophthalmic Product Index

**Adverse Effects/Warnings** - Adverse effects reported in dogs include neurologic disorders, lethargy, weakness, neutropenias, hepatotoxicity, hematuria, anorexia, nausea, vomiting and diarrhea.

Neurologic toxicity may be manifested after acute high dosages or, more likely, with chronic moderate to high-dose therapy. Symptoms reported are described below in the Overdosage section.

**Overdosage/Acute Toxicity** - Signs of intoxication associated with metronidazole in dogs and cats, include anorexia and/or vomiting, depression, mydriasis, nystagmus, ataxia, head-tilt, deficits of proprioception, joint knuckling, disorientation, tremors, seizures, bradycardia, rigidity and stiffness. These effects may be seen with either acute overdoses or in some animals with chronic therapy when using “recommended” doses.

Acute overdoses should be handled by attempting to limit the absorption of the drug using standard protocols. Extreme caution should be used before attempting to induce vomiting in patients demonstrating CNS effects or aspiration may result. If acute toxicity is seen after chronic therapy, the drug should be discontinued and the patient treated supportively and symptomatically. Neurologic symptoms may require several days before showing signs of resolving.

**Drug Interactions** - Metronidazole may prolong the PT in patients taking **warfarin** or other coumarin anticoagulants. Avoid concurrent use if possible; otherwise, intensify monitoring.
**Phenobarbital or phenytoin** may increase the metabolism of metronidazole, thereby decreasing blood levels. **Cimetidine** may decrease the metabolism of metronidazole and increase the likelihood of dose-related side effects occurring. **Alcohol** may induce a disulfiram-like (nausea, vomiting, cramps, etc.) reaction when given with metronidazole.

**Drug/Laboratory Interactions** - Metronidazole causes falsely decreased readings of **AST** (SGOT) and **ALT** (SGPT) when determined using methods measuring decreases in ultraviolet absorbance when NADH is reduced to NAD.

**Doses -**

**Horses**:

For susceptible anaerobic infections:

a) 15 - 25 mg/kg PO q6h (Sweeney et al. 1986)
b) 20 - 25 mg/kg PO q12h as crushed tablets in an aqueous suspension. (Baggot, Wilson, and Hietela 1988)

**Elephants:**

a) 15 mg/kg per rectum. Gulland,F.M. and Carwardine,P.C. 1987. **Plasma metronidazole levels in an Indian elephant (Elephas maximus) after rectal administration.** Veterinary Record 120:440
**Summary:** A female Asian elephant was treated for a mixed aerobic and anaerobic tusk sulcus infection with 15/kg metronidazole administered rectally once daily for 10 days using 1 gram suppositories. Plasma metronidazole levels of 4.4, 7.7, and 6.6 ug/ml were achieved at three, six, and 24 hours respectively. These levels are similar to those obtained in man following therapeutic use of metronidazole suppositories. Plasma minimum inhibitory concentrations of metronidazole for the majority of human pathogens including Bacteriods species, Fusobacter species, and Clostridia species are in the range of 0.3 to 3 ug/ml. After seven days of antibiotic therapy and daily flushing of the gingival sulcus with dilute hydrogen peroxide through a 4FG plastic urinary catheter, clinical recovery was achieved. No digestive disturbances were noted.

b) **PHARMACOKINETICS OF A SINGLE DOSE OF METRONIDAZOLE AFTER RECTAL ADMINISTRATION IN CAPTIVE ASIAN ELEPHANTS (ELEPHAS MAXIMUS).** S. J. Sander, J. L. Siegal-Willott, J. Ziegler, E. Lee, L. Tell and S. Murray. J Zoo Wildl Med 2016 Vol. 47 Issue 1 Pages 1-5.
Accession Number: 27010257 DOI: 10.1638/2015-0160.1

To Drug Monograph Index To Ophthalmic Product Index

Metronidazole is a nitroimidazole antibacterial and antiprotozoal drug with bacteriocidal activity against a broad range of anaerobic bacteria. It is a recognized treatment for elephants diagnosed with anaerobic bacterial infection or protozoal disease or exhibiting signs of colonic impaction, diarrhea, and colic. This study evaluated the pharmacokinetics of rectally administered metronidazole (15 mg/kg) in five adult female Asian elephants (Elephas maximus). Serum samples were collected from each animal for 96 hr after rectal administration of metronidazole. Serum concentrations of metronidazole and its primary metabolite, hydroxymetronidazole, were measured via ultraperformance liquid chromatography. Data were analyzed via a noncompartmental pharmacokinetic approach. Results indicated that serum levels of metronidazole were quantifiable at the 0.25 hr time point and absent in all elephants by the 96 hr time point. The serum peak concentration (mean +/- SD, 13.15 +/- 2.59 mug/ml) and area under the curve from time 0 to infinity (mean +/- SD, 108.79 +/- 24.77 hr x mug/ml) were higher than that reported in domestic horses after similar usage. Concurrently, the time of maximum serum concentration (mean +/- SD, 1.2 +/- 0.45 hr) and terminal elimination half-life (harmonic mean +/- pseudo-SD, 7.85 +/- 0.93 hr) were longer when compared to equine reports. Rectal administration of metronidazole was well tolerated and rapidly absorbed in all study elephants. Based on the findings in this study, metronidazole administered at a single dose of 15 mg/kg per rectum in the Asian elephant is likely to result in serum concentrations above 4 mug/ml for 8 hr and above 2 mug/ml for 24 hr after treatment is administered. Dosing recommendations should reflect the mean inhibitory concentration of metronidazole for each pathogen.

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects (clients should report any neurologic symptomatology)

**Client Information** - Report any neurologic symptoms to veterinarian (see Overdose section).

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Metronidazole Tablets 250 mg, 500 mg; Capsules 375 mg; *Flagyl*® (Searle); *Metric 21*® (Fielding); *Protostat*® (Ortho); *Flagyl 375*® (Searle); generic; (Rx)

Metronidazole HCl Powder for Injection 500 mg/vial; *Flagyl*®*IV* (Searle); (Rx)

Metronidazole 500 mg/100 ml injection (ready to use); *Flagyl*®*I.V.* (Searle); *Metro*®*I.V.* (McGaw); *Metronidazole Redi-Infusion*® (Elkins-Sinn); *Metronidazole*® (Abbott); (Rx)

## MIDAZOLAM HCL

**Chemistry** - An imidazobenzodiazepine, midazolam occurs as a white to light yellow crystalline powder with a $pK_a$ of 6.15. Midazolam HCl's aqueous solubility is pH dependent. At 25°C and a pH of 3.4, 10.3 mg are soluble in 1 ml of water. The pH of the commercially prepared injection is approximately 3.

**Storage/Stability/Compatibility** - It is recommended to store midazolam injection at room temperature (15°-30°C) and protect from light. After being frozen for 3 days and allowed to thaw at room temperature, the injectable product was physically stable. Midazolam is stable at a pH from 3-3.6.

To Drug Monograph Index To Ophthalmic Product Index

Midazolam is reportedly **compatible** when mixed with the following products: D5W, normal saline, lactated Ringer's, atropine sulfate, fentanyl citrate, glycopyrrolate, hydroxyzine HCl, ketamine HCl, meperidine HCl, morphine sulfate, nalbuphine HCl, promethazine HCl, sufantanil citrate, and scopolamine Hbr. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** - Midazolam exhibits similar pharmacologic actions as other benzodiazepines (refer to the diazepam monograph for more information). Its unique solubility characteristics (water soluble injection but lipid soluble at body pH) give it a very rapid onset of action after injection.

**Uses/Indications** - In humans, midazolam has been suggested to be used as a premedicant before surgery, and when combined with potent analgesic/anesthetic drugs (*e.g.,* ketamine or fentanyl), as a conscious sedative. In humans, midazolam reduces the incidences of "dreamlike" emergence reactions and increases in blood pressure and cardiac rate that ketamine causes.

When compared to the thiobarbiturate induction agents (*e.g.,* thiamylal, thiopental), midazolam has less cardiopulmonary depressant effects, is water soluble, can be mixed with several other agents, and does not tend to accumulate in the body after repeated doses. There is much interest in using the drug alone as an induction agent. Several veterinary anesthesiologists are studying the clinical applications of this agent in veterinary medicine and additional information regarding its use should be forthcoming.

**Pharmacokinetics** - Following IM injection, midazolam is rapidly and nearly completely (91%) absorbed. Although no oral products are being marketed, midazolam is well absorbed after oral administration, but because of a rapid first-pass effect, bioavailibilities suffer (31-72%). The onset of action following IV administration is very rapid due to the high lipophilicity of the agent. In humans, the loss of the lash reflex or counting occurs within 30-97 seconds of administration.

The drug is highly protein bound (94-97%) and rapidly crosses the blood-brain barrier. Because only unbound drug will cross into the CNS, changes in plasma protein concentrations and resultant protein binding may significantly alter the response to a given dose.

Midazolam is metabolized in the liver, principally by microsomal oxidation. An active metabolite (alpha-hydroxymidazolam) is formed, but because of its very short half-life and lower pharmacologic activity, it probably has negligible clinical effects. The serum half-life and duration of activity of midazolam in humans is considerably shorter than that of diazepam. Elimination half-lives measured in humans average approximately 2 hours (vs. approx. 30 hrs for diazepam).

**Contraindications/Precautions** - The manufacturer lists the following contraindications for use in humans: hypersensitivity to benzodiazepines, or acute narrow-angle glaucoma. Additionally, intra-carotid artery injections must be avoided.

Use cautiously in patients with hepatic or renal disease and in debilitated or geriatric patients. Patients with congestive heart failure may eliminate the drug more slowly. The drug should be administered to patients in coma, shock or having significant respiratory depression very cautiously.

Although midazolam has not been demonstrated to cause fetal abnormalities, in humans other benzodiazepines have been implicated in causing congenital abnormalities if administered during the first trimester of pregnancy. Infants born of mothers receiving large doses of benzodiazepines shortly before delivery have been reported to suffer from apnea, impaired metabolic response to cold stress, difficulty in feeding, hyperbilirubinemia, hypotonia, etc. Withdrawal symptoms have occurred in infants whose mothers chronically took benzodiazepines during pregnancy. The veterinary significance of these effects is unclear, but the use of these agents during the first trimester of pregnancy should only occur when the benefits

To Drug Monograph Index To Ophthalmic Product Index

clearly outweigh the risks associated with their use. It is unknown if midazolam is distributed into milk, but other benzodiazepines and their metabolites are distributed into milk and may cause CNS effects in nursing neonates.

**Adverse Effects/Warnings** - Few adverse effects have been reported in human patients receiving midazolam. Most frequently effects on respiratory rate, cardiac rate and blood pressure have been reported. Respiratory depression has been reported in patients who have received narcotics or have COPD. The following adverse effects have been reported in more than 1%, but less than 5% of patients receiving midazolam: pain on injection, local irritation, headache, nausea, vomiting, and hiccups.

The principle concern in veterinary patients is the possibility of respiratory depression occurring.

**Overdosage** - Very limited information is currently available. The IV $LD_{50}$ in mice has been reported to be 86 mg/kg. It is suggested that accidental overdoses be managed in a supportive manner, similar to diazepam.

**Drug Interactions** - Use with **barbiturates or other CNS depressants** may increase the risk of respiratory depression occurring. **Narcotics** (including Innovar®) may increase the hypnotic effects of midazolam and hypotension has been reported when used with **meperidine**. Midazolam may decrease the dosages required for **inhalation anesthetics or thiopental**.

**Doses -**
**Horses**:
As a preoperative agent: 0.011 - 0.0.44 mg/kg IV (Mandsager 1988)

**Monitoring Parameters** -
1) Level of sedation
2) Respiratory and cardiac signs

**Client Information** - This agent should be used in an inpatient setting only or with direct professional supervision where cardiorespiratory support services are available.

**Dosage Forms/Preparations** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**
Midazolam HCl for Injection 1mg/ml in 2, 5, & 10 ml vials; 5 mg/ml in 1, 2, 5, & 10 ml vials, 2 ml syringes; *Versed*® (Roche); (Rx)
Midazolam is a Class-IV controlled substance.

## MINERAL OIL
## WHITE PETROLATUM

**Chemistry** - Mineral Oil, also known as liquid petrolatum, liquid paraffin or white mineral oil occurs as a tasteless, odorless (when cold), transparent, colorless, oily liquid that is insoluble in both water and alcohol. It is a mixture of complex hydrocarbons and is derived from crude petroleum. For pharmaceutical purposes, heavy mineral oil is recommended over light mineral oil, as it is believed to have a lesser tendency to be absorbed in the gut or aspirated after oral administration.

To Drug Monograph Index To Ophthalmic Product Index

White petrolatum, also known as white petroleum jelly or white soft paraffin occurs as a white or faintly yellow unctious mass. It is insoluble in water and almost insoluble in alcohol. White petrolatum differs from petrolatum only in that it is further refined to remove more of the yellow color.

**Storage/Stability/Compatibility** - Petrolatum products should be stored at temperatures less than 30°C.

**Pharmacology** - Mineral oil and petrolatum act as a laxatives by lubricating fecal material and the intestinal mucosa. They also reduce reabsorption of water from the GI tract, thereby increasing fecal bulk and decreasing intestinal transit time.

**Uses/Indications -** Mineral oil is commonly used in horses to treat constipation and fecal impactions. It is also employed as a laxative in other species as well, but used less frequently. Mineral oil has been administered after ingesting lipid-soluble toxins (*e.g.,* kerosene, metalaldehyde) to retard the absorption of these toxins through its laxative and solubility properties.

Petrolatum containing products (*e.g., Felaxin®, Laxatone®, Kat-A-Lax®*, etc.) may be used in dogs and cats as a laxative or to prevent/reduce "hair-balls" in cats.

**Pharmacokinetics** - It has been reported that after oral administration, emulsions of mineral oil may be up to 60% absorbed, but most reports state that mineral oil preparations are only minimally absorbed from the gut.

**Contraindications/Precautions** - No specific contraindications were noted with regard to veterinary patients. In humans, mineral oil (orally administered) is considered to be contraindicated in patients less than 6 yrs. old, debilitated or pregnant patients, and in patients with hiatal hernia, dysphagia, esophogeal or gastric retention. Use caution when administering by tube to avoid aspiration, especially in debilitated or recalcitrant animals. To avoid aspiration in small animals, orally administered mineral oil should not be attempted when there is an increased risk of vomiting, regurgitation or other preexisting swallowing difficulty.

**Adverse Effects/Warnings** - When used on a short-term basis and at recommended doses, mineral oil or petrolatum should cause minimal adverse effects. The most serious effect that could be encountered is aspiration of the oil with resultant lipid pneumonitis. This can be prevented by using the drug in appropriate cases and when "tubing" to ascertain that the tube is in the stomach and to administer the oil at a reasonable rate.

Granulomatous reactions have occurred in the liver, spleen and mesenteric lymph nodes when significant quantities of mineral oil are absorbed from the gut. Oil leakage from the anus may occur and be of concern in animals with rectal lesions or in house pets. Long-term administration of mineral oil/petrolatum may lead to decreased absorption of fat-soluble vitamins (A, D, E, & K). No reports were found documenting clinically significant hypovitaminosis in cats receiving long-term petrolatum therapy, however.

**Overdosage** - No specific information was located regarding overdoses of mineral oil; but it would be expected that with the exception of aspiration, the effects would be self-limiting. See adverse effects section for more information.

**Drug Interactions** - Theoretically, mineral oil should not be given with **docusate** (**DSS**) as enhanced absorption of the mineral oil could occur. However, this does not appear to be of significant clinical concern with large animals.

To Drug Monograph Index To Ophthalmic Product Index

Chronic administration of mineral oil may affect **Vitamin K and other fat soluble vitamin** absorption. It has been recommended to administer mineral oil products between meals to minimize this problem.

**Doses** -
**Horses:** Administer via stomach tube
As a laxative:
a) For large colon impactions: 2 - 4 quarts q12-24 hours, may take up to 5 gallons. Mix 1 - 2 quarts of warm water with the oil to ease administration and give more fluid to the horse. Pumping in at a moderate speed is desirable over gravity flow. (Sellers and Lowe 1987)
b) Adults: 2 - 4 liters, may be repeated daily; Foals: 240 mls (Clark and Becht 1987)
c) Adults: 0.5 - 2 liters; Foals: 60 - 120 mls (Jenkins 1988)

**Monitoring Parameters** -
1) Clinical efficacy
2) If possibility of aspiration: auscultate, radiograph if necessary

**Client Information** - Follow veterinarian's instructions or label directions for "cat laxative" products. Do not increase dosage or prolong treatment beyond veterinarian's recommendations.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** - These products and preparations are available without a prescription (OTC).

**Veterinary-Approved Products**: Mineral oil products have not been formally approved for use in food animals.
Petrolatum Oral Preparations
Products may vary in actual composition; some contain liquid petrolatum in place of white petrolatum.
Trade names include: *Felaxin*® (Schering), *Kat-A-Lax*® (P/M; Mallinckrodt), *Laxatone*® (Evsco), *Kit-Tonne*® (Miles), *Lax 'aire*® (Beecham)

**Human-Approved Products**:
Mineral Oil, Heavy in pints, quarts, gallons and drums
Mineral Oil, Extra Heavy in pints, quarts, gallons and drums
Mineral Oil Emulsions
There are several products available that are emulsions of mineral oil and may be more palatable for oral administration. Because of expense and with no increase in efficacy they are used only in small animals. They may be dosed as described above, factoring in the actual percentage of mineral oil in the preparation used. Trade names include: *Agoral*® *Plain* (Parke-Davis), *Kondremul*® *Plain* (Fisons), and *Milkinol*® (Kremers-Urban).

## MORANTEL TARTRATE

**Chemistry** - A tetrahydropyrimidine anthelmintic, morantel tartrate occurs as a practically odorless, off-white to pale yellow, crystalline solid that is soluble in water. It has a melting range of 167-171°C. The tartrate salt is equivalent to 59.5% of base activity.

**Storage/Stability/Compatibility** - Morantel tartrate products should be stored at room temperature (15-30°C) unless otherwise instructed by the manufacturer.

**Pharmacology** - Like pyrantel, morantel acts as depolarizing neuromuscular blocking agent in susceptible parasites, thereby paralyzing the organism. The drug possesses nicotine-like properties and acts similarly to

acetylcholine. Morantel also inhibits fumarate reductase in *Haemonchus spp.*. Morantel is slower than pyrantel in its onset of action, but is approximately 100 times as potent.

**Uses/Indications** - Morantel is indicated (labeled) for the removal of the following parasites in **cattle**: Mature forms of: *Haemonchus spp., Ostertagia spp., Trichostrongylus spp., Nematodirus spp., Cooperia spp. and Oesophagostomum radiatum*. It is also used in other ruminant species.

**Pharmacokinetics** - After oral administration, morantel is absorbed rapidly from the upper abomasum and small intestine. Peak levels occur about 4-6 hours after dosing. The drug is promptly metabolized in the liver. Within 96 hours of administration, 17% of the drug is excreted in the urine and the remainder in the feces.

**Contraindications/Precautions** - There are no absolute contraindications to using this drug. The sustained-release oral cartridges (*Paratect*®) are not to be used in cattle weighing less than 90 kg. Morantel is considered to be generally safe to use during pregnancy.

**Adverse Effects/Warnings** - At recommended doses, adverse effects are not commonly seen. For more information, see Overdosage section below.

**Overdosage/Acute Toxicity** - Morantel tartrate has a large safety margin. In cattle, dosages of up to 200 mg/kg (20 times recommended dose) resulted in no toxic reactions. The $LD_{50}$ in mice is 5 g/kg. Symptoms of toxicity that might possibly be seen include increased respiratory rates, profuse sweating (in animals able to do so), ataxia or other cholinergic effects.

Chronic toxicity studies have been conducted in cattle and sheep. Doses of 4 times recommended were given to sheep with no detectable deleterious effects. Cattle receiving 2.5 times recommended dose for 2 weeks showed no toxic signs.

**Drug Interactions** - *Paratect*® cartridges should not be administered with **mineral bullets** as decreased anthelmintic efficacy can result. Because of similar mechanisms of action (and toxicity), morantel is recommended not to be used concurrently with **pyrantel** or **levamisole**.
Observation for adverse effects should be intensified if used concomitantly with an **organophosphate** or **diethylcarbamazine**. **Piperazine** and morantel have antagonistic mechanisms of action; do not use together. Do not add to feeds containing **bentonite**.

**Doses** -
**Cattle**:

For susceptible parasites:

a) 9.68 mg/kg PO. (Paul 1986), (Label Directions; Nematel®—Pfizer)
b) 8.8 mg/kg PO. (Roberson 1988b)
c) *Paratect*® Cartridges: One cartridge PO when animal placed onto spring pasture. All cattle grazing on same pasture must be treated. Effective for 90 days. (Label Directions; *Paratect*®—Pfizer)

**Elephants:**

a) Morantel tartrate 2-4 mg/kg orally as a single dose; Morantel citrate 2-3 mg/kg orally as a single dose for helminthiasis. a) Chandrasekharan,K. 2002. **Specific diseases of Asian elephants**. Journal of Indian Veterinary Association Kerala 7:(3):31-34

To Drug Monograph Index  To Ophthalmic Product Index

a) Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T., 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference to Kerala**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-449

a) Chandrasekharan,K., 1992. **Prevalence of infectious diseases in elephants in Kerala and their treatment**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur,India pp. 148-155

b) 5 mg/kg orally for strongylosis. Chandrasekharan,K., Cheeran,J.V., Nair,K.N.M., Ramanujam,K.N., and Radhakrishnan,K. 1982. **Comparative efficacy of 6 anti-helminthics against strongylosis in elephants**. Kerala Journal of Veterinary Science 13:15-20 **Summary:** Anthelmintic efficacy of six drugs was compared under field conditions against strongylosis in elephants. Mebendazole at 3 and 4 mg/kg, Levamisole 3 mg/kg and Morantel tartrate 5 mg/kg were proved to be 100% effective. Mebendazole at 2 mg/kg and 2.5 mg/kg, Thiabendazole at 32 mg/kg. Bephenium hydroxynaphthoate at 25 mg/kg and Disophenol at 3 mg/kg were found to be effective only in 79.1 to 92.2 %, 88.1 to 100%, 84.6 to 95.3 %, 85.9 to 100% and 68.3 to 84 % cases respectively.

**Dosage Forms/Preparations/FDA Approval Status/Withdrawal Times** -

Morantel Tartrate Oral Boluses 2.2 g (equiv. to 1.3 g base)

*Nematel® Cattle Wormer Boluses* (Pfizer); (OTC) Approved for use in beef or dairy cattle. Milk withdrawal = none; Slaughter withdrawal = 14 days

Morantel Tartrate Medicated Premix, 88 g morantel tartrate per lb.

*Rumatel® Medicated Premix-88* (Pfizer); (OTC) Approved for use in beef or dairy cattle. Milk withdrawal = none; Slaughter withdrawal = 14 days

Morantel Tartrate Sustained-Release Oral Cartridges, 22.7 g per cartridge (13.5 g base)

*Paratect® Cartridge* (Pfizer); (OTC) Approved for use in beef or dairy cattle. Milk withdrawal = none; Slaughter withdrawal = 160 days

## MORPHINE SULFATE

**Chemistry** - The sulfate salt of a natural (derived from opium) occurring opiate analgesic, morphine sulfate occurs as white, odorless, crystals. Solubility: 1 g in 16 ml of water (62.5 mg/ml), 570 ml (1.75 mg/ml) of alcohol. Insoluble in chloroform or ether. The pH of morphine sulfate injection ranges from 2.5-6.

**Storage/Stability/Compatibility** - Morphine gradually darkens in color when exposed to light; protect from prolonged exposure to bright light. Does not appear to adsorb to plastic or PVC syringes, tubing or bags. Morphine sulfate has been shown to be compatible at a concentration of 16.2 mg/l with the following intravenous fluids: Dextrose 2.5%, 5%, 10% in water; Ringer's injection and Lactated Ringer's injection; Sodium Chloride 0.45% and 0.9% for injection. The following drugs have been shown to **incompatible** when mixed with morphine sulfate: aminophylline, chlorothiazide sodium, heparin sodium, meperidine, pentobarbital sodium, phenobarbital sodium, phenytoin sodium, sodium bicarbonate, and thiopental sodium. Morphine sulfate has been demonstrated to be generally **compatible** when mixed with the following agents: Atropine sulfate, benzquinamide HCl, butorphanol tartrate, chlorpromazine HCl, diphenhydramine HCl,

dobutamine HCl, droperidol, fentanyl citrate, glycopyrrolate, hydroxyzine HCl, metoclopramide, pentazocine lactate, promazine HCl, scopolamine HBr, and succinylcholine chloride.

**Pharmacology** - Refer to the monograph: Narcotic (opiate) Analgesic Agonists, Pharmacology of, for more information. Morphine's CNS effects are irregular and are species specific. Cats, horses, sheep, goats, cattle and swine may exhibit stimulatory effects after morphine injection, while dogs, humans, and other primates exhibit CNS depression. Both dogs and cats are sensitive to the emetic effects of morphine, but significantly higher doses are required in cats before vomiting occurs. This effect is a result of a direct stimulation of the chemorecepetor trigger zone (CTZ). Other species (horses, ruminants and swine) do not respond to the emetic effects of morphine. Like meperidine, morphine can effect the release of histamine from mast cells.

Morphine is an effective centrally acting antitussive in dogs. Following morphine administration, hypothermia may be seen in dogs and rabbits, while hyperthermia may be seen in cattle, goats, horses, and cats. Morphine can cause miosis (pinpoint pupils) in humans, rabbits and dogs.

While morphine is considered to be a respiratory depressant, initially in dogs respirations are stimulated. Panting may ensue which may be a result of increased body temperature. Often however, body temperature may be reduced due to a resetting of the "body's thermostat". As CNS depression increases and the hyperthermia resolves, respirations can become depressed. Morphine at moderate to high doses can also cause bronchoconstriction in dogs.

The cardiovascular effects of morphine in dogs are in direct contrast to its effects on humans. In dogs, morphine causes coronary vasoconstriction with resultant increase in coronary vascular resistance, and a transient decrease in arterial pressure. Both bradycardias and tachycardias have also been reported in dogs. While morphine has been used for years as a sedative/analgesic in the treatment of myocardial infarction and congestive heart failure in people, its effects on dogs make it a less than optimal choice in canine patients with symptoms of cardiopulmonary failure. However, its use has been recommended by several clinicians in the initial treatment for cardiogenic edema in dogs.

The effects of morphine on the gastrointestinal (GI) tract consist primarily of a decrease in motility and secretions. The dog however, will immediately defecate following an injection of morphine and then exhibit the signs of decreased intestinal motility and ultimately constipation can reesult. Both biliary and gastric secretions are reduced following administration of morphine, but gastric secretion of HCl will later be compensated by increased (above normal) acid secretion.

Initially, morphine can induce micturation, but with higher doses (>2.4 mg/kg IV) urine secretion can be substantially reduced by an increase in anti-diuretic hormone (ADH) release. Morphine may also cause bladder hypertonia, which can lead to increased difficulty in urination.

**Pharmacokinetics** - Morphine is absorbed when given by IV, IM, SQ, and rectal routes. Although absorbed when given orally, bioavailability is reduced, probably as a result of a high first-pass effect. Morphine concentrates in the kidney, liver, and lungs; lower levels are found in the CNS. Although at lower levels then in the parenchymatous tissues, the majority of free morphine is found in skeletal muscle. Morphine crosses the placenta and narcotized newborns can result if mothers are given the drug before giving birth. These effects can be rapidly reversed with naloxone. Small amounts of morphine will also be distributed into the milk of nursing mothers.

The major route of elimination of morphine is by metabolism in the liver; primarily by glucuronidation. Because cats are deficient in this metabolic pathway, half-lives in cats are probably prolonged. The glucuronidated metabolite is excreted by the kidney.

To Drug Monograph Index To Ophthalmic Product Index

In horses, the serum half-life of morphine has been reported to be 88 minutes after a dose of 0.1 mg/kg IV. At this dose the drug was detectable in the serum for 48 hours and in the urine for up to 6 days. The half-life in cats has been reported to be approximately 3 hours.

**Uses/Indications** - Morphine is used for the treatment of acute pain in dogs, cats, horses, swine, sheep, and goats. It may be also be used as a preanesthetic agent in dogs and swine. Additionally, it has been used as an antitussive, antidiarrheal, and as adjunctive therapy for some cardiac abnormalities (see doses) in dogs.

**Contraindications/Precautions** - All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's), and in geriatric or severely debilitated patients. Morphine is contraindicated in cases where the patient is hypersensitive to narcotic analgesics, and in patients taking monamine oxidase inhibitors (MAOIs). It is also contraindicated in patients with diarrhea caused by a toxic ingestion until the toxin is eliminated from the GI tract.

Morphine should be used with extreme caution in patients with head injuries, increased intracranial pressure and acute abdominal conditions (*e.g.,* colic) as it may obscure the diagnosis or clinical course of these conditions. Morphine may also increase intracranial pressure secondary to cerebral vasodilatation as a result of increased $p_aCO_2$ stemming from respiratory depression. It should be used with extreme caution in patients suffering from respiratory disease or from acute respiratory dysfunction (*e.g.,* pulmonary edema secondary to smoke inhalation).
Because of its effects on vasopressin (ADH), morphine must be used cautiously in patients suffering from acute uremia. Urine flow has been reported to be decreased by as much as 90% in dogs given large doses of morphine.

Neonatal, debilitated or geriatric patients may be more susceptible to the effects of morphine and may require lower dosages. Patients with severe hepatic disease may have prolonged durations of action of the drug.

Opiate analgesics are contraindicated in patients who have been stung by the scorpion species *Centruroides sculpturatus* Ewing and *C. gertschi* Stahnke as they can potentiate these venoms.

**Adverse Effects/Warnings** - At usual doses, the primary concern is the effect the opioids have on respiratory function. Decreased tidal volume, depressed cough reflex and the drying of respiratory secretions may all have a detrimental effect on a susceptible patient. Bronchoconstriction (secondary to histamine release?) following IV doses has been noted in dogs.

Gastrointestinal effects may include: nausea, vomiting and decreased intestinal persitalsis. Dogs will usually defecate after an initial dose of morphine. Horses exhibiting signs of mild colic may have their symptoms masked by the administration of narcotic analgesics.

The CNS effects of morphine are dose and species specific. Animals that are stimulated by morphine, may elucidate changes in behavior, appear restless, and at very high doses, have convulsions. The CNS depressant effects seen in dogs may encumber the abilities of working animals.

Body temperature changes may be seen. Cattle, goats, horses and cats may exhibit signs of hyperthermia. while rabbits and dogs may develop hypothermia.

Chronic administration may lead to physical dependence.

**Overdosage** - Overdosage may produce profound respiratory and/or CNS depression in most species. Newborns may be more susceptible to these effects than adult animals. Parenteral doses greater than 100

mg/kg are thought to be fatal in dogs. Other toxic effects can include cardiovascular collapse, hypothermia, and skeletal muscle hypotonia. Some species such as horses, cats, swine, and cattle may demonstrate CNS excitability (hyperreflexia, tremors) and seizures at high doses or if given intravenously (rapidly). Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated, animals should be closely observed as naloxone's effects may diminish before sub-toxic levels of morphine are attained. Mechanical respiratory support should also be considered in cases of severe respiratory depression.

Pentobarbital has been suggested as a treatment for CNS excitement and seizures in cats. Extreme caution should be used as barbiturates and narcotics can have additive effects on respiratory depression.

**Drug Interactions** - Other **CNS depressants** (*e.g.,* anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with morphine. Morphine is contraindicated in patients receiving **monamine oxidase (MOA) inhibitors** (rarely used in veterinary medicine) for at least 14 days after receiving MOA inhibitors in humans. Some human patients have exhibited signs of opiate overdose after receiving therapeutic doses of morphine while on these agents.

**Laboratory Interactions** - Plasma **amylase** and **lipase** values may be increased for up to 24 hours following administration of opiate analgesics as they may increase biliary tract pressure.

**Doses -**
**Horses**:

For analgesia:

a) 0.22 mg/kg IM or slow IV (Booth 1988a)
b) 0.2 - 0.6 mg/kg IV (slowly); premedicate with xylazine (1 mg/kg IV) to reduce excitement (Jenkins 1987)
c) 0.02 - 0.04 mg/kg IV (Muir 1987)
d) 0.05 - 0.12 mg/kg IV (Thurmon and Benson 1987)

**Note**: Narcotics may cause CNS excitement in the horse. Some clinicians recommend pretreatment with acepromazine (0.02 - 0.04 mg/kg IV), or xylazine (0.3 - 0.5 mg/kg IV) to reduce the behavioral changes these drugs can cause.

**Warning:** Narcotic analgesics can mask the behavioral and cardiovascular symptoms associated with mild colic.

**Elephants:**

a) For analgesia: 3-6 mg/100 kg qid; for analgesia and sedation: 6-20 mg/100 kg qid. Schmidt, M: Elephants (Proboscidea). In: Fowler, M.E. (ed): Zoo and Wild Animal Medicine. 1986. Saunders, Philadelphia. p.892

**Monitoring Parameters** -

1) Respiratory rate/depth
2) CNS level of depression/excitation
3) Blood pressure if possible and indicated (especially with IV use)
4) Analgesic activity

**Client Information** - When given parenterally, this agent should be used in an inpatient setting or with direct professional supervision.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

To Drug Monograph Index To Ophthalmic Product Index

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Morphine Sulfate for Injection: 0.5 mg/ml in 2, & 10 ml amps and 10 ml vials; 1 mg/ml in 2, 10, 30 & 60 ml amps and 10 ml vials; 2 mg/ml in 50 ml vials and 1 & 2 ml syringes; 3 mg/ml in 50 ml vials; 4 mg/ml in 1& 2 ml syringes; 5 mg/ml in 1 & 30 ml vials; 8 mg/ml in 1 ml vials, amps & syringes; 10 mg/ml in 1 ml amps, vials, 10 ml vials and 20 ml amps; 15 mg/ml in 1 & 20 ml amps, & vials; 25 mg/ml in 4, 10 , 20, & 40 ml syringes and 20 ml ampuls; 50 mg/ml in 10, 20 and 40 ml syringes

Morphine Sulfate for Injection (preservative-free): 0.5 mg/ml, 10 ml amps & vials; 1 mg/ml, 10 ml amps & vials;*Infumorph*® (Elkins-Sinn); *Astramorph PF*® (Astra)

Morphine Sulfate Soluble Tablets: 10 mg, 15 mg, 30 mg

Morphine Sulfate Tablets: 15 mg, 30 mg

Morphine Sulfate Capsules: 15 mg, 30 mg

Morphine Sulfate Oral Solution; 10 mg/5ml in 100, 120 & 500 ml btls & unit dose (2.5, 5, 10 ml); 20 mg/5ml in 100, 120 & 500 ml btls & unit dose 5 ml; 20 mg/ml in 30 & 120 ml, in UD 1 ml and 1.5 ml vials; 100 mg/5 ml in 120 & 240 ml

Morphine Sulfate Controlled-release Tablets 15 mg, 30 mg, 60 mg, 100 mg, 200 mg

Morphine Sulfate Rectal Suppositories 5 mg, 10 mg & 20 mg, 30 mg in UD 12's and 50's

**Note:** All morphine products are Rx and a **Class-II controlled substance**. Very accurate record keeping is required as to use and disposition of stock. See the appendix for more information.

## NALMEFENE

**Nalmefene** is an opioid antagonist with no agonist activity.

**Elephants:**

a) Carfentanil at 2.1±0.3 µg/kg as a single IM injection in captive elephants was reversed with nalmefene, at a mean ratio for nalmefene/carfentanil of 26:. Raath,J.P., 1999. **Relocation of African elephants**. In: Fowler,M.E. and Miller,R.E. (Editors), Zoo and Wild Animal Medicine: Current Therapy 4. W.B. Saunders, Philadelphia, PA, USA pp. 525-533.

b) Four juvenile African elephants immobilized with carfentanil (2.4 µg/kg based on estimated weights) were reversed with nalmefene. One was given nalmefene 166.7 µg/kg both IV and SC. Two were given nalmefene IV and IM. The dosage was 88.9 µg/kg IV and IM in one elephant and 53.3 µg/kg IV and IM in the other. One elephant was given nalmefene (88.9 µg/kg IV) followed by diprenorphine (8.9 µg/kg IM). Reversal was rapid and uneventful and no cases of renarcotization were noted. Schumacher,J., Heard,D.J., Caligiuri,R., Norton,T., and Jacobson,E.R. 1995. **Comparative effects of etorphine and carfentanil on cardiopulmonary parameters in juvenile African elephants (*Loxodonta africana*).** Journal of Zoo and Wildlife Medicine 26:(4):503-507

**Abstract:** Fourteen African elephants (Loxodonta africana) were immobilized with either etorphine hydrochloride (3.2 ± 0.5 µg/kg i.m.) or carfentanil citrate (2.4 µg/kg i.m.). Induction time with etorphine was significantly longer (30 ± 21 min) than with carfentanil (8 ± 2 min). Immediately following immobilization all elephants were placed in lateral recumbency and respiratory rate, heart rate, and rectal body temperature were monitored every 5 min throughout the immobilization period. Arterial blood samples, collected from an auricular artery, were taken 10 min after immobilization and every 15 min thereafter for up to 1 hr. At the first sampling, mean values for arterial blood gas variables for etorphine immobilized elephants were pHa, 7.29 ± 0.03; $PaCO_2$, 53.4 ± 5.2 mmHg; $PaO_2$, 71.8 ± 13.8 mmHg; standard base excess (SBE), -1.6 ± 2.9 mEq/L; and HCO3, 25.7 ± 2.7 mEq/L. After 1 hr of immobilization, mean arterial blood gas values were pHa,

To Drug Monograph Index To Ophthalmic Product Index

7.32 ± 0.06; $PaCO_2$ , 57.2 ± 9.6 mm Hg; and $PaO_2$ , 53.8 ± 10.5 mm Hg; SBE, 2.7 ± 1.4 mEq/L; and $HCO_{3-}$, 30.6 ± 1.6 mEq/L.

For carfentanil immobilized elephants, blood gas values at the first time of collection were pHa, 7.28 ± 0.04; $PaCO_2$, 52.1 ± 2.8 mmHg; $PaO_2$, 78.3 ± 14.7 mmHg; SBE, -2.3 ± 24 mEq/L; and $HCO_{3-}$, 24.3 ± 2.1 mEq/L. Sixty minutes after the first sampling, blood gas values of one elephant were pHa, 7.38; $PaCO_2$, 48.7 mmHg; $PaO_2$, 52 mmHg; SBE, 3.4 mEq/L, and $HCO_{3-}$, 28.8 mEq/L. Over time there was a progressive decline in arterial PO2 in all elephants. It is concluded that elephants immobilized with either etorphine HCl or carfentanil developed hypoxemia ($PaO_2$ < 60 mmHg) after 30 min of immobilization. It is recommended that the administration of one of these opioid drugs be accompanied by supplemental oxygen, or followed by an inhalant anesthetic in 100% oxygen for prolonged procedures. Diprenorphine or nalmefene reversal was rapid and uneventful in both the etorphine and carfentanil group. No cases of renarcotization were noted. **Additional excerpt:** All elephants in the etorphine group (n=8) received diprenorphine at a mean dosage of 8.3 ± 1.1 µg/kg IV. Two elephants in the carfentanil group (n=6) were administered diprenorphine at a dosage of 8.9 µg/kg IV and IM. Three elephants in this group received nalmefene hydrochloride. One of the three elephants was given nalmefene 166.7 µg/kg both IV and SC. Two of the three elephants were given nalmefene IV and IM. The dosage was 88.9 µg/kg IV and IM in one elephant and 53.3 µg/kg IV and IM in the other. One elephant in the carfentanil group was administered nalmefene (88.9 µg/kg IV) followed by diprenorphine (8.9 µg/kg IM).

c) To reverse carfentanil, give nalmefene at 26 times the carfentanil dose. Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants**. In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441

d) Seventeen African elephants immobilized with carfentanil (2.1±0.3 µg/kg) were reversed with nalmefene (n=13), diprenorphine (n=2), or diprenorphine and nalmefene (n=2). Antagonists were administered IV and IM or IV and SC. Sixteen of 17 elephants were standing in 2.9±1.4 minutes. Jacobson,E.R., Kollias,G.V., Heard,D.J., and Caligiuri,R. 1988. **Immobilization of African elephants with carfentanil and antagonism with nalmefene and diprenorphine**. Journal of Zoo Animal Medicine 19:1-7 **Abstract:** Sixteen African elephants (*Loxodonta africana*) were immobilized with single i.m. injections of carfentanil citrate (2.1 ± 0.3 µg/kg body weight). All elephants were laterally recumbent in 10.1 ± 3.7 min. An additional elephant which received 1.4 µg /kg carfentanil did not become recumbent and additional carfentanil was required for immobilization. Following immobilization, nine elephants were maintained in lateral recumbency by administration of multiple i.v. injections of carfentanil, one elephant received a single i.v. dose of ketamine hydrochloride, and four were intubuted and administered 1-1.5% halothane in oxygen. Because a short duration of immobilization was desired, three elephants were not given additional drugs. The duration of immobilization ranged from 4 to 187 min. Following a variety of medical and surgical procedures, 13 elephants received nalmefene hydrochloride, two elephants received diprenorphine, and two elephants received both diprenorphine and nalmefene; antagonists were administered either i.v. and i.m. or i.v. and s.c. Sixteen of 17 elephants were standing in 2.9 ± 1.4 min; the standing time of one elephant was not recorded. See also nalmefene monograph.

e) Fourteen African elephants immobilized with etorphine or carfentanil were reversed with nalmefene. Jacobson,E.R., Heard,D.J., Caligiuri,R., and Kollias,G.V. 1987. **Physiologic effects of etorphine and carfentanil in African elephants**. Proc.1st.Intl.Conf.Zool.Avian Med. Pages: 525-527 **Abstract:** (Full text): The effects of etorphine hydrochloride and carfentanil citrate on blood pressure, heart rate, respiration and body temperature were determined in a group of captive African elephants (Loxodonta africana). Fourteen African elephants, weighing 450 kg to 4000 kg, divided into 2 groups of 6 and 8 elephants each, received either etorphine hydrochloride (2.9 ± 0.7 µg/kg of body weight; mean ± SD) or carfentanil citrate (2.0 ± 0.2 µg/kg of body weight) respectively. The mean time for lateral recumbency in elephants which received etorphine was 31 ± 9.1 minutes while the mean time for lateral recumbency in elephants which received carfentanil was 10.3 ± 4.1 minutes. Following immobilization, a 18 gauge catheter was inserted into an

To Drug Monograph Index To Ophthalmic Product Index

auricular artery, the catheter connected to a pressure transducer system and systolic, diastolic, and mean arterial pressures were monitored by use of a multichannel oscilloscope. Systolic, diastolic, mean arterial pressures, heart rate, respiration, and temperature were recorded every 5 minutes over a 45 to 60 minute period. Elephants were maintained in lateral recumbency over the period of monitoring by intravenous injections of either etorphine or carfentanil.

Following immobilization with etorphine, mean physiological values for elephants were: systolic pressure, 229 ± 33 mm Hg; diastolic pressure, 141 ± 30 mm Hg; mean arterial pressure, 177 ± 30 mm Hg; heart rate 64 ± 10 beats/minute; respiratory rate 10 ± 4 breaths/minute; body temperature, 97 ± 2°F. Mean physiological values at the final time period of monitoring prior to antagonism were: systolic pressure, 217 ± 40 mm Hg; diastolic pressure, 147 ± 36 mm Hg; mean arterial pressure, 176 ± 38mm Hg; heart rate 77 ± 13 beats/minute; respiratory rate 12 ± 1 breaths/minute; body temperature, 98 ± 2°F. Immediately following the last recording, all 8 elephants received the experimental opioid antagonist, nalmefene hydrochloride, administered at 38 ± 11 µg/kg of body weight given both subcutaneously and intravenously. The mean standing time following administration of nalmefene was 1.4 ± 0.7 minutes.

Immediately following immobilization with carfentanil, mean physiological values for elephants were: systolic pressure, 232 ± 28 mm Hg; diastolic pressure, 148 ± 14 mm Hg; mean arterial pressure, 183 ± 24 mm Hg; heart rate 57 ± 11 beats/minute; respiratory rate 11 ± 3 breaths/minute; body temperature, 99 ± 1°F. Mean physiological values at the final time period of monitoring prior to antagonism were: systolic pressure, 224 ± 29 mm Hg; diastolic pressure, 146 ± 13 mm Hg; mean arterial pressure, 179 ± 18mm Hg; heart rate 65 ± 11 beats/minute; respiratory rate 12 ± 1 breaths/minute; body temperature, 99 ± 1°F. Immediately following the last recording, all 6 elephants received the opioid antagonist, nalmefene hydrochloride administered at 62 ± 17 µg/kg of body weight given both subcutaneously and intravenously. The mean standing time following administration of nalmefene was 2.6 ± 1.6 minutes.

The results of this study indicated that both etorphine and carfentanil resulted in high blood pressure over the duration of the period of monitoring. Based upon these findings, both etorphine hydrochloride and carfentanil citrate are not recommended as the primary agent in performing major invasive surgical procedures in African elephants.

## NALOXONE HCL

**Chemistry** - An opiate antagonist, naloxone HCl is structurally related to oxymorphone. It occurs as a white to slightly off-white powder with a $pK_a$ of 7.94. Naloxone is soluble in water and slightly soluble in alcohol. The pH range of commercially available injectable solutions are from 3-4.5. Naloxone HCl may also be known as *N*-allylnoroxymorphone HCl.

**Storage/Stability/Compatibility** - Naloxone HCl for injection should be stored at room temperature (15-30°C) and protected from light.

Sterile water for injection is the recommended diluent for naloxone injection. When given as an IV infusion, either $D_5W$ or normal saline should be used. Naloxone HCl injection should not be mixed with solutions containing sulfites, bisulfites, long-chain or high molecular weight anions or any solutions at alkaline pH.

**Pharmacology** - Naloxone is considered to be a pure opiate antagonist and it has basically no analgesic activity. The exact mechanism for its activity is not understood, but it is believed that the drug acts as a competitive antagonist by binding to the *mu*, *kappa*, and *sigma* opioid receptor sites. The drug apparently has its highest affinity for the *mu* receptor.

To Drug Monograph Index To Ophthalmic Product Index

Naloxone reverses the majority of effects associated with high-dose opiate administration (respiratory and CNS depression). In dogs, naloxone apparently does not reverse the emetic actions of apomorphine.

Naloxone also has other pharmacologic activity at high doses, including effects on dopaminergic mechanisms (increases dopamine levels) and GABA antagonism.

**Uses/Indications** - Naloxone is used in veterinary medicine almost exclusively for its opiate reversal effects, but the drug is being investigated for treating other conditions (*e.g.,* septic, hypovolemic or cardiogenic shock). Naloxone may also be employed as a test drug to see if endogenous opiate blockade will result in diminished tail-chasing or other self-mutilating behaviors.

**Pharmacokinetics** - Naloxone is only minimally absorbed when given orally as it is rapidly destroyed in the GI tract. Much higher doses are required if using this route of administration for any pharmacologic effect. When given IV, naloxone has a very rapid onset of action (usually 1-2 minutes). If given IM, the drug generally has an onset of action within 5 minutes of administration. The duration of action usually persists from 45-90 minutes, but may act for up to 3 hours.

Naloxone is distributed rapidly throughout the body with high levels found in the brain, kidneys, spleen, skeletal muscle, lung and heart. The drug also readily crosses the placenta.
Naloxone is metabolized in the liver, principally via glucuronidative conjugation with metabolites excreted into the urine. In humans, the serum half-life is approximately 60-100 minutes.

**Contraindications/Precautions/Reproductive Safety** - Naloxone is contraindicated in patients hypersensitive to it. It should be used cautiously in animals that have preexisting cardiac abnormalities or in animals that may be opioid dependent. The veterinary manufacturer states to use the drug "...cautiously in animals who have received exceedingly large doses of narcotics. ... may produce an acute withdrawal syndrome and smaller doses should be employed." (Package Insert; *P/M® Naloxone HCl Injection*—P/M; Mallinckrodt)

Naloxone is generally considered to be non-teratogenic in animals, but has precipitated withdrawal in opioid-dependent human fetuses.

**Adverse Effects/Warnings** - At usual doses, naloxone is relatively free of adverse effects in non-opioid dependent patients. Because the duration of action of naloxone may be shorter than that of the narcotic being reversed, animals that are being treated for opioid intoxication or with symptoms of respiratory depression should be closely monitored as additional doses of naloxone and/or ventilatory support may be required.

**Overdosage/Acute Toxicity** - Naloxone is considered to be a very safe agent with a very wide margin of safety, but very high doses have initiated seizures (secondary to GABA antagonism?) in a few patients.

**Drug Interactions** - Naloxone also reverses the effects of opioid agonists/antagonists such as **butorphanol, pentazocine or nalbuphine**.

**Doses -**
**Horses**:

For opioid reversal:

a) 0.01 - 0.022 mg/kg to reverse sedative and excitatory effects of narcotic agonists. (Clark and Becht 1987)
b) 0.01 mg/kg IV to limit increases in locomotor activity secondary to narcotic agonists. (Muir 1987)
c) 0.01 - 0.02 mg/kg IV (Robinson 1987)

To Drug Monograph Index To Ophthalmic Product Index

**Elephants:**

To reverse the effects of etorphine, morphine, and meperidine:
a,b,c) 10 mg total dose in small elephants; up to 30-50 mg in adults. Smuts, 1975).

a) Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants** . In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

b) Schmidt,M.J., 1986. **Proboscidea (Elephants)**. In: Fowler,M.E. (Editor), Zoo and wild animal medicine. W.B. Saunders, Philadelphia,PA, USA pp. 884-923

c) Smuts,G.L. 1975. **An appraisal of naloxone hydrochloride as a narcotic antagonist in the capture and release of wild herbivores**. J Am Vet Med Assoc 167:(7):559-561
**Abstract:** Naloxone hydrochloride was used as the narcotic antagonist during capture operations conducted on 84 specimens of 11 game species in the Kruger National Park, South Africa. It was found that 10 mg of naloxone was sufficient to antagonize wide dosage ranges of etorphine hydrochloride or fentanyl, used in combination with a variety of tranquilizers. The absence of undesirable side effects and the fact that naloxone can be administered without fear of over dosage make it a unique and valuable drug in the capture and release of wild animals.

**Monitoring Parameters** -
1) Respiratory rate/depth
2) CNS function
3) Pain associated with opiate reversal

**Client Information** - Should be used with direct professional supervision only.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Naloxone HCl Injection 0.4 mg/ml in 10 ml vials; *P/M*® *Naloxone HCl Injection* (Schering Plough); (Rx) Approved for use in dogs.

**Human-Approved Products**:

Naloxone HCl Injection 0.4 mg/ml in 1 ml amps, syringes & 1, 2, & 10 ml vials; *Narcan*® (Dupont Pharm.), Generic; (Rx)

Naloxone HCl Injection 1 mg/ml in 2 ml amps, vials & 1, 5, & 10 ml vials; *Narcan*® (Dupont Pharm.), Generic; (Rx)

Naloxone HCl Neonatal Injection 0.02 mg/ml in 2 ml amps, & vials; *Narcan*® (Dupont Pharm); Generic; (Rx)

## NALTREXONE HCL

**Chemistry** - A synthetic opiate antagonist, naltrexone HCl occurs as white crystals having a bitter taste. 100 mg are soluble in one ml of water.

To Drug Monograph Index To Ophthalmic Product Index

**Storage/Stability/Compatibility** - Naltrexone tablets should be stored at room temperature in well-closed containers.

**Pharmacology** - Naltrexone is an orally available narcotic antagonist. It competitively binds to opiate receptors in the CNS, thereby preventing both endogenous opiates (*e.g.*, endorphins) and exogenously administered opiate agonists or agonist/antagonists from occupying the site. Naltrexone may be more effective in blocking the euphoric aspects of the opiates and less effective at blocking the respiratory depressive or miotic effects.

Naltrexone may also increase plasma concentrations of luteinizing hormone (LH), cortisol and ACTH. In dogs with experimentally-induced hypovolemic shock, naltrexone (like naloxone) given IV in high dosages increased mean arterial pressure, cardiac output, stroke volume, and left ventricular contractility.

**Uses/Indications** - Naltrexone may be useful in the treatment of self-mutilating or tail-chasing behaviors in dogs or cats.

**Pharmacokinetics** - In humans, naltrexone is rapidly and nearly completed absorbed, but undergoes a significant first-pass effect as only 5-12% of a dose reaches the systemic circulation. Naltrexone circulates throughout the body and CSF levels are approximately 30% of those found in the plasma. Only about 20-30% is bound to plasma proteins. It is unknown whether naltrexone crosses the placenta or enters milk. Naltrexone is metabolized in the liver primarily to 6-beta-naltrexol, which has some opiate blocking activity. In humans, serum half life of naltrexone is about 4 hours; 6-beta-naltrexol, about 13 hours. Naltrexone, as metabolites are then eliminated primarily via the kidney.

**Contraindications/Precautions/Reproductive Safety** - Naltrexone is generally considered to be contraindicated in patients physically dependent on opiate drugs, in hepatic failure or with acute hepatitis. The benefits of the drug versus its risks should be weighed in patients with hepatic dysfunction or who have had a history of allergic reaction to naltrexone or naloxone.

Very high doses have caused increased embryotoxicity in some laboratory animals. It should be used during pregnancy only when the benefits outweigh any potential risks. It is unknown whether naltrexone enters maternal milk.

**Adverse Effects/Warnings** - At usual doses, naltrexone is relatively free of adverse effects in non-opioid dependent patients. Some human patients have developed abdominal cramping, nausea and vomiting, nervousness, insomnia, joint or muscle pain, skin rashes. Dose-dependent hepatotoxicity has been described in humans on occasion.

Naltrexone will block the analgesic, antidiarrheal and antitussive effects of opiate agonist or agonist/antagonist agents. Withdrawal symptoms may be precipitated in physically dependent patients.

**Overdosage/Acute Toxicity** - Naltrexone appears to be relatively safe even after very large doses. The $LD_{50}$ in dogs after subcutaneous injection has been reported to be 200 mg/kg. Oral $LD_{50}$'s in species tested range from 1.1 g/kg in mice to 3 g/kg in monkeys (dogs or cats not tested). Death at these doses were a result of respiratory depression and/or tonic-clonic seizures. Massive overdoses should be treated using gut emptying protocols when warranted and giving supportive treatment.

**Drug Interactions** - In addition to blocking the effects of pure opiate agonists (*e.g.*, **morphine, meperidine, codeine, oxymorphone**, etc.) naltrexone also reverses the effects of opioid agonist/antagonists such as **butorphanol, pentazocine** or **nalbuphine**.

To Drug Monograph Index To Ophthalmic Product Index

**Laboratory Considerations -** Naltrexone reportedly does not interfere with TLC, GLC, or HPLC methods of determining **urinary morphine, methadone or quinine**. Naltrexone may cause increases in hepatic function tests (*e.g.,* **AST, ALT**) (see adverse effects above).

**Doses** –

**Elephants:**

a) Five adult wild African elephants weighing 3000-3500 kg were immobilized with 10 or 12 mg etorphine (28-40 µg/kg). Naltrexone was administered at 100 times the etorphine dose (1000 or 1200 mg). Recovery time was 2-4 minutes. Horne,W.A., Tchamba,M.N., and Loomis,M.R. 2001. **A simple method of providing intermittent positive-pressure ventilation to etorphine-immobilized elephants (Loxodonta africana) in the field**. Journal of Zoo and Wildlife Medicine 32:(4):519-522 **Abstract:** Five African elephants (Loxodonta africana) were immobilized with etorphine in Waza National Park, Cameroon, for the purpose of deploying radio/satellite tracking collars. A portable ventilator constructed from two high-flow demand valves and the Y-piece of a large animal anesthesia circuit was used to provide intermittent positive-pressure ventilation with 100% oxygen. Oxygenation status improved dramatically in all five elephants. In one hypoxemic elephant, arterial PaO2 increased from 40 to 366 mm Hg. The results of this study demonstrate that both oxygenation and ventilation can be readily controlled etorphine-immobilized elephants even under remote field conditions.

b,c) A 2817 kg female Asian elephant was induced with 1.75 mg etorphine IM, followed by 0.75 mg etorphine at 40 minutes. The elephant was intubated with a 30 mm endotracheal tube and maintained with 1.5-2.0% isoflurane. Additional etorphine (total additional 1.4 mg) was supplemented IV during the procedure to surgically remove P-3. Thirty minutes prior to the completion of the procedure isoflurane was discontinued, but oxygen continued to flow. Additional etorphine was given intermittently IV (0.4 mg total) during the remaining 45 minutes of recumbency. Naltrexone (250 mg) was given IV and the elephant was standing within 3 minutes. (b) Fowler,M.E., Steffey,E.P., Galuppo,L., and Pascoe,J.R. 2000. **Facilitation of Asian elephant (Elephas maximus) standing immobilization and anesthesia with a sling**. Journal of Zoo and Wildlife Medicine 31:(1):118-123 **Abstract:** An Asian elephant (Elephas maximus) required general anesthesia for orthopedic foot surgery. The elephant was unable to lie down, so it was placed in a custom-made sling, administered i.m. etorphine hydrochloride in the standing position, and lowered to lateral recumbency. General anesthesia was maintained with isoflurane administered through an endotracheal tube. After surgery, the isoflurane anesthesia was terminated, with immobilization maintained with additional i.v. etorphine. The elephant was lifted to the vertical position, and the immobilizing effects of etorphine were reversed with naltrexone. The suspension system and hoist for the sling were designed specifically for the elephant house.

c) Fowler,M.E., Steffey,E.P., Galuppo,L., and Pascoe,J.R. 1999. **Standing immobilization and anesthesia in an Asian elephant (*Elephas maximus*)**. Proc. Am. Assoc. Zoo Vet. Pages: 107-110

d) Thirty-seven wild African elephants were immobilized as follows: Calves (4-6 years; n=4) were immobilized with 1 mg carfentanil and adults with 3 mg carfentanil mixed with 1500 IU of hyaluronidase. All animals were reversed with naltrexone at a rate of 100 mg for every mg of carfentanil used. For 15 elephants, mean minutes elapsed for initial effect of standing still, recumbency, and recovery following reversal were 5.0 ±1.6, 10.7±3.9, and 5.9±3.9 respectively. Karesh,W.B., Smith,K.H., Smith,F., Atalia,M., Morkel,P., Torres,A., House,C., Braselton,W.E., and Dierenfeld,E.S. 1997. **Elephants, buffalo, kob, and rhinoceros: immobilization, telemetry, and health evaluations.** Proceedings American Association of Zoo Veterinarians. Pages: 296-230

e) Naltrexone dose (mg) = 50 times the carfentanil dose. Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants**. In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441

To Drug Monograph Index To Ophthalmic Product Index

f) To reverse carfentanil in wild African elephants naltrexone is used at 40 times the carfentanil dose. Raath,J.P. 1993. **Chemical capture of the African elephant**. In: The Capture and care manual : capture, care, accommodation and transportation of wild African animals. Pretoria : Wildlife Decision Support Services : South African Veterinary Foundation, Pretoria pp. 484-511

g) For reversal of carfentanil, 100 mg naltrexone per mg of carfentanil .Lance,W.R. 1991. **New pharmaceutical tools for the 1990's**. Proceedings of the American Association of Zoo Veterinarians 354-359

**Monitoring Parameters** - 1) Efficacy; 2) Liver enzymes if using very high dose prolonged therapy

**Client Information** - Stress the importance of compliance with prescribed dosing regimen. Additional behavior modification techniques may be required to alleviate symptoms.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: Trexonil (Wildlife Pharmaceuticals)

**Human-Approved Products**:

Naltrexone HCl Oral Tablets 50 mg; *ReVia*®(DuPont); (Rx)

## NAPROXEN

**Chemistry** - Naproxen is a propionic acid derivative, and has similar structure and pharmacologic profiles as ibuprofen and ketoprofen. It is a white to off-white crystalline powder with an apparent $pK_a$ of 4.15. It is practically insoluble in water and freely soluble in alcohol. The sodium salt is also available commercially for human use.

**Storage/Stability/Compatibility** - Naproxen should be stored in well-closed, light resistant containers and stored at room temperature. Temperatures above 40° C (104°F) should be avoided.

**Pharmacology** - Like other NSAIDs, naproxen exhibits analgesic, anti-inflammatory, and antipyrexic activity probably through its inhibition of cyclooxygenase with resultant impediment of prostaglandin synthesis.

**Pharmacokinetics** - In horses, the drug is reported to have a 50% bioavailability after oral dosing and a half-life of approximately 4 hours. Absorption does not appear to be altered by the presence of food. It may take 5-7 days to see a beneficial response after starting treatment. Following a dose, the drug is metabolized in the liver. It is detectable in the urine for at least 48 hours in the horse after an oral dose.

In dogs, absorption after oral dosing is rapid and bioavailability is between 68-100%. The drug is highly bound to plasma proteins. The average half-life in dogs is very long at 74 hours.

In humans, naproxen is highly bound to plasma proteins (99%). It crosses the placenta and enters milk at levels of about 1% of those in serum.

**Uses/Indications** - The manufacturer lists the following indications: ".... for the relief of inflammation and associated pain and lameness exhibited with myositis and other soft tissue diseases of the musculoskeletal system of the horse." (Package Insert; *Equiproxen*®—Syntex). It has also been used as an antiinflammatory/analgesic in dogs for the treatment of osteoarthritis and other musculoskeletal inflammatory diseases (see adverse reactions below).

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions** - Naproxen is relatively contraindicated in patients with a history of, or preexisting hematologic, renal or hepatic disease. It is contraindicated in patients with active GI ulcers or with a history of hypersensitivity to the drug. It should be used cautiously in patients with a history of GI ulcers, or heart failure (may cause fluid retention). Animals suffering from inflammation secondary to concomitant infection, should receive appropriate antimicrobial therapy.

In studies in rodents and in limited studies in horses, no evidence of teratogenicity or adverse effects in breeding performance have been detected following the use of naproxen. However, the potential benefits of therapy must be weighed against the potential risks of its use in pregnant animals.

**Adverse Effects/Warnings** - Adverse effects are apparently uncommon in horses. The possibility exists for GI (distress, diarrhea, ulcers), hematologic (hypoproteinemia, decreased hematocrit), renal (fluid retention) and CNS (neuropathies) effects.

Reports of GI ulcers and perforation associated with naproxen has occurred in dogs. Dogs may also be overly sensitive to the adverse renal effects (nephritis/nephrotic syndrome) and hepatic (increased liver enzymes) effects with naproxen. Because of the apparent very narrow therapeutic index and the seriousness of the potential adverse reactions that can be seen in dogs, many clinicians feel that the drug should not be used in this species.

**Overdosage** - There is very limited information regarding acute overdoses of this drug in humans and domestic animals. The reported oral $LD_{50}$ in dogs is >1000 mg/kg. Treatment should follow standard overdose procedures (empty gut following oral ingestion, etc.). Animal studies have demonstrated that activated charcoal may bind significant amounts of naproxen. Supportive treatment should be instituted as necessary. Because naproxen may cause renal effects, monitor electrolyte and fluid balance carefully and manage renal failure using established guidelines.

One report of a dog who received 5.6 mg/kg for 7 days has been published (Gilmour and Walshaw 1987). The dog presented with symptoms of melena, vomiting, depression, regenerative anemia, and pale mucous membranes. Laboratory indices of note included, neutrophilia with a left shift, BUN of 66 mg/dl, serum creatinine of 2.1 mg/dl, serum protein:albumin of 4.0:2.1 g/dls. The dog recovered following treatment with fluids/blood, antibiotics, vitamin/iron supplementation, oral antacids and cimetidine.

**Drug Interactions** - Because naproxen is highly bound to plasma proteins and may displace other highly bound drugs, increased serum levels and duration of actions of **phenytoin, valproic acid, oral anticoagulants**, other **anti-inflammatory agents, salicylates, sulfonamides**, and the **sulfonylurea antidiabetic agents** can occur. If naproxen is used concurrently with **warfarin**, enhanced hypoprothrombinemic effects have not been noted, but because of the tendency of naproxen to induce GI bleeding it should be used cautiously in patients on warfarin therapy. When **aspirin** is used concurrently with naproxen, plasma levels of naproxen may decrease as well as an increased likelihood of GI adverse effects (blood loss) developing. Concomitant administration of aspirin with naproxen is not recommended. **Probenicid** may cause a significant increase in serum levels and half-life of naproxen.
Serious toxicity has occurred when NSAIDs have been used concomitantly with **methotrexate**; use together with extreme caution. Naproxen may reduce the saluretic and diuretic effects of **furosemide**. Use with caution in patients with severe cardiac failure.

**Doses -**
**Horses**:

a) 5 mg/kg by slow IV, then 10 mg/kg PO (top dressed in feed) twice daily for up to 14 days or 10 mg/kg PO (top dressed in feed) *bid* for up to 14 consecutive days. (Package Insert; *Equiproxen*® - Syntex Animal Health)

To Drug Monograph Index To Ophthalmic Product Index

**Monitoring Parameters** -

1) Analgesic/anti-inflammatory efficacy
2) GI: appetite, feces (occult blood, diarrhea)
3) PCV (packed cell volume), hematocrit if indicated or on chronic therapy
4) WBC's if indicated or on chronic therapy

**Client Information** - Notify veterinarian if symptoms of GI distress (anorexia, vomiting in dogs, diarrhea, black feces or blood in stool) occur, or if animal becomes depressed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Naproxen 10% (100 mg/ml) Veterinary Solution for Injection; 2 gm vial with 19 ml vial of sterile water for injection. Use entire contents immediately after reconstituting. Makes 20 ml of 10% (100 mg/ml) solution.; *Equiproxen*® (Fort Dodge); (Rx) Approved for us in horses not intended for food.

Naproxen Veterinary Granules; Each 8 gram packet contains 4 grams of naproxen. Cartons of 14 - 8 gram packets; *Equiproxen*® (Fort Dodge); (Rx) Approved for us in horses not intended for food.

**Human-Approved Products:**

Naproxen Oral tablets (scored) 250 mg, 375 mg, 500 mg; *Naprosyn*® (Syntex); Generic (Rx)

Naproxen Oral Suspension 125 mg/5 ml in pints; *Naprosyn*® (Syntex); Generic (Rx)

## NARCOTIC (OPIATE) AGONIST ANALGESICS

Receptors for opiate analgesics are found in high concentrations in the limbic system, spinal cord, thalamus, hypothalamus, striatum, and midbrain. They are also found in tissues such as the gastrointestinal tract, urinary tract, and in other smooth muscle.

Opiate receptors are further broken down into five main sub-groups. *Mu* receptors are found primarily in the pain regulating areas of the brain. They are thought to contribute to the analgesia, euphoria, respiratory depression, physical dependence, miosis, and hypothermic actions of opiates. *Kappa* receptors are located primarily in the deep layers of the cerebral cortex and spinal cord. They are responsible for analgesia, sedation and miosis. *Sigma* receptors are thought to be responsible for the dysphoric effects (struggling, whining), hallucinations, respiratory and cardiac stimulation, and mydriatic effects of opiates. *Delta* receptors, located in the limbic areas of the CNS and *epsilon* receptors have also been described, but their actions have not been well explained at this time.

The morphine-like agonists (morphine, meperidine, oxymorphone) have primary activity at the *mu* receptors, with some activity possible at the *delta* receptor. The primary pharmacologic effects of these agents include: analgesia, antitussive activity, respiratory depression, sedation, emesis, physical dependence, and intestinal effects (constipation/defecation). Secondary pharmacologic effects include: CNS: euphoria, sedation, & confusion. Cardiovascular: bradycardia due to central vagal stimulation, alpha-adrenergic receptors may be depressed resulting in peripheral vasodilation, decreased peripheral resistance, and baroreceptor inhibition. Orthostatic hypotension and syncope may occur. Urinary: Increased bladder sphincter tone can induce urinary retention.

Various species may exhibit contradictory effects from these agents. For example, horses, cattle, swine, and cats may develop excitement after morphine injections and dogs may defecate after morphine. These effects are in contrast to the expected effects of sedation and constipation. Dogs and humans may develop

miosis, while other species (especially cats) may develop mydriasis. For more information see the individual monographs for each agent.

## NEOMYCIN SULFATE

**Chemistry** - An aminoglycoside antibiotic obtained from *Streptomyces fradiae*, neomycin is actually a complex of three separate compounds, neomycin A (neamine; inactive), neomycin C and neomycin B (framycetin). The commercially available product almost entirely consists of the sulfate salt of neomycin B. It occurs as an odorless or almost odorless, white to slightly yellow, hygroscopic powder or cryodessicated solid. It is freely soluble in water and very slightly soluble in alcohol. One mg of pure neomycin sulfate is equivalent to not less than 650 Units. Oral or injectable (after reconstitution with normal saline) solutions of neomycin sulfate have a pH from 5-7.5.

**Storage/Stability/Compatibility** - Neomycin sulfate oral solution should be stored at room temperature (15-30°C) in tight, light-resistant containers. Unless otherwise instructed by the manufacturer, oral tablets/boluses should be stored in tight containers at room temperature. The sterile powder should be stored at room temperature and protected from light. In the dry state, neomycin is stable for at least 2 years at room temperature.

**Pharmacology** - Neomycin has a mechanism of action and spectrum of activity (primarily gram negative aerobes) similar to the other aminoglycosides, but in comparison to either gentamicin or amikacin, it is significantly less effective against several species of gram negative organisms, including strains of *Klebsiella*, *E. coli* and *Pseudomonas*. However, most strains of neomycin-resistant bacteria of these species remain susceptible to amikacin. More information on the aminoglycosides mechanism of action and spectrum of activity is outlined in more detail in the amikacin monograph.

**Uses/Indications** - Because neomycin is more nephrotoxic and less effective against several bacterial species than either gentamicin or amikacin, its use is generally limited to the oral treatment of enteral infections, to reduce microbe numbers in the colon prior to colon surgery, and orally or in enema form to reduce ammonia-producing bacteria in the treatment of hepatic encephalopathy. Doses for parenteral administration are listed below, but should be used only with extreme caution due to the drug's toxic potential.

**Pharmacokinetics** - Approximately 3% of a dose of neomycin is absorbed after oral or rectal (retention enema) administration, but this can be increased if gut motility is slowed or if the bowel wall is damaged. Therapeutic levels are not attained in the systemic circulation after oral administration.

After IM administration, therapeutic levels can be attained with peak levels occurring within 1 hour of dosing. The drug apparently distributes to tissues and is eliminated like the other aminoglycosides (refer to Amikacin monograph for more details). Orally administered neomycin is nearly all excreted unchanged in the feces.

**Contraindications/Precautions/Reproductive Safety** - More detailed information on the contraindications, precautions and reproductive safety of the aminoglycoside antibiotics can be found in the amikacin monograph.

Oral neomycin is contraindicated in the presence of intestinal obstruction or if the patient is hypersensitive to aminoglycosides.

Chronic usage of oral aminoglycosides may result in bacterial or fungal superinfections.

To Drug Monograph Index To Ophthalmic Product Index

Because oral neomycin is only minimally absorbed, it is unlikely significant systemic or teratogenic effects should occur. However, one group of authors (Caprile and Short 1987) recommends that the drug not be used orally in foals.

**Adverse Effects/Warnings**, **Overdosage/Acute Toxicity -** Refer to the amikacin monograph for more information regarding these topics with parenteral neomycin. Rarely, oral neomycin may cause ototoxicity, nephrotoxicity, severe diarrhea and intestinal malabsorption.

**Drug Interactions**, **Drug/Laboratory Interactions** - Refer to the amikacin monograph for more information regarding drug interactions with parenteral neomycin. In addition: Oral neomycin should not be given concurrently with oral **penicillin VK** as malabsorption of the penicillin may occur.

Oral neomycin with orally administered **digitalis preparations (***e.g.,* **digoxin)** may result in decreased absorption of the digitalis. Separating the doses of the two medications may not alleviate this effect. Some human patients (<10%) metabolize digoxin in the GI tract and neomycin may increase serum digoxin levels in these patients. It is recommended that if oral neomycin is added or withdrawn from the drug regimen of a patient stabilized on a digitalis glycoside, that enhanced monitoring be performed.

Oral neomycin may decrease the amount of **vitamin K** absorbed from the gut; this may have ramifications for patients receiving **oral anticoagulants**. **Methotrexate** absorption may be reduced by oral neomycin but is increased by oral kanamycin (found in *Amforal*®).
Although only minimal amounts of neomycin are absorbed after oral or rectal administration, the concurrent use of **other ototoxic or nephrotoxic drugs** with neomycin should be done with caution.

**Doses** -
**Horses**:

For oral administration to treat susceptible enteral infections:

a) Adults: 4 - 7.5 g/day PO divided 2-4 times daily at regular intervals. Foals: 2 - 3 g/day PO divided 2-4 times daily at regular intervals. Doses are not standardized; use for general guidance only. (Brander, Pugh, and Bywater 1982)
b) 5 - 15 mg/kg PO once daily (Robinson 1987)

For respiratory tract infections:

a) For pleuritis and less frequently pneumonia: 4.4 mg/kg IM or IV q8-12h. Nephrotoxicity and/or ototoxicity can occur; nephrotoxicity more common in foals. Local myositis seen with IM dosing particularly if treatment is longer than 7 days. Systemic use of oral form is not approved, but is used with penicillin to increase gram negative coverage (Beech 1987b)

**Monitoring Parameters** -
For oral use:

1) Clinical efficacy
2) Systemic and GI adverse effects with prolonged use

For parenteral use: Refer to Amikacin monograph

**Client Information** - Clients should understand that the potential exists for severe toxicity (nephrotoxicity, ototoxicity) developing from this medication when used parenterally.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Neomycin Sulfate Oral Liquid 200 mg/ml

To Drug Monograph Index To Ophthalmic Product Index

*Biosol*® (Upjohn); (OTC) Approved for use in cattle, swine, sheep, turkeys, laying hens, and broilers. Withdrawal times: Cattle = 30 days; Sheep and swine = 20 days, Turkeys and Layers = 14 days; Broilers = 5 days.

Also available as generically labeled products.

Neomycin Sulfate Oral Solution 50 mg/ml in 10 ml dropper bottles

*Biosol Aquadrops*® (Upjohn); (OTC) Approved for use in dogs and cats.

Neomycin Sulfate Oral Tablets 100 mg

*Biosol*® *Tablets* (Upjohn); (OTC) Approved for use in dogs and cats.

Neomycin Sulfate Intrauterine or Oral Boluses 500 mg; *Biosol*® *Boluses* (Upjohn); (OTC) Approved for use in cattle, foals, swine, and sheep. Slaughter withdrawal times: Cattle = 30 days; Sheep and swine = 20 days. Milk withdrawal = 48 hours.

Neomycin Sulfate Soluble Powder 3.125 g/ounce;*Biosol*® *Soluble Powder* (Upjohn); (OTC) Approved for use in dogs, cats, cattle, swine, sheep, and horses. Slaughter withdrawal times: Cattle = 30 days; Sheep and swine = 20 days.

Neomycin Powder Water/Feed Additive 325 g/lb; *Biosol 325*® (Upjohn), *Neomix Ag*® *325* (Upjohn); (OTC) Approved for use in chickens, turkeys, ducks, nonlactating dairy cattle, beef cattle, goats, horses, mink, sheep, and swine. Slaughter withdrawal times: Cattle = 30 days; Sheep and swine = 20 days, Turkeys & layers = 14 days; Broilers = 5 days.

There are several combination neomycin veterinary products, the following are examples:

Neomycin 25 mg, isopropamide 1.67 mg, prochlorperazine 3.33 mg capsules; Neomycin 75 mg, isopropamide 5 mg, prochlorperazine 10 mg capsules; *Neo-Darbazine*® *#1* (Pfizer); (Rx) Approved for use in dogs. *Neo-Darbazine*® *#3* (SKB); (Rx) Approved for use in dogs.

**Human-Approved Products**:

Neomycin Sulfate Oral Tablets 500 mg; *Neo-Tabs*® (Pharma-Tek) (Rx), generic (Rx)

Neomycin Sulfate Oral Solution 25 mg/ml in pints;*Mycifradin*® (Upjohn);*Neo-fradin*® (Pharma-Tek); (Rx)

## NEOSTIGMINE
## NEOSTIGMINE METHYLSULFATE

**Chemistry** - Synthetic quaternary ammonium parasympathomimetic agents, neostigmine bromide and neostigmine methylsulfate both occur as odorless, bitter-tasting, white, crystalline powders that are very soluble in water and soluble in alcohol. The melting point of neostigmine methylsulfate is from 144-149°. The pH of the commercially available neostigmine methylsulfate injection is from 5-6.5.

**Storage/Stability/Compatibility** - Neostigmine bromide tablets should be stored at room temperature in tight containers. Neostigmine methylsulfate injection should be stored at room temperature and protected from light; avoid freezing.

Neostigmine methylsulfate injection is reportedly **compatible** with the commonly used IV replacement solutions and the following drugs: glycopyrrolate, pentobarbital sodium, and thiopental sodium.

**Pharmacology** - Neostigmine competes with acetylcholine for acetylcholinesterase. As the neostigmine-acetylcholinesterase complex is hydrolyzed at a slower rate than that of the acetylcholine-enzyme complex, acetylcholine will accumulate with a resultant exaggeration and prolongation of its effects. These effects can include increased tone of intestinal and skeletal musculature, stimulation of salivary and sweat glands,

bronchoconstriction, ureter constriction, miosis and bradycardia. Neostigmine also has a direct cholinomimetic effect on skeletal muscle.

**Uses/Indications -** Neostigmine is indicated for rumen atony, initiating peristalsis, emptying the bladder and stimulating skeletal muscle contractions in cattle, horses, sheep and swine (Package insert; *Stiglyn*® 1:500 - P/M; Mallinckrodt). It has also been used in the diagnosis and treatment of myasthenia gravis and in treating non-depolarizing neuromuscular blocking agents (curare-type) overdoses in dogs.

**Pharmacokinetics** - Information on the pharmacokinetics of neostigmine in veterinary species was not located. In humans, neostigmine bromide is poorly absorbed after oral administration with only 1-2% of the dose absorbed. Neostigmine effects on peristaltic activity in humans begin within 10-30 minutes after parenteral administration and can persist for up to 4 hours.

Neostigmine is 15-25% bound to plasma proteins. It has not been detected in human milk nor would be expected to cross the placenta when given at usual doses.
In humans, the half-life of the drug is approximately one hour. It is metabolized in the liver and also hydrolyzed by cholinesterases to 3-OH PTM which is weakly active. When administered parenterally, approximately 80% of the drug is excreted in the urine within 24 hours, with 50% excreted unchanged.

**Contraindications/Precautions** - Neostigmine is contraindicated in patients with peritonitis, mechanical intestinal or urinary tract obstructions, late stages of pregnancy, in animals hypersensitive to this class of compounds or treated with other cholinesterase inhibitors.

Use neostigmine with caution in patients with epilepsy, peptic ulcer disease, bronchial asthma, cardiac arrhythmias, hyperthyroidism, vagotonia or megacolon.

**Adverse Effects/Warnings** - Adverse effects of neostigmine are dose-related and cholinergic in nature. See overdosage section below.

**Overdosage** - Overdosage of neostigmine can induce a cholinergic crisis. Symptoms can include nausea, vomiting, diarrhea, excessive salivation and drooling, sweating (in animals with sweat glands), miosis, lacrimation, increased bronchial secretions, bradycardia or tachycardia, cardiospasm, bronchospasm, hypotension, muscle cramps and weakness, agitation, restlessness or paralysis. In patients with myasthenia gravis, it may be difficult to distinguish between a cholinergic crisis and myasthenic crisis. A test dose of edrophonium, should differentiate between the two.

Cholinergic crisis is treated by temporarily ceasing neostigmine therapy and instituting treatment with atropine (doses are listed in the Atropine monograph). Maintain adequate respirations using mechanical assistance if necessary.

**Drug Interactions** - Anticholinesterase therapy may be antagonized by administration of parenteral **magnesium** therapy, as it can have a direct depressant effect on skeletal muscle.
**Drugs that possess some neuromuscular blocking activity** (*e.g.,* aminoglycoside antibiotics, some antiarrhythmic and anesthetic drugs) may necessitate increased dosages of neostigmine in treating or diagnosing myasthenic patients. **Corticosteroids** may decrease the anticholinesterase activity of neostigmine. After stopping corticosteroid therapy, neostigmine may cause increased anticholinesterase activity. Neostigmine may prolong the Phase I block of **depolarizing muscle relaxants** (*e.g.,* succinylcholine, decamethonium). Neostigmine antagonizes the actions of **non-depolarizing neuromuscular blocking agents** (pancuronium, tubocurarine, gallamine, etc.). **Atropine** will antagonize the muscarinic effects of neostigmine and is often used to reduce neostigmine's side effects. Use cautiously however, as atropine can mask the early symptoms of cholinergic crisis. Theoretically, **dexpanthenol** may have additive effects when used with neostigmine.

To Drug Monograph Index To Ophthalmic Product Index

**Doses -**

**Horses**:

a) 1 mg/100 lbs of body weight SQ; repeat as indicated (Package Insert; *Stiglyn*® 1:500 - P/M; Mallinckrodt)

For treatment of paralytic ileus of large colon:

a) 2 - 4 mg SQ q2h. Use after correction of large bowel displacement; discontinue when GI motility returns. May cause increased secretion into GI tract and therefore may be harmful in small intestinal disease. Does not produce progressive contractions of small intestine. (Stover 1987)
b) 0.02 mg/kg SQ; duration of action may be very short (15-30 minutes); does not increase propulsive motility of jejunum and may delay gastric emptying time. (Clark and Becht 1987)

**Elephants:**

a) 4-5 mg/animal IM as a purgative in impactions; author's clinical experience. a) Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1995. **Principles and Practice of Fixing Dose of Drugs for Elephants**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 430-438

**Monitoring Parameters** - Dependent on reason for use.

1) Adverse reactions (see Adverse Reactions and Overdosage above)
2) Clinical efficacy

**Client Information** - This product should be used by professionals in situations where the drug's effects can be monitored.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Neostigmine Tablets 15 mg; *Prostigmin*® (ICN); (Rx)

Neostigmine Methylsulfate Injection 1:1000 (1 mg/ml), 1:2000 (0.5 mg/ml), 1:4000 (0.25 mg/ml) in 1 ml amps and 10 ml vials; *Prostigmin*® (ICN); Generic; (Rx)

## NITROFURANTOIN

**Chemistry** - A synthetic, nitrofuran antibacterial, nitrofurantoin occurs as a bitter tasting, lemon-yellow, crystalline powder with a $pK_a$ of 7.2. It is very slightly soluble in water or alcohol.

**Storage/Stability/Compatibility** - Nitrofurantoin preparations should be stored in tight containers at room temperature and protected from light. The oral suspension should not be frozen. Nitrofurantoin will decompose if contacted with metals other than aluminum or stainless steel.

**Pharmacology** - Nitrofurantoin acts usually as a bacteriostatic antimicrobial, but may be bactericidal depending on the concentration of the drug and the susceptibility of the organism. The exact mechanism of action of nitrofurantoin has not been fully elucidated, but the drug apparently inhibits various bacterial enzyme systems, including acetyl coenzyme A. Nitrofurantoin has greater antibacterial activity in acidic environments.

To Drug Monograph Index To Ophthalmic Product Index

Nitrofurantoin has activity against several gram negative and some gram positive organisms, including many strains of *E. coli, Klebsiella, Enterobacter, Enterococci, Staphylococcus aureus* and *epidermidis, Enterobacter, Citrobacter, Salmonella*, Shigella, and Corynebacterium. It has little or no activity against most strains of *Proteus*, *Serratia* or *Acinetobacter* and has no activity against *Pseudomonas sp*..

**Uses/Indications** - Considered a urinary tract antiseptic, nitrofurantoin is used primarily in small animals, but also occasionally in horses in the treatment of lower urinary tract infections caused by susceptible bacteria. It is not effective in treating renal cortical or perinephric abscesses or other systemic infections.

**Pharmacokinetics** - Nitrofurantoin is rapidly absorbed from the GI tract and the presence of food may enhance the absorption of the drug. Macrocrystalline forms of the drug may be absorbed more slowly with less GI upset. Because of its slower absorption, urine levels of the drug may be prolonged.

Because of the rapid elimination of the drug after absorption, therapeutic levels in the systemic circulation are not maintained. Approximately 20-60% of the drug is bound to serum proteins. Peak urine levels occur within 30 minutes of dosing. The drug crosses the placenta and only minimal quantities of the drug are found in milk.

Approximately 40-50% of the drug is eliminated into urine unchanged via both glomerular filtration and tubular secretion. Some of the drug is metabolized, primarily in the liver. Elimination half-lives in humans with normal renal function average 20 minutes.

**Contraindications/Precautions/Reproductive Safety** - Nitrofurantoin is contraindicated in patients with renal impairment as the drug is much less efficacious and the development of toxicity is much more likely. The drug is also contraindicated in patients hypersensitive to it.

In humans, the drug is contraindicated in pregnant patients at term and in neonates as hemolytic anemia can occur secondary to immature enzyme systems. Safe use of the drug during earlier stages of pregnancy has not been determined. Nitrofurantoin has been implicated in causing infertility in male dogs. Use only when the benefits of therapy outweigh the potential risks.

**Adverse Effects/Warnings** - In dogs and cats, gastrointestinal disturbances and hepatopathy can occur with this drug. Neuropathies, chronic active hepatitis, hemolytic anemia and pneumonitis have been described in humans, but are believed to occur very rarely in animals.

**Overdosage/Acute Toxicity** - No specific information was located. Because the drug is rapidly absorbed and excreted. Patients with normal renal function should require little therapy when mild overdoses occur. Massive overdoses should be handled by emptying the gut using standard protocols if the ingestion was relatively recent, and then monitoring the patient for adverse effects (see above).

**Drug Interactions** - The uricosuric agents **sulfinpyrazone** or **probenecid** may inhibit the renal excretion of nitrofurantoin and potentially increase its toxicity and reduce its effectiveness in urinary tract infections. Nitrofurantoin may antagonize the antimicrobial activity of the fluoroquinolones (*e.g.,* **enrofloxacin, ciprofloxacin**) and their concomitant use is not recommended. **Magnesium trisilicate** containing antacids may inhibit the oral absorption of nitrofurantoin. **Food** or **anticholinergic drugs** may increase the oral bioavailability of nitrofurantoin.

**Drug/Laboratory Interactions** - Nitrofurantoin may cause **false-positive urine glucose** determinations if using cupric sulfate solutions (Benedict's reagent, *Clinitest*®). Tests using glucose oxidase methods (*Tes-Tape*®*, Clinistix*®) are not affected by nitrofurantoin.

To Drug Monograph Index To Ophthalmic Product Index

Nitrofurantoin may cause decreases in **blood glucose**, and increases in serum **creatinine, bilirubin and alkaline phosphatase**.

**Doses** -
**Horses**:
For susceptible urinary tract infections:
a) 2.5 - 4.5 mg/kg PO *tid* (Robinson 1987)
b) 10 mg/kg PO daily (Huber 1988a)

**Monitoring Parameters** -
1) Clinical efficacy
2) Adverse effects
3) Periodic liver function tests should be considered with chronic therapy

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:
Nitrofurantoin Macrocrystals Capsules 25 mg, 50 mg, and 100 mg; *Macrodantin*® (Procter & Gamble Pharm); *Macrobid*® (Procter & Gamble Pharm); generic; (Rx)

Nitrofurantoin Oral Suspension 5 mg/ml in 60 ml and pint bottles; *Furadantin*® (Dura); (Rx)

## NOVOBIOCIN SODIUM

**Chemistry** - An antibiotic obtained from *Streptomyces niveus* or *spheroides*, novobiocin sodium occurs as white to light yellow, crystalline powder and is very soluble in water.

**Storage/Stability/Compatibility** - Novobiocin should be stored in tight containers and at room temperature unless otherwise directed.

**Pharmacology** - Novobiocin is believed to act in several ways in a bactericidal manner. It inhibits bacterial DNA gyrase, thereby interfering with protein and nucleic acid synthesis. It also interferes with bacterial cell wall synthesis. Activity of the drug is enhanced in an alkaline medium.

The spectrum of activity of novobiocin includes some gram positive cocci (Staphs, *Streptococcus pneumonia*, and some group A streps). Activity is variable against other Streptococci and weak against the Enterococci. Most gram negative organisms are resistant to the drug, but some *Haemophilus sp., Neisseria sp*., and *Proteus sp.* may be susceptible.

**Uses/Indications** - As a single agent, novobiocin is approved for use in dry dairy cattle as a mastitis tube and as a premix for chickens, turkeys, ducks, and mink. It is available in combination with procaine penicillin G to treat mastitis in lactating dairy cattle. Novobiocin is available in combination with tetracycline ± prednisolone for oral use in dogs.

**Pharmacokinetics** - After oral administration, novobiocin is well absorbed from the GI tract. Peak levels occur within 1-4 hours. The presence of food can decrease peak concentrations of the drug.

Novobiocin is only poorly distributed to body fluids with concentrations in synovial, pleural and

ascitic fluids less than those found in the plasma. Only minimal quantities of the drug cross the blood-brain barrier, even when meninges are inflamed. Highest concentrations of novobiocin are found in the small intestine and liver. The drug is approximately 90% protein bound and is distributed into milk.

Novobiocin is primarily eliminated in the bile and feces. Approximately 3% is excreted into the urine and urine levels are usually less than those found in serum.

**Contraindications/Precautions/Reproductive Safety** - Novobiocin is contraindicated in patients hypersensitive to it. Additionally, the drug should be used with extreme caution in patients with preexisting hepatic or hematopoietic dysfunction. Safety during pregnancy has not been established; use only when clearly indicated.

**Adverse Effects/Warnings** - Adverse effects reported with the systemic use of this drug include fever, GI disturbances (nausea, vomiting, diarrhea), rashes and blood dyscrasias. In humans, occurrances of hypersensitivity reactions, hepatotoxicity and blood dyscrasias have significantly limited the use of this drug.

**Overdosage/Acute Toxicity** - Little information is available regarding overdoses of this drug. It is suggested that large oral overdoses be handled by emptying the gut following standard protocols; monitor and treat adverse effects symptomatically if necessary.

**Drug Interactions** - Novobiocin reportedly acts similarly to probenecid by blocking the tubular transport of drugs. Although the clinical significance of this is unclear, the elimination rates of drugs excreted in this manner (*e.g.,* **penicillins, cephalosporins**) could be decreased and half-lives prolonged.

**Drug/Laboratory Interactions** - Novobiocin can be metabolized into a yellow-colored product that can interfere with **serum bilirubin** determinations. It may also interfere with the determination **BSP** (bromosulfophthalein, sulfobromophthaelein) uptake tests by altering BSP uptake or biliary excretion.

**Doses** -
**Dogs**:

For susceptible infections:

a) 10 mg/kg q8h PO (Greene 1984)

For susceptible infections using the combination product (with tetracycline):

a) 22 mg/kg of each antibiotic PO q12h (Package insert; *Albaplex*®—Upjohn)

**Cattle**:

For treatment of mastitis in dry cows:

a) Infuse contents of one syringe into each quarter at the time of drying off; not later than 30 days prior to calving. (Package directions; *Drygard*® *Suspension* —Upjohn)

For treatment of mastitis in lactating cows:

a) Using the penicillin/novobiocin product (Special Formula 17900-Forte®): Infuse contents of one syringe in each infected quarter. Repeat once in 24 hours. (Package Directions; *Special Formula 17900-Forte*®—Upjohn)

**Client Information**: Shake mastitis tubes well before using.

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects
3 Periodic liver function tests and CBC's are recommended if using long-term systemically.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

To Drug Monograph Index To Ophthalmic Product Index

**Veterinary-Approved Products**:

Novobiocin (as the sodium) Oil Suspension 400 mg per 10 ml Mastitis tube; *Drygard*® *Suspension* (Upjohn); (OTC) Approved for use in dry cows. Not to be used within 30 days of calving. Slaughter withdrawal = 30 days.

Novobiocin Premix 17.5 g/lb, and 25 g/lb; *Albamix*® *Premix* (Upjohn); (OTC) Approved for use in chickens (not layers), turkeys (not layers for human consumption), ducks, and mink. Slaughter withdrawal = chickens and turkeys (4 days), ducks (3 days), and mink (none).

Novobiocin Combination Products:

Novobiocin (as the sodium salt) 150 mg and Penicillin G Procaine 100,000 IU per 10 ml Mastitis Syringe; *Special Formula 17900-Forte*® (Upjohn); (OTC) Approved for use in lactating dairy cattle. Milk withdrawal = 72 hours. Slaughter withdrawal = 15 days.

Novobiocin Sodium 60 mg and Tetracycline HCl 60 mg tablets; Novobiocin Sodium 180 mg and Tetracycline HCl 180 mg tablets; *Albaplex*® and *Albaplex*® *3X* (Upjohn); (Rx) Approved for use in dogs.

Novobiocin Sodium 60 mg, Tetracycline HCl 60 mg & Prednisolone 1.5 mg tablets; Novobiocin Sodium 180 mg, Tetracycline HCl 180 mg & Prednisolone 4.5 mg tablets; *Delta Albaplex*® and *Delta Albaplex*® *3X* (Upjohn); (Rx) Approved for use in dogs.

**Human-Approved Products**:

Novobiocin (as the sodium) 250 mg Capsules; *Albamycin*® (Upjohn); (Rx)

## OMEPRAZOLE

**Chemistry** - A substituted benzimidazole proton pump inhibitor, omeprazole has a molecular weight of 345.4 and $pK_a$'s of 4 and 8.8.

**Storage/Stability/Compatibility** - Omeprazole tablets should be stored at room temperature in light-resistant, tight containers. Omeprazole pellets found in the capsules are fragile and should not be crushed. If needed to administer as a slurry, it has been suggested to mix the pellets carefully with fruit juices and not water, milk or saline.

**Pharmacology** - A representative of a new class of agent, the substituted benzimidazoles, omeprazole is a gastric acid (proton) pump inhibitor. In an acidic environment, omeprazole is activated to a sulphenamide derivative that binds irreversibly at the secretory surface of parietal cells to the enzyme, $H^+/K^+$ ATPase. There it inhibits the transport of hydrogen ions into the stomach. Omeprazole inhibits acid secretion during both basal and stimulated conditions. Omeprazole also inhibits the hepatic cytochrome P-450 mixed function oxidase system (see Drug Interactions below).

**Uses/Indications** - Omeprazole is potentially useful in treating both gastroduodenal ulcer disease and to prevent or treat gastric erosions caused by ulcerogenic drugs (*e.g.*, aspirin). Because of the drugs recent availability and high cost, experience is limited in domestic animals.

**Pharmacokinetics** - Omeprazole is rapidly absorbed from the gut; the commercial product is in an enteric coated granule form as the drug is rapidly degraded by acid. Peak serum levels occur within 0.5 to 3.5 hours and onset of action within 1 hour. Omeprazole is distributed widely, but primarily in gastric parietal cells. In humans, approximately 95% is bound to albumin and $alpha_1$-acid glycoprotein. It is unknown whether omeprazole enters maternal milk.

To Drug Monograph Index To Ophthalmic Product Index

Omeprazole is extensively metabolized in the liver to at least six different metabolites, these are excreted principally in the urine, but also via the bile into feces. Significant hepatic dysfunction will reduce the first pass effect of the drug. In humans with normal hepatic function, serum half life averages about 1 hour, but the duration of therapeutic effect may persist for 72 hours or more.

**Contraindications/Precautions/Reproductive Safety** - Omeprazole is contraindicated in patients hypersensitive to it. Omeprazole should be used when the benefits outweigh the risks in patients with hepatic disease or a history of hepatic disease, as the drug's half life may be prolonged and dosage adjustment may be necessary.

Omeprazole's safety during pregnancy has not been established, but a study done in rats at doses of up to 345 times those recommended did not demonstrate any teratogenic effects. Increased embryo-lethality has been noted in lab animals at very high dosages. It is unknown whether omeprazole is excreted in milk.

**Adverse Effects/Warnings** - While veterinary use is quite limited, the drug appears to be quite well tolerated in both dogs and cats at effective dosages. Potentially, GI distress (anorexia, colic, nausea, vomiting, flatulence, diarrhea) could occur as well as hematologic abnormalities (rare in humans), urinary tract infections, proteinuria, or CNS disturbances. Chronic very high doses in rats caused enterochromaffin-like cell hyperplasia and gastric carcinoid tumors; effects occurred in dose related manner. The clinical significance of these findings for long term low-dose clinical usage is not known. However, at the current time in humans, dosing for longer than 8 weeks is rarely recommended unless the benefits of therapy outweigh the potential risks.

**Overdosage/Acute Toxicity** - The $LD_{50}$ in rats after oral administration is reportedly >4 g/kg. Humans have tolerated oral dosages of 360 mg/day without significant toxicity. Should a massive overdose occur, treat symptomatically and supportively.

**Drug Interactions** - Because omeprazole can inhibit the cytochrome P-450 enzyme system, omeprazole may decrease the hepatic clearance of **diazepam, phenytoin or warfarin**, thereby enhancing their effects and causing potential toxicity. Additional monitoring and dosage adjustments may be required. Because omeprazole can increase gastric pH, drugs that require low gastric pH for optimal absorption (*e.g.*, **ketoconazole, ampicillin esters or iron salts)** may have their absorption reduced. Although omeprazole causes bone marrow depression only rarely in humans, use with **other drugs that cause bone marrow depression** may lead to additive hematologic abnormalities.

**Laboratory Considerations -** Omeprazole may cause **increased liver enzymes.** Omeprazole will increase **serum gastrin levels** early in therapy.

**Doses** -
**Horses**:

For ulcer management:

a) 0.7 - 1.4 mg/kg PO once daily. While dosage has not been firmly established, these dosages have been shown to suppress gastric acid output for up to 24 hours. Use should probably be limited to those cases where the client prefers once a day only dosing. (Geor 1992)

**Monitoring Parameters** - 1) Efficacy; 2) Adverse Effects

**Client Information** - Brief client on drug's cost before prescribing. Give before meals, preferably in the morning.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

To Drug Monograph Index To Ophthalmic Product Index

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Omeprazole Oral Sustained Release 10 mg & 20 mg Capsules; *Prilosec*® (*Losec*® in Canada); (Astra Merck); (Rx)

## OPIATE ANTIDIARRHEALS
## PAREGORIC
## DIPHENOXALATE HCL/ATROPINE SULFATE
## LOPERAMIDE HCL

**Chemistry** - Paregoric, also known as camphorated tincture of opium, contains 2 mg of anhydrous morphine (usually as powdered opium or opium tincture). Also included (per 5 ml) is 0.02 ml anise oil, 0.2 ml glycerin, 20 mg benzoic acid, 20 mg camphor and a sufficient quantity of diluted alcohol to make a total of 5 ml. Paregoric should not be confused with opium tincture (tincture of opium), which contains 50 mg or anhydrous morphine per 5 ml.

Structurally related to meperidine, diphenoxylate HCl is a synthetic phenylpiperidine-derivative opiate agonist. It occurs as an odorless, white, crystalline powder that is slightly soluble in water and sparingly soluble in alcohol. Commercially available preparations also contain a small amount of atropine sulfate to discourage the abuse of the drug for its narcotic effects. At therapeutic doses the atropine has no clinical effect.

A synthetic piperidine-derivative antidiarrheal, loperamide occurs as a white to faintly yellow, powder with a $pK_a$ of 8.6 that is soluble in alcohol and slightly soluble in water.

**Storage/Stability/Compatibility** - Paregoric should be stored in tight, light-resistant containers. Avoid exposure to excessive heat or direct exposure to sunlight.

Diphenoxalate/atropine tablets should be stored at room temperature in well-closed, light-resistant containers. Diphenoxalate/atropine oral solution should be stored at room temperature in tight, light-resistant containers; avoid freezing.

Loperamide capsules or oral solution should be stored at room temperature in well-closed containers. It is recommended that the oral solution not be diluted with other solvents.

**Pharmacology** - Among their other actions, opiates inhibit GI motility and excessive GI propulsion. They also decrease intestinal secretion induced by cholera toxin, prostaglandin $E_2$ and diarrheas caused by factors in which calcium is the second messenger (non-cyclic AMP/GMP mediated). Opiates may also enhance mucosal absorption.

**Uses/Indications -** The opiate antidiarrheal products are generally considered to be the motility modifiers of choice in dogs with diarrhea. Their use in cats is controversial and many clinicians do not recommend their use in this species. Paregoric has also been used in large animals (see Doses below).

**Pharmacokinetics** - The morphine in paregoric is absorbed in a variable fashion from the GI tract. It is rapidly metabolized in the liver and serum morphine levels are considerably less than when morphine is administered parenterally.

To Drug Monograph Index To Ophthalmic Product Index

In humans, diphenoxylate is rapidly absorbed after administration of either the tablets or oral solution. The bioavailability of the tablets is approximately 90% that of the solution, however. Generally, onset of action occurs within 45 minutes to one hour after dosing and is sustained for 3-4 hours. Diphenoxylate is found in maternal milk. Diphenoxylate is metabolized into diphenoxylic acid, an active metabolite. The serum half-lives of diphenoxylate and diphenoxylic acid, are approximately 2.5 hours and 3-14 hours respectively.

In dogs, loperamide reportedly has a faster onset of action and longer duration of action than diphenoxylate, but clinical studies confirming this appear to be lacking. In humans, loperamide's half-life is about 11 hours. It is unknown if the drug enters milk or crosses the placenta.

**Contraindications/Precautions** - All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's) and in geriatric or severely debilitated patients. Opiate antidiarrheals are contraindicated in cases where the patient is hypersensitive to narcotic analgesics and in patients taking monoamine oxidase inhibitors (MAOIs). They are also contraindicated in patients with diarrhea caused by a toxic ingestion until the toxin is eliminated from the GI tract.

Opiate antidiarrheals should be used with caution in patients with head injuries or increased intracranial pressure and acute abdominal conditions (*e.g.,* colic) as it may obscure the diagnosis or clinical course of these conditions. It should be used with extreme caution in patients suffering from respiratory disease or from acute respiratory dysfunction (*e.g.,* pulmonary edema secondary to smoke inhalation). Opiate antidiarrheals should be used with extreme caution in patients with hepatic disease with CNS symptoms of hepatic encephalopathy. Hepatic coma may result.

Many clinicians recommend not using diphenoxylate or loperamide in dogs weighing less than 10 kg, but this is probably a result of the potency of the tablet or capsule forms of the drugs. Dosage titration using the liquid forms of these agents should allow their safe use in dogs when indicated.

**Adverse Effects/Warnings** - In dogs, constipation, bloat and sedation are the most likely adverse reactions encountered when usual doses are used. Potentially, paralytic ileus, toxic megacolon, pancreatitis and CNS effects could be seen.
Use of antidiarrheal opiates in cats is controversial; this species may react with excitatory behavior.

Opiates used in horses with acute diarrhea (or in any animal with a potentially bacterial-induced diarrhea) may have a detrimental effect. Opiates may enhance bacterial proliferation, delay the disappearance of the microbe from the feces and prolong the febrile state.

**Overdosage** - Acute overdosage of the opiate antidiarrheals could result in CNS, cardiovascular, GI or respiratory toxicity. Because the opiates may significantly reduce GI motility, absorption from the GI may be delayed and prolonged. For more information, refer to the meperidine and morphine monographs found in the CNS section. Naloxone may be necessary to reverse the opiate effects.

Massive overdoses of diphenoxylate/atropine sulfate may also induce atropine toxicity. Refer to the atropine monograph for more information. **Drug Interactions** - Other **CNS depressants** (*e.g.,* anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with opiate antidiarrheal agents. Opiate antidiarrheal agents are contraindicated in patients receiving **monoamine oxidase (MOA) inhibitors** (rarely used in veterinary medicine) for at least 14 days after receiving MOA inhibitors in humans.

**Drug/Laboratory Interactions -** Plasma **amylase** and **lipase** values may be increased for up to 24 hours following administration of opiates.

**Doses -**
**Horses**:

To Drug Monograph Index To Ophthalmic Product Index

Paregoric:
a) Foals: 15 - 30 ml PO; Adults: 15 - 60 ml PO (Cornell 1985)

**Monitoring Parameters** -
1) Clinical efficacy
2) Fluid & electrolyte status in severe diarrhea
3) CNS effects if using high dosages

**Client Information** - If diarrhea persists, contact veterinarian. If animal appears listless or develops a high fever, contact veterinarian.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Paregoric (camphorated tincture of opium) 2 mg of morphine equiv. per 5 ml; 45% alcohol. Available in 60 ml, pints, and gallons & UD 5 ml; Generic; (Rx; Class-III controlled substance)

Diphenoxylate HCl 2.5 mg with 0.025 mg Atropine Sulfate Tablets (Class-V controlled substance; prescription only); *Logen*® (Goldline); *Lomotil*® (Searle); *Lonox*® (Geneva); Generic; (C-V)

Diphenoxylate HCl 2.5 mg with 0.025 mg Atropine Sulfate per 5 ml Oral Liquid in 60 ml dropper bottles, UD 4 & 10 ml. (Class-V controlled substance; prescription only). There are many trade names for this combination, included are: *Lomotil*® (Searle), *Lonox*® (Geneva), *Diphenatol*® (Rugby); *Lofene*® (Lannett), *Logen*® (Goldline), Generic

Loperamide HCl 1 mg/5 ml (0.2 mg/ml) & 1 mg/ml Oral Liquid; *Imodium*® *A-D* (McNeil-CPC); *Pepto Diarrhea Control*® (Procter & Gamble); generic (OTC)

Loperamide HCl 2 mg Capsules & Tablets; *Imodium* ® (Janssen) (OTC); *Kaopectate II Caplets*® (Upjohn) (OTC); *Maalox Anti-Diarrheal Caplets*® (R-P Rorer); *Imodium A-D Caplets*® (McNeil-CPC) (OTC); *Neo-Diaral*® (Roberts) (OTC); generic (OTC)

## OXACILLIN SODIUM

For general information on the penicillins, including adverse effects, contraindications, overdosage, drug interactions and monitoring parameters, refer to the monograph: Penicillins, General Information.

**Chemistry** - An isoxazolyl-penicillin, oxacillin sodium is a semisynthetic penicillinase-resistant penicillin. It is available commercially as the monohydrate sodium salt which occurs as a fine, white, crystalline powder that is odorless or has a slight odor. It is freely soluble in water and has a $pK_a$ of about 2.8. One mg of oxacillin sodium contains not less than 815-950 micrograms of oxacillin. Each gram of the commercially available powder for injection contains 2.8 -3.1 mEq of sodium. Oxacillin sodium may also be known as sodium oxacillin or methylphenyl isoxazolyl penicillin.

**Storage/Stability/Compatibility** - Oxacillin sodium capsules, powder for oral solution, and powder for injection should be stored at room temperature (15-30°C) in tight containers. After reconstituting with water, refrigerated and discard any remaining oral solution after 14 days. If kept at room temperature, the oral solution is stable for 3 days.

To Drug Monograph Index To Ophthalmic Product Index

After reconstituting the sterile powder for injection with sterile water for injection or sterile sodium chloride 0.9%, the resultant solution with a concentration of 167 mg/ml is stable for 3 days at room temperature or 7 days if refrigerated. The manufacturer recommends using different quantities of diluent depending on whether the drug is to be administered IM, IV directly, or IV (piggyback). Refer to the package insert for specific instructions.

Oxacillin sodium injection is reportedly **compatible** with the following fluids/drugs: dextrose 5% & 10% in water, dextrose 5% & 10% in sodium chloride 0.9%, lactated Ringer's injection, sodium chloride 0.9% amikacin sulfate, cephapirin sodium, choramphenicol sodium succinate, dopamine HCl, potassium chloride, sodium bicarbonate and verapamil.

Oxacillin sodium injection is reportedly **incompatible** with the following fluids/drugs: oxytetracycline HCl and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology/Uses/Indications** - Refer to the Cloxacillin monograph and the Doses section for Oxacillin for more information regarding this drug.

**Pharmacokinetics (specific)** - Oxacillin sodium is resistant to acid inactivation in the gut, but is only partially absorbed after oral administration. The bioavailability after oral administration in humans has been reported to range from 30-35%, and, if given with food, both the rate and extent of absorption is decreased. After IM administration, oxacillin is rapidly absorbed and peak levels generally occur within 30 minutes.

The drug is distributed to the lungs, kidneys, bone, bile, pleural fluid, synovial fluid and ascitic fluid. The volume of distribution is reportedly 0.4 L/kg in human adults and 0.3 L/kg in dogs. As with the other penicillins, only minimal amounts are distributed into the CSF, but levels are increased with meningeal inflammation. In humans, approximately 89-94% of the drug is bound to plasma proteins.

Oxacillin is partially metabolized to both active and inactive metabolites. These metabolites and the parent compound are rapidly excreted in the urine via both glomerular filtration and tubular secretion mechanisms. A small amount of the drug is also excreted in the feces via biliary elimination. The serum half-life in humans with normal renal function ranges from about 18-48 minutes. In dogs, 20-30 minutes has been reported as the elimination half-life.

**Doses -**
**Horses**:

For susceptible infections:

a) Foals: 20 - 30 mg/kg IV q6-8h (Dose extrapolated from adult horse data; use lower dose or longer interval in premature foals or those less than 7 days old.) (Caprile and Short 1987)
b) 25 - 50 mg/kg IM, IV *bid* (Robinson 1987)

**Client Information** - Unless otherwise instructed by the veterinarian, this drug should be given on an empty stomach, at least 1 hour before feeding or 2 hours after. Keep oral solution in the refrigerator and discard any unused suspension after 14 days.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Oxacillin Sodium Capsules 250 mg, 500 mg; *Prostaphlin*® (Apothecon) (Rx), *Bactocill*® (Beecham); (Rx); generic, (Rx)

Oxacillin Sodium Powder for Oral Solution 250 mg/5 ml in 100 ml bottles; *Prostaphlin*® (Apothecon); (Rx)

Oxacillin Sodium Powder for Injection 250 mg vials, 500 mg vials, 1 g, 2 g, & 4 g vials; 1 g & 2 g piggyback vials, 4 g and 10 g bulk vials; *Prostaphlin*® (Apothecon) (Rx); *Bactocill*® (S-K Beecham); (Rx); Oxacillin Sodium® (Apothecon) (Rx)

## OXFENDAZOLE

**Chemistry** - A benzimidazole anthelmintic, oxfendazole occurs as white or almost white powder possessing a characteristic odor. It is practically insoluble in water. Oxfendazole is the sulfoxide metabolite of fenbendazole.

**Storage/Stability/Compatibility** - Unless otherwise directed by the manufacturer, oxfendazole products should be stored at room temperature and protected from light. The manufacturer recommends discarding any unused suspension 24 hours after it has been reconstituted.

**Uses/Indications** - Oxfendazole is indicated (labeled) for the removal of the following parasites in **horses**: large roundworms (*Parascaris equorum*), large strongyles (*S. edentatus, S. equinus, S. vulgaris*), small strongyles and pinworms (*Oxyuris equi*).
Oxfendazole has also been used in cattle, sheep, goats, and swine; see Dosage section for more information.

**Pharmacokinetics** - Limited information is available regarding this compound's pharmacokinetics. Unlike most of the other benzimidazole compounds, oxfendazole is absorbed more readily from the GI tract. The elimination half-life has been reported to be about 7.5 hours in sheep and 5.25 hours in goats. Absorbed oxfendazole is metabolized (and vice-versa) to the active compound, fenbendazole (sulfoxide) and the sulfone.

**Contraindications/Precautions** - There are no contraindications to using this drug in horses, but it is recommended to use oxfendazole cautiously in debilitated or sick horses. Oxfendazole may be safely used in pregnant mares and foals.

**Adverse Effects/Warnings** - When used as labeled, it is unlikely any adverse effects will be noted. Hypersensitivity reactions secondary to antigen release by dying parasites are theoretically possible, particularly at high dosages.

**Overdosage/Toxicity** - Doses of 10 times those recommended elicited no adverse reactions in horses tested. It is unlikely that this compound would cause serious toxicity when given alone.

**Drug Interactions** - Oxfendazole or fenbendazole should not be given concurrently with the **bromsalan flukicides (Dibromsalan, Tribromsalan**). Abortions in cattle and death in sheep have been reported after using these compounds together.

**Doses** -
**Horses**:

For susceptible parasites: 10 mg/kg PO. (Package insert; Benzelmin®—Syntex), (Roberson 1988b)

**Cattle**:

For susceptible parasites:

a) 4.5 mg/kg PO. (Roberson 1988b)
b) 5 mg/kg PO. (Brander, Pugh, and Bywater 1982)

**Monitoring Parameters** - Efficacy

**Client Information** - Not to be used in horses intended for food purposes.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products: None**

Oxfendazole Powder for Suspension 75.6 mg/gram in 30 gram packets and 300 gram bulk powder.

*Benzelmin*® (Fort Dodge); (Rx) Approved for use in horses.

Oxfendazole Suspension 90.6 mg/ml in 1 liter bottles.

*Benzelmin*® (Fort Dodge); (Rx) Approved for use in horses. Shake well before using.

Oxfendazole Oral Paste 375 mg/gram in 12 g and 72 g syringes. *Benzelmin*® *Paste* (Fort Dodge); (OTC) Approved for use in horses.

Oxfendazole may be known in the U.K. by the proprietary names: *Synanthic*® (Syntex) or *Systamex*® (Coopers).

**Human-Approved Products:** None

## OXIBENDAZOLE

**Chemistry** - A benzimidazole anthelmintic, oxibendazole occurs as a white powder that is practically insoluble in water.

**Storage/Stability/Compatibility** - Unless otherwise directed by the manufacturer, oxibendazole products should be stored at room temperature; protect from freezing.

**Uses/Indications** - Oxibendazole is indicated (labeled) for the removal of the following parasites in horses: large roundworms (*Parascaris equorum*), large strongyles (*S. edentatus, S. equinus, S. vulgaris*), small strongyles, threadworms, and pinworms (*Oxyuris equi*).

Oxfendazole has also been used in cattle, sheep, and swine; see Dosage section for more information.

**Pharmacokinetics** - No information was located.

**Contraindications/Precautions** - Oxibendazole is stated by the manufacturer (SKB) to be contraindicated in severely debilitated horses or in horses suffering from colic, toxemia or infectious disease. Oxibendazole is considered to be safe to use in pregnant mares.

**Adverse Effects/Warnings** - When used in horses at recommended doses, it is unlikely any adverse effects would be seen. Hypersensitivity reactions secondary to antigen release by dying parasites are theoretically possible, particularly at high dosages.

Oxibendazole in combination with diethylcarbamazine (*Filaribits Plus*®) has been implicated in causing periportal hepatitis in dogs.

**Overdosage/Toxicity** - Doses of 60 times those recommended elicited no adverse reactions in horses tested. It is unlikely that this compound would cause serious toxicity when given alone to horses.

To Drug Monograph Index To Ophthalmic Product Index

**Doses** -
**Horses**:

For susceptible parasites:

a) 10 mg/kg PO; 15 mg/kg PO for strongyloides. (Package insert; *Anthelcide EQ*®—SKB)
b) 10 mg/kg PO (Robinson 1987), (Roberson 1988b)

**Elephants:**

a) 2.5 mg/kg orally as a single dose for helminthiasis

a) Chandrasekharan,K. 2002. **Specific diseases of Asian elephants.** Journal of Indian Veterinary Association Kerala 7:(3):31-34

a) Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T., 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference to Kerala**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-449

a) Chandrasekharan,K., 1992. **Prevalence of infectious diseases in elephants in Kerala and their treatment**. In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 148-155

**Monitoring Parameters** -

1) Efficacy

**Client Information** - Protect suspension from freezing. Shake suspension well before using. Not for use in horses intended for food.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:**

Oxibendazole Suspension 100 mg/ml (10%) gallons. *Anthelcide EQ*® *Suspension* (Pfizer); (Rx) Approved for use in horses not used for food.

Oxibendazole Oral Paste 227 mg/gram (22.7%) in 24 gram syringes. *Anthelcide EQ*® *Paste* (Pfizer), (OTC) Approved for use in horses not used for food.

A combination product (*Filaribits Plus*®—Pfizer) containing diethylcarbamazine and oxibendazole for the prophylactic treatment of heartworm and hookworms is available for dogs. See the product's literature for more information. Oxibendazole may be known in the U.K. by the proprietary names: *Dio*® (Alan Hitchings), *Equidin*® (Univet), *Equitac*® (SKF) or *Loditac*® (SKF).

**Human-Approved Products**: None

## OXYCLOZANIDE

To Drug Monograph Index  To Ophthalmic Product Index

**Elephants:**

a) 7.5 mg/kg (not exceeding 6.8 g/animal) for fascioliasis. Islam,S. 1997. **Studies on some aspects of fascioliasis in Asian elephants (Elephas maximus)**. Journal of Veterinary Parasitology 11:(1):109 **Summary of abstract:** The epidemiology of Fasciola jacksoni in wild and captive elephants (Elephas maximus) was studied in Assam, India. Wild elephants had an overall prevalence rate of 33.78%. Captive elephants showed prevalence rates of 42.50, 62.28 and 18.18% according to locality. The egg, miracidium and adult stages of F. jacksoni were studied by light and scanning electron microscopy, and their morphology is described. A diurnal fluctuation in faecal egg count was recorded, with average counts of 4.89, 2.47 and 2.76 during the morning, noon and evening, respectively. Young animals were most affected by the parasite and showed anorexia, constipation, diarrhea, anaemia and icterus, with death occurring in severe cases. Some old adults survived the disease with no apparent clinical manifestations. The adult parasites caused massive liver damage. Treatment with triclabendazole (9 mg/kg, not exceeding 7200 mg/animal) and oxyclozanide (7.5 mg/kg, not exceeding 6.8 g/animal) were 100 and 72.16% effective, respectively.

b) 5.0 - 7.5 mg/kg orally for amphistomiasis. (Chandrsekharan, 2002), (Chandrsekharan et.al.,1995)

c) 3.4 mg/kg orally for cestodiasis (Chandrsekharan, 2002), (Chandrsekharan et.al.,1995)

b,c,) Chandrasekharan,K. 2002. **Specific diseases of Asian elephants**. Journal of Indian Veterinary Association Kerala 7:(3):31-34

b,c) Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T., 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference to Kerala**. In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-449

## OXYMORPHONE HCL

**Chemistry** - A semi-synthetic phenanethrene narcotic agonist, oxymorphone HCl occurs as odorless white crystals or white to off-white powder. It will darken in color with prolonged exposure to light. One gram of oxymorphone HCl is soluble in 4 ml of water and it is sparingly soluble in alcohol and ether. The commercially available injection has a pH of 2.7 - 4.5.

**Storage/Stability/Compatibility** - The injection should be stored protected from light and at room temperature (15-30° C); avoid freezing. The commercially available suppositories should be stored at temperatures between 2° and 15° C. Oxymorphone has been reported to be **compatible** when mixed with acepromazine, atropine, and glycopyrrolate. It is **incompatible** when mixed with barbiturates, and diazepam.

**Pharmacology** - See the monograph: Narcotic (Opiate) Analgesics for more infortmation. Oxymorphone is approximately 10 times more potent an analgesic on a weight basis when compared to morphine. It has less antitussive activity than does morphine. In humans, it has more of a tendency to cause increased nausea and vomiting than does morphine, while in dogs the opposite appears to be true. At the usual doses employed, oxymorphone alone has good sedative qualities in dog. Respiratory depression can occur especially in debilitated, neonatal or geriatric patients. Bradycardia, as well as a slight decrease in cardiac contractility and blood pressure may also be seen. Like morphine, oxymorphone does initially increase the respiratory rate (panting in dogs) while actual oxygenation may be decreased and blood $CO_2$ levels may

increase by 10 mmHg or more. Gut motility is decreased with resultant increases in stomach emptying times. Unlike either morphine or meperidine, oxymorphone does not appear to cause histamine release.

**Pharmacokinetics** - Oxymorphone is absorbed when given by IV, IM , SQ, and rectal routes. Although absorbed when given orally bioavailability is reduced, probably from a high first-pass effect. After IV administration, analgesic efficacy usually occurs within 3-5 minutes.

Like morphine, oxymorphone concentrates in the kidney, liver, and lungs; lower levels are found in the CNS. Oxymorphone crosses the placenta and narcotized newborns can result if mothers are given the drug before giving birth, but these effects can be rapidly reversed with naloxone.

The drug is metabolized in the liver; primarily by glucuronidation. Because cats are deficient in this metabolic pathway, half-lives in cats are probably prolonged. The glucuronidated metabolite is excreted by the kidney.

**Uses/Indications** - Oxymorphone is used in dogs and cats as a sedative/restraining agent, analgesic and preanesthetic and occassionally in horses as an analgesic and anesthesia induction agent. It may also be used in swine as an adjunctive analgesic with ketamine/xylazine anesthesia and in small rodents as an analgesic/anesthetic for minor surgical procedures.

**Contraindications/Precautions** - All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's), and in geriatric or severely debilitated patients. Oxymorphone is contraindicated in patients hypersensitive to narcotic analgesics, and in patients taking monamine oxidase inhibitors (MAOIs). It is also contraindicated in patients with diarrhea caused by a toxic ingestion until the toxin is eliminated from the GI tract.

Oxymorphone should be used with extreme caution in patients with head injuries, increased intracranial pressure and acute abdominal conditions (*e.g.,* colic) as it may obscure the diagnosis or clinical course of these conditions. It should be used with extreme caution in patients suffering from respiratory disease or from acute respiratory dysfunction (*e.g.,* pulmonary edema secondary to smoke inhalation).

Oxymorphone can cause bradycardia and therefore should be used cautiously in patients with preexisting bradyarrhythmias.

Neonatal, debilitated or geriatric patients may be more susceptible to the effects of oxymorphone and may require lower dosages. Patients with severe hepatic disease may have prolonged durations of action of the drug. If used in cats at high dosages, the drug has been recommended to be given along with a tranquilizing agent, as oxymorphone can produce bizarre behavioral changes in this species. This also is true in cats also for the other opiate agents, such as morphine.

Opiate analgesics are also contraindicated in patients who have been stung by the scorpion species *Centruroides sculpturatus* Ewing and *C. gertschi* Stahnke as it may potentiate these venoms.

**Adverse Effects/Warnings** - Oxymorphone may cause respiratory depression and bradycardia (see above). When used in cats at high dosages, oxymorphone may cause ataxia, hyperesthesia and behavioral changes (without concomitant tranquilization). Decreased GI motility with resultant constipation has also been described.

**Overdosage** - Massive overdoses may produce profound respiratory and/or CNS depression in most species. Other effects may include cardiovascular collapse, hypothermia, and skeletal muscle hypotonia. Naloxone is the agent of choice in treating respiratory depression. In massive overdoses, naloxone doses may need to be repeated, and animals should be closely observed as naloxone's effects may diminish before sub-toxic levels of oxymorphone are attained.

To Drug Monograph Index  To Ophthalmic Product Index

Mechanical respiratory support should also be considered in cases of severe respiratory depression.

**Drug Interactions** - Other **CNS depressants** (*e.g.,* anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression when used with oxymorphone. Oxymorphone is contraindicated in patients receiving **monoamine oxidase (MOA) inhibitors** (rarely used in veterinary medicine) for at least 14 days after receiving MOA inhibitors in humans. Some human patients have exhibited signs of opiate overdose after receiving therapeutic doses of oxymorphone while on these agents.

**Laboratory Interactions** - Plasma **amylase** and **lipase** values may be increased for up to 24 hours following administration of opiate analgesics as they may increase biliary tract pressure.

**Doses -**
**Horses**:

As an analgesic:

a) 0.01 - 0.02 mg/kg IV (Muir 1987)
b) 0.01 - 0.022 mg/kg IV; up to 15mg total (divide dose into 3-4 increments and give several minutes apart (Shaw et al. 1986)
c) 0.02 - 0.03 mg/kg IM (Robinson 1987)
d) 0.015 - 0.03 mg/kg IV (Thurmon and Benson 1987)

Anesthetic induction in severely compromised horses:

a) 0.01 - 0.022 mg/kg IV (after approx. 45 minutes, may be necessary to "top off" with another 1/3 of the original dose) (Shaw et al. 1986)

**Note**: Narcotics (oxymorphone included) may cause CNS excitement in the horse. Some clinicians recommend pretreatment with acepromazine (0.02 - 0.04 mg/kg IV), or xylazine (0.3 - 0.5 mg/kg IV) to reduce the behavioral changes these drugs can cause.

**Warning**: Narcotic analgesics can mask the behavioral and cardiovascular symptoms associated with mild colic.

**Monitoring Parameters** -

1) Respiratory rate/depth
2) CNS level of depression/excitation
3) Blood pressure if possible and indicated (especially with IV use)
4) Analgesic activity
5) Cardiac rate

**Client Information** - When given parenterally, this agent should be used in an inpatient setting or with direct professional supervision.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: The veterinary labeled product is reportedly discontinued.

**Human-Approved Products**:

Oxymorphone HCl for Injection 1 mg/ml in 1 ml amps; 1.5 mg/ml in 1 ml amps and 10 ml vials; *Numorphan*® (Du Pont); (Rx)

Oxymorphone HCl 5 mg suppositories in 6s.; *Numorphan*® (Du Pont); (Rx)

**Note:** Oxymorphone is a **Class-II controlled substance**. Very accurate record keeping is required as to use and disposition of stock.

To Drug Monograph Index To Ophthalmic Product Index

## OXYTETRACYCLINE PK

**Chemistry** - A tetracycline derivative obtained from *Streptomyces rimosus*, oxytetracycline base occurs as a pale yellow to tan, crystalline powder that is very slightly soluble in water and sparingly soluble in alcohol. Oxytetracycline HCl occurs as a bitter-tasting, hygroscopic, yellow, crystalline powder that is freely soluble in water and sparingly soluble in alcohol. Commercially available 50 mg/ml and 100 mg/ml oxytetracycline HCl injections are usually available in either propylene glycol or povidone based products.

**Storage/Stability/Compatibility** - Unless otherwise directed by the manufacturer, oxytetracycline HCl and oxytetracycline products should be stored in tight, light-resistant containers at temperatures of less than 40°C (104°) and preferably at room temperature (15-30°C); avoid freezing.

Oxytetracycline HCl is generally considered to be **compatible** with most commonly used IV infusion solutions, including $D_5W$, sodium chloride 0.9%, and lactated Ringer's, but can become relatively unstable in solutions with a pH > 6, particularly in those containing calcium. This is apparently more of a problem with the veterinary injections that are propylene glycol based, rather than those that are povidone based. Other drugs that are reported to be **compatible** with oxytetracycline for injection include: colistimethate sodium, corticotropin, dimenhydrinate, insulin (regular), isoproterenol HCl, methyldopate HCl, norepinephrine bitartrate, polymyxin B sulfate, potassium chloride, tetracycline HCl, and vitamin B-complex with C.

Drugs that are reportedly **incompatible** with oxytetracycline, data conflicts, or compatibility is concentration/time dependent, include: amikacin sulfate, aminophylline, amphotericin B, calcium chloride/gluconate, carbenicillin disodium, cephalothin sodium, cephapirin sodium, chloramphenicol sodium succinate, erythromycin gluceptate, heparin sodium, hydrocortisone sodium succinate, iron dextran, methicillin sodium, methohexital sodium, oxacillin sodium, penicillin G potassium/sodium, pentobarbital sodium, phenobarbital sodium, and sodium bicarbonate. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Tetracyclines generally act as bacteriostatic antibiotics and inhibit protein synthesis by reversibly binding to 30S ribosomal subunits of susceptible organisms, thereby preventing binding to those ribosomes of aminoacyl transfer-RNA. Tetracyclines also are believed to reversibly bind to 50S ribosomes and additionally alter cytoplasmic membrane permeability in susceptible organisms. In high concentrations, tetracyclines can also inhibit protein synthesis by mammalian cells.

As a class, the tetracyclines have activity against most *mycoplasma*, spirochetes (including the Lyme disease organism), *Chlamydia*, and *Rickettsia*. Against gram positive bacteria, the tetracyclines have activity against some strains of *staphylococcus* and *streptococci*, but resistance of these organisms is increasing. Gram positive bacteria that are usually covered by tetracyclines, include *Actinomyces sp., Bacillus anthracis*, *Clostridium perfringens* and *tetani*, *Listeria monocytogenes,* and *Nocardia*. Among gram negative bacteria that tetracyclines usually have *in vitro* and *in vivo* activity against include *Bordetella sp., Brucella, Bartonella, Haemophilus sp., Pasturella multocida, Shigella,* and *Yersinia pestis*. Many or most strains of *E. coli, Klebsiella, Bacteroides, Enterobacter, Proteus* and *Pseudomonas aeruginosa* are resistant to the tetracyclines. While most strains of *Pseudomonas aeruginosa* show *in vitro* resistance to tetracyclines, those compounds attaining high urine levels (*e.g.,* tetracycline, oxytetracycline) have been associated with clinical cures in dogs with UTI secondary to this organism.

Oxytetracycline and tetracycline share nearly identical spectrums of activity and patterns of cross-resistance and a tetracycline susceptibility disk is usually used for *in vitro* testing for oxytetracycline susceptibility.

To Drug Monograph Index  To Ophthalmic Product Index

**Uses/Indications** - Oxytetracycline products are approved for use in dogs and cats (no known products are being marketed, however), calves, non-lactating dairy cattle, beef cattle, swine, fish, and poultry. For more information refer to the Doses section, below.

**Pharmacokinetics** - Both oxytetracycline and tetracycline are readily absorbed after oral administration to fasting animals. Bioavialabilities are approximately 60-80%. The presence of food or dairy products can significantly reduce the amount of tetracycline absorbed, with reductions of 50% or more possible. After IM administration of oxytetracycline (not long-acting), peak levels may occur in 30 minutes to several hours, depending on the volume and site of injection. The long-acting product (LA-200®) has significantly slower absorption after IM injection.

Tetracyclines as a class, are widely distributed in the body, including to the heart, kidney, lungs, muscle, pleural fluid, bronchial secretions, sputum, bile, saliva, urine, synovial fluid, ascitic fluid, and aqueous and vitreous humor. Only small quantities of tetracycline and oxytetracycline are distributed to the CSF and therapeutic levels may not be attainable. While all tetracyclines distribute to the prostate and eye, doxycycline or minocycline penetrate better into these and most other tissues. Tetracyclines cross the placenta, enter fetal circulation and are distributed into milk. The volume of distribution of oxytetracycline is approximately 2.1 L/kg in small animals, 1.4 L/kg in horses, and 0.8 L/kg in cattle. The amount of plasma protein binding is about 10-40% for oxytetracycline.

Both oxytetracycline and tetracycline are eliminated unchanged primarily via glomerular filtration. Patients with impaired renal function can have prolonged elimination half-lives and may accumulate the drug with repeated dosing. These drugs apparently are not metabolized, but are excreted into the GI tract via both biliary and nonbiliary routes and may become inactive after chelation with fecal materials. The elimination half-life of oxytetracycline is approximately 4-6 hours in dogs and cats, 4.3 - 9.7 hours in cattle, 10.5 hours in horses, 6.7 hours in swine, and 3.6 hours in sheep.

**Contraindications/Precautions/Reproductive Safety** - Oxytetracycline is contraindicated in patients hypersensitive to it or other tetracyclines. Because tetracyclines can retard fetal skeletal development and discolor deciduous teeth, they should only be used in the last half of pregnancy when the benefits outweigh the fetal risks. Oxytetracycline and tetracycline are considered to be more likely to cause these abnormalities than either doxycycline or minocycline.

In patients with renal insufficiency or hepatic impairment, oxytetracycline and tetracycline must be used cautiously. Lower than normal dosages are recommended with enhanced monitoring of renal and hepatic function. Avoid concurrent administration of other nephrotoxic or hepatotoxic drugs if tetracyclines are administered to these patients. Monitoring of serum levels should be considered if long-term therapy is required.

**Adverse Effects/Warnings** - Oxytetracycline and tetracycline given to young animals can cause discoloration of bones and teeth to a yellow, brown, or gray color. High dosages or chronic administration may delay bone growth and healing.

Tetracyclines in high levels can exert an antianabolic effect which can cause an increase in BUN and/or hepatotoxicity, particularly in patients with preexisting renal dysfunction. As renal function deteriorates secondary to drug accumulation, this effect may be exacerbated.

In ruminants, high oral doses can cause ruminal microflora depression and ruminoreticular stasis. Rapid intravenous injection of undiluted propylene glycol-based products can cause intravascular hemolysis with resultant hemoglobinuria. Propylene glycol based products have also caused cardiodepressant effects when administered to calves. When administered IM, local reactions, yellow staining and necrosis may be seen at the injection site.

To Drug Monograph Index  To Ophthalmic Product Index

In small animals, tetracyclines can cause nausea, vomiting, anorexia and diarrhea. Cats do not tolerate oral tetracycline or oxytetracycline very well, and may also present with symptoms of colic, fever, hair loss and depression.

Horses who are stressed by surgery, anesthesia, trauma, etc., may break with severe diarrheas after receiving tetracyclines (especially with oral administration).

Tetracycline therapy (especially long-term) may result in overgrowth (superinfections) of non-susceptible bacteria or fungi. Tetracyclines have also been associated with photosensitivity reactions and, rarely, hepatotoxicity or blood dyscrasias.

**Overdosage/Acute Toxicity** - Tetracyclines are generally well tolerated after acute overdoses. Dogs given more than 400 mg/kg/day orally or 100 mg/kg/day IM of oxytetracycline did not demonstrate any toxicity. Oral overdoses would most likely be associated with GI disturbances (vomiting, anorexia, and/or diarrhea). Should the patient develop severe emesis or diarrhea, fluids and electrolytes should be monitored and replaced if necessary. Chronic overdoses may lead to drug accumulation and nephrotoxicity.

High oral doses given to ruminants, can cause ruminal microflora depression and ruminoreticular stasis. Rapid intravenous injection of undiluted propylene glycol-based products can cause intravascular hemolysis with resultant hemoglobinuria.

Rapid intravenous injection of tetracyclines has induced transient collapse and cardiac arrhythmias in several species, presumably due to chelation with intravascular calcium ions. Overdose quantities of drug could exacerbate this effect if given too rapidly IV. If the drug must be given rapidly IV (less than 5 minutes), some clinicians recommend pre-treating the animal with intravenous calcium gluconate.

**Drug Interactions** - When orally administered, tetracyclines can chelate **divalent or trivalent cations** which can decrease the absorption of the tetracycline or the other drug if it contains these cations. Oral antacids, saline cathartics or other GI products containing aluminum, calcium, magnesium, zinc or bismuth cations are most commonly associated with this interaction. It is recommended that all oral tetracyclines be given at least 1-2 hours before or after the cation-containing product. **Oral iron products** are also associated with decreased tetracycline absorption, and administration of iron salts should preferably be given 3 hours before or 2 hours after the tetracycline dose. **Oral sodium bicarbonate, kaolin, pectin, or bismuth subsalicylate** may impair tetracycline absorption when given together orally.
Bacteriostatic drugs like the tetracyclines, may interfere with bactericidal activity of the **penicillins, cephalosporins,** and **aminoglycosides**. There is some amount of controversy regarding the actual clinical significance of this interaction, however.
Tetracyclines may increase the bioavailability of **digoxin** in a small percentage of patients (human) and lead to digoxin toxicity. These effects may persist for months after discontinuation of the tetracycline.

Tetracyclines may depress plasma prothrombin activity and patients on **anticoagulant (***e.g.,* **warfarin)** therapy may need dosage adjustment. Tetracyclines have been reported to increase the nephrotoxic effects of **methoxyflurane** and tetracycline HCl or oxytetracycline are not recommended to used with methoxyflurane. GI side effects may be increased if tetracyclines are administered concurrently with **theophylline** products. Tetracyclines have reportedly reduced **insulin** requirements in diabetic patients, but this interaction is yet to be confirmed with controlled studies.

**Drug/Laboratory Interactions** - Tetracyclines (not minocycline) may cause falsely elevated values of **urine catecholamines** when using fluorometric methods of determination.
Tetracyclines reportedly can cause false-positive **urine glucose** results if using the cupric sulfate method of determination (Benedict's reagent, *Clinitest*®), but this may be the result of ascorbic acid which is found in

some parenteral formulations of tetracyclines. Tetracyclines have also reportedly caused false-negative results in determining urine glucose when using the glucose oxidase method (*Clinistix®, Tes-Tape®*).

**Doses -**
**Horses**:

For susceptible infections:

a) 5 - 10 mg/kg IV *bid* (Robinson 1987)
b) For respiratory tract infections: 5 mg/kg IV q12h; do not give too rapidly. (Beech 1987b)
c) 3 mg/kg IV q12h (Baggot and Prescott 1987)
d) 5 - 11 mg/kg IV q12h (Upson 1988)

**Elephants:**

a) 18mg/kg IM q 48 -72 h. The authors state that this dose does not achieve a serum concentration of > 4µg /ml, as recommended by the National Committee for Clinical Laboratory Standards. They further suggest that the efficacy of oxytetracycline against specific pathogens isolated from elephants is important to determine because the susceptibility to tetracyclines varies greatly. Bush,M., Stoskopf,M.K., Raath,J.P., and Papich,M.G. 2000. **Serum oxytetracycline concentrations in African elephant (Loxodonta africana) calves after long-acting formulation injection**. Journal of Zoo and Wildlife Medicine 31:(1):41-46 **Abstract:** Serum oxytetracycline pharmacokinetics were studied in 18 African elephant calves. Each elephant received separate injections of oxytetracycline at approximately 18 mg/kg i.m. and 8 mg/kg i.v. in a cross-over study. Blood samples were drawn at 0, 24, 48, 72 and 96 h postinjection. An additional sample was drawn 110 h before the animals were reinjected in the cross-over study and a final blood sample was drawn 48 h after the second dose. No lameness or stiffness was observed following i.m. injections. Serum oxytetracycline concentrations >0.5 µg/ml were present 48 h after initial dosing for all elephants (i.m., i.v., high or low dosage). Only elephants given the high i.m. dosage (18 mg/kg) maintained levels >0.5 µg/ml 72 h postinjection. No significant difference in serum oxytetracycline concentration with time was observed between the groups given different i.v. dosages. These studies demonstrated that quantifiable serum oxytetracycline concentrations can be maintained in young African elephants with a low-dosage multidose i.m. regimen.

b) 52 – 133 mg/cm IM q 48-72 h. Note that the weights of the African elephants in this study were estimated by using the sum of the elephant's girth and length in cm and that the dose is expressed in mg/cm. Bush,M., Raath,J.P., de Vos,V., and Stoskopf,M. 1996. **Serum oxytetracycline levels in free-ranging male African elephants (*Loxodonta africana*) injected with a long-acting formulation.** Journal of Zoo and Wildlife Medicine 27:(3):382-385 **Abstract:** Thirteen adult free-living male African elephants (*Loxodonta africana*) were anesthetized and given 20-100 g of a long-acting tetracycline (OTC) preparation either i.m. or i.v. Five dosages were established based on body measurements (the sum of the body length and the girth in centimeters) Serum concentrations of OTC were measured 48 hr after injection. Serum concentrations >/= 0.5 µg /ml were measured in 11 of 12 elephants receiving OTC dosages of 52-133 mg/cm either i.v. or i.m. The i.m. administration route produced serum concentrations from 0.75-1.6 µg g/ml in four of four elephants. A dosage of 60-80 mg/cm i.m. or i.v. should provide a therapeutic serum concentration of OTC for at least 48 hr. The use of an i.v. catheter avoids multiple i.m. injections of large drug volumes.

c) 20 mg/kg IM q 48-72 h. Peak plasma levels of 1.09 – 2.87 µg /ml were achieved between 1 and 48 hours post-injection and were higher than the MIC reported for most susceptible pathogens (0.5 µg /ml OTC) for approximately 84 hours except for E. coli. The MIC for E.coli has been reported to be 4 ug/ml and this organism would probably be little affected by this IM dose. Limpoka,P., Chai Anan,S., Sirivejpandu,R., Kanchanomai,S., Rattanamonthianchai, and Puangkum,P. 1987. **Plasma concentrations of oxytetracycline in elephants**

To Drug Monograph Index To Ophthalmic Product Index

**following intravenous and intramuscular administration of Terramycin/LA injectable solution**. ACTA VET.BRNO 56:173-179 **Abstract:** The blood concentrations of oxytetracycline were studied in Asian elephants following the intravenous and intramuscular administration of Terramycin/LA solution. The drug was administered as 200 mg of oxytetracycline base/ml in aqueous 2-pyrrolidone at a dose of 20mg/kg body mass. The blood samples were collected from the ear veins of each animal. Plasma concentrations of oxytetracycline were analyzed by microbiological method and high pressure liquid chromatography. An average peak plasma concentration of 6.2 µg /ml was obtained in one hour following intravenous administration in elephants No oxytetracycline was detected in plasma after the 60th post dosing hour. The average peak plasma concentration of 2.87 µg /ml was found in two hours following intramuscular administration of the drug. Concentrations exceeding 1 ug/ml were maintained for 48 hours after intramuscular dose. The drug was shown to result in sustained oxytetracycline blood concentrations over a three-day period following a single intramuscular administration of the drug to elephants.

**See also:**
Kirkwood,J.K. and Widdowson,M.A. 1990. **Interspecies variation in the plasma half-life of oxytetracycline in relation to body weight**. Res.Vet Sci. 48:180-183

**Monitoring Parameters** -

1) Adverse effects
2) Clinical efficacy
3) Long-term use or in susceptible patients: periodic renal, hepatic, hematologic evaluations

**Client Information** - Avoid giving this drug orally within 1-2 hours of feeding, giving milk or dairy products.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Oxytetracycline HCl 50 mg/ml, 100 mg/ml Injection. There are many approved oxytetracycline products marketed in these concentrations. Some are labeled for Rx (legend) use only, while some are over-the-counter (OTC). Depending on the actual product, this drug may be approved for use in swine, non-lactating dairy cattle, beef cattle, chickens or turkeys. Products may also be labeled for IV, IM, or SQ use. Withdrawal times vary with regard to individual products. Slaughter withdrawal times vary in cattle from 15-22 days, swine 20-26 days, and 5 days for chickens and turkeys. Refer to the actual labeled information for the product used for more information. Some trade names for these products include: *Terramycin*®, *Liquamycin*®, *Biomycin* (Bio-Ceutic), *Medamycin*® (TechAmerica), *Biocyl*® (Anthony), *Oxyject*® (Fermenta), and *Oxytet*® (BI).

Oxytetracycline base 200 mg/ml Injection in 100, 250, and 500 ml bottles; *Liquamycin*® *LA-200*® (Pfizer); (OTC or Rx) Approved for use in swine, non-lactating dairy cattle and beef cattle. Slaughter withdrawal = 28 days for swine and cattle.

Oxytetracycline Oral Tablets (Boluses) 250 mg tablet; *Terramycin*® *Scours Tablets* (Pfizer); (OTC) Approved for use in non-lactating dairy and beef cattle. Slaughter withdrawal = 7 days.

Oxytetracycline is also available in feed additive, premix, ophthalmic and intramammary products.

Established residue tolerances: Uncooked edible tissues of swine, cattle, salmonids, catfish and lobsters: 0.10 ppm. Uncooked kidneys of chickens or turkeys: 3 ppm. Uncooked muscle, liver, fat or skin of chickens or turkeys: 1 ppm.

**Human-Approved Products**:

Oxytetracycline Oral Capsules 250 mg; *Terramycin*® (Pfizer); *Uri-Tet*® (American Urologicals); generic; (Rx)

To Drug Monograph Index To Ophthalmic Product Index

Oxytetracycline For Injection (IM only) 50 mg/ml or 125 mg/ml (both with 2% lidocaine) in 2 ml amps and 10 ml vials; *Terramycin® I.M.* (Roerig); generic, (Rx)

## OXYTOCIN

**Chemistry** - A nonapeptide hypothalamic hormone stored in the posterior pituitary (in mammals), oxytocin occurs as a white powder that is soluble in water. The commercially available preparations are highly purified and have virtually no antidiuretic or vasopressor activity when administered at usual doses. Oxytocin potency is standardized according to its vasopressor activity in chickens and is expressed in USP Posterior Pituitary Units. One unit is equivalent of approximately 2.0 - 2.2 micrograms of pure hormone.

Commercial preparations of oxytocin injection have their pH adjusted with acetic acid to 2.5-4.5 and multi-dose vials generally contain chlorbutanol 0.5% as a preservative.

**Storage/Stability/Compatibility** - Oxytocin injection should be stored at temperatures of less than 25°C, but should not be frozen. Some manufacturers recommend storing the product under refrigeration (2-8°C), but some products have been demonstrated to be stable for up to 5 years if stored at less than 26°C.

Oxytocin is reportedly **compatible** with most commonly used intravenous fluids and the following drugs: chloramphenicol sodium succinate, metaraminol bitartrate, netilmicin sulfate, sodium bicarbonate, tetracycline HCl, thiopental sodium and verapamil HCl.

Oxytocin is reportedly **incompatible** with the following drugs: fibrinolysin, norepinephrine bitartrate, prochlorperazine edisylate and warfarin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - By increasing the sodium permeability of uterine myofibrils, oxytocin stimulates uterine contraction. The threshold for oxytocin-induced uterine contraction is reduced with pregnancy duration, in the presence of high estrogen levels and in patients already in labor.

Oxytocin can facilitate milk ejection, but does not have any galactopoietic properties. While oxytocin only has minimal antidiuretic properties, water intoxication can occur if it is administered at too rapid a rate and/or if excessively large volumes of electrolyte-free intravenous fluids are administered.

**Uses/Indications -** In veterinary medicine, oxytocin has been used for induction or enhancement of uterine contractions at parturition, treatment of postpartum retained placenta and metritis, uterine involution after manual correction of prolapsed uterus in dogs, and in treating agalactia.

**Pharmacokinetics** - Oxytocin is destroyed in the GI tract and, therefore, must be administered parenterally. After IV administration, uterine response occurs almost immediately. Following IM administration, the uterus responds generally within 3-5 minutes. The duration of effect in dogs after IV or IM/SQ administration has been reported to be 13 minutes and 20 minutes, respectively. While oxytocin can be administered intranasally, absorption can be erratic.
Oxytocin is distributed throughout the extracellular fluid. It is believed that small quantities of the drug cross the placenta and enter the fetal circulation.

In humans, the plasma half-life of oxytocin is about 3-5 minutes. In goats, this value has been reported to be about 22 minutes. Oxytocin is metabolized rapidly in the liver and kidneys and a circulating enzyme, oxytocinase can also destroy the hormone. Very small amounts of oxytocin are excreted in the urine unchanged.

To Drug Monograph Index To Ophthalmic Product Index

**Contraindications/Precautions** - Oxytocin is considered to be contraindicated in animals with dystocia due to abnormal presentation of fetus(es), unless correction is made. When used prepartum, oxytocin should be used only when the cervix is relaxed naturally or by the prior administration of estrogens (Note: Most clinicians avoid the use of estrogens, as natural relaxation is a better indicator for the proper time to induce contractions).

In humans, oxytocin is considered to be contraindicated in patients with significant cephalopelvic disproportion, unfavorable fetal positions, in obstetrical emergencies when surgical intervention is warranted, severe toxemia or when vaginal delivery is contraindicated. Oxytocin is also contraindicated in patients who are hypersensitive to it. Nasally administered oxytocin is contraindicated in pregnancy. Before using oxytocin, treat hypoglycemia or hypocalcemia if present.

**Adverse Effects/Warnings** - When used appropriately at reasonable dosages, oxytocin rarely causes significant adverse reactions. Most adverse effects are as a result of using the drug in inappropriate individuals (adequate physical exam and monitoring of patient are essential) or at too high doses (see Overdosage below). Hypersensitivity reactions are a possibility in non-synthetically produced products. Repeated bolus injections of oxytocin may cause uterine cramping and discomfort.

**Overdosage** - Effects of overdosage on the uterus depend on the stage of the uterus and the position of the fetus(es). Hypertonic or tetanic contractions can occur leading to tumultuous labor, uterine rupture, fetal injury or death.

Water intoxication can occur if large doses are infused for a long period of time, especially if large volumes of electrolyte-free intravenous fluids are concomitantly being administered. Early symptoms can include listlessness or depression. More severe intoxication symptoms can include coma, seizures and eventually death. Treatment for mild water intoxication is stopping oxytocin therapy and restricting water access until resolved. Severe intoxication may require the use of osmotic diuretics (mannitol, urea, dextrose) with or without furosemide.

**Drug Interactions** - If **sympathomimetic agents** are used concurrently with oxytocin, post-partum hypertension may result. Monitor and treat if necessary. Oxytocin used concomitantly with **cyclopropane** anesthesia can result in hypotension, maternal sinus bradycardia with atrioventricular dysrhythmias. One case in humans has been reported where **thiopental** anesthesia was delayed when oxytocin was being administered. The clinical significance of this interaction has not been firmly established.

**Doses -**
**Horses**:

To augment or initiate uterine contractions during parturition in properly evaluated mares:

a) 20 Units IM causes slow, quiet foaling;
40 - 60 Units IM produces, quiet, safe foaling within an hour;
100 Units or more will result in rapid completion of a more active foaling;
IV (bolus) doses of 2.5 - 10 Units may be used to initiate parturition. (Hillman 1987)

b) For induction: If cervix is dilated at least 2 cm (internal measurement): 40 - 60 Units given as IV bolus, delivery should occur within 90 minutes.
If the cervix is closed or less than 2 cm dilated: give oxytocin in 10 unit increments IV at 15-30 minute intervals. If the cervix dilates, but no signs of labor are shown, give additional oxytocin of 40 - 60 Units. (Carleton and Threlfall 1986)

To aid in removal of retained placenta:

a) Oxytocin Bolus: 30 - 40 Units IM at intervals of 60-90 minutes. If parturition occurred more than 24 hours prior to oxytocin, doses up to 80 - 100 Units IM may be used. Alternatively, IV doses of 30 - 60 Units may be used until an adequate response is detected via rectal palpation of the uterus.

To Drug Monograph Index To Ophthalmic Product Index

Oxytocin Infusion: Add 80 - 100 Units oxytocin to 500 ml normal saline and begin IV infusion. Adjust rate of infusion according to mare's reactions. Slow rate if mare exhibits symptoms of excessive abdominal pain. Retained placenta generally expelled within 30 minutes. Gentle traction may help speed up expulsion. If several days have past since parturition, doses of up to 300 Units (administered rapidly) may be necessary to activate uterine motility. (Held 1987)

For mild to moderate cases of acute post-partum metritis:

a) 20 Units IM 3-4 times a day for 2-3 days (Hameida, Gustafsson, and Whitmore 1986)

For obstetrical use in mares:

a) 100 Units IV, IM or SQ (Package Insert; Oxytocin Injection—Anthony Products)

**Elephants:**

For dystocia:

a) Oxytocin for labor induction in elephants should be used judiciously. To induce labor, give 20-30 IU IM or IV as the initial dose; increase if needed every 20-30 minutes in increments of 20-30 IU. For milk letdown, give 40-60 IU intravenously. Give one injection only when needed for the calf to nurse or to collect milk for bottle feeding. Schmitt,D.L. 2001 (personal communication)

b) See abstract below for guidelines on oxytocin use. Schaftenaar,W., Hildebrandt,T.B., Flugger,M., Goritz,F., Schmitt,D., and West,G. 2001. **Guidelines for veterinary assistance during the reproduction process in female elephants.** Proceedings American Association of Zoo Veterinarians, American Association of Wildlife Veterinarians, Association of Reptilian and Amphibian Veterinarians, and the National Association of Zoo and Wildlife Veterinarians Joint Conference. Pages: 348-355 **Abstract:** In February 2000, a group of European zoo veterinarians met at Tierpark Hagenbeck, Hamburg to evaluate a questionnaire about 31 parturitions in Asian elephants. The results were presented at the 40th International Symposium on Diseases of Zoo and Wild Animals. The results were combined with the experiences of some North-American zoo veterinarians, which resulted in the protocol presented in this paper. The protocol may serve as a guideline for institutions that wish to breed elephants. The proper application of the recommendations given in these guidelines should increase the reproductive success in elephants. It is the moral obligation of everyone who is responsible for the management and breeding of elephants to consider utilizing the guidelines as they may apply to their situation and to collect data that may help increase our knowledge. The breeding process in elephants requires monitoring of several parameters in both males and females. The most crucial parameters are the determination of the estrous cycle through progesterone and, perhaps, LH assay, evaluation of the genital tract in both sexes, determination of the number of fetuses and finally, parturition. The first part of the paper will mention briefly the tools that can be used in female elephants to achieve these goals. The second part describes a protocol for veterinary intervention in elephant parturition. **Additional excerpt:** The calf should be born within 2 hours after rupture of the fetal membranes. If not, veterinary intervention should take place according to the following schedule. Two hours after rupture of the membranes or 120 hours after progesterone drop, collect a blood samples for calcium determination. Store an EDTA and heparin sample for Herpes virus diagnosis (both cells and plasma in freezer after separation). Perform a rectal palpation, transrectal ultrasonographic examination, transrectal massage of the pelvic area with two arms for at least 10 minutes (keep hands gripped together and press with the wrists or the palmer sides of the hands against the pelvic roof and the genital tract). This may stimulate labor activities. Care must be taken not to damage the rectal wall, which may get very edematous. Insert at least one catheter IV. To stimulate further relaxation of the cervix, the parenteral administration of estrogens may be considered. However, no data are available for elephants. Administer 50 IU oxytocin IM or SC if there is (some) relaxation of the cervix. Four hours after rupture of membranes or 122 hours after progesterone drop, treat for hypocalcemia if applicable. Perform a rectal palpation, transrectal ultrasongraphic examination, and transrectal massage of the pelvic area and give 50 IU of oxytocin IM or SC. If parts of the fetus are in the pelvic canal, the dose may be increased to 100 IU, given IM. Six hours after rupture of the membranes or 124 hours after progesterone drop, perform a rectal

To Drug Monograph Index To Ophthalmic Product Index

palpation, transrectal ultrasonographic examination, check blood Ca level again, and perform transrectal massage of the pelvic area. If no progress was made, prepare everything to perform a vaginal vestibulotomy. Administer 100 IU of oxytocin in a 1-hr infusion. Eight hours after rupture of he membranes or 126 hr after progesterone drop, perform a rectal palpation, transrectal ultrasongraphic examination, and transrectal massage of the pelvic area. If no progress was made, perform a vaginal vestibulotomy. See original article for further details.

c) 5-20 mg IV with or without prior estrogenation. Repeated doses have been unrewarding in producing a primary delivery and lack of productive response to oxytocin after cessation of natural labor signals the existence of a serious dystocia. Foerner,J.J., 1999. **Dystocia in the elephant.** In: Fowler,M.E. and Miller.R.E. (Editors), Zoo and Wild Animal Medicine: Current Therapy 4. W.B. Saunders, Philadelphia; USA pp. 522-525

d) A 17- year-old Asian elephant in labor for almost 9 hours was treated with 20 ml of oxytocin 0.5% vol/wt intravenously along with 500 ml of dextrose 5%. A healthy calf was delivered within 16 minutes from the time of initiation of the infusion. Raju,R., Rao,B.S.G., Khadri,S.M., and Asha,D. 1997. **Chemical manipulation of delayed parturition in captive Asiatic elephant at Mysore Zoo.** Indian Forester 123:(10):910-916

e) An Asian cow was given 50 IU of oxytocin (0.013 mg/kg) SC which induced strong uterine contractions. When this dose was repeated SC but failed to elicit delivery, the same dose was given IV. Uterine contractions followed almost immediately and lasted about 30 minutes. Although a vaginal vestibulotomy was eventually performed, the author felt the dose of 50 IU to be correct as higher doses may have carried the risk of a uterine rupture or displacement of the placenta. Schaftenaar,W. 1996. **Vaginal vestibulotomy in an Asian elephant (*Elephas maximus*).** Proceedings American Association of Zoo Veterinarians. Pages: 434-439
**Abstract:** Due to its dimensions, dystocia in elephants presents a difficult problem. This paper describes the delivery of a dead calf by surgical intervention. A vestibulotomy was performed under local anesthesia. Complications in wound healing resulted in a permanent fistula of the vestibulum. The difficulties in decision making and the interpretation of clinical signs are discussed

For retained placenta:
f) Intermittent oxytocin therapy on days 2-14 postpartum failed to result in the expulsion of a retained placenta and produced only transient abdominal contractions and minimal increases in milk letdown. On day 15, 10 mg estradiol cypionate was administered i.m. followed by 200 IU oxytocin i.v. An additional 10 IU oxytocin was administered i.v. on day 16 and the placenta was palpable within the vaginal vault on day 17. Murray,S., Bush,M., and Tell,L.A. 1996**. Medical management of postpartum problems in an Asian elephant (*Elephas maximus*) cow and calf.** Journal of Zoo and Wildlife Medicine 27:(2):255-258 **Abstract:** An 18-yr old female Asian elephant (*Elephas maximus*) gave birth to a 120-kg female calf following 22 mo of gestation. Immediately after parturition, the cow became agitated and aggressive towards the calf. Before the keepers were able to safely intervene and remove the calf, the cow stepped on the calf's head and right front leg. Within 30 min, the cow calmed down, allowing the calf's safe reintroduction under close keeper supervision and control. The cow had a retained placenta, poor mammary development, and low milk production. The calf's injuries, in combination with the cow's low milk production, impeded the calf's ability to nurse and gain weight. Within 10 days, the calf lost 10% of its weight. Serum protein electrophoresis indicated failure of passive transfer of maternal immunoglobulin. On day 10, the calf received a transfusion of concentrated immunoglobulin extracted and concentrated from the cow's previously banked plasma. On day 13, the calf developed a urinary tract infection, as diagnosed by white blood cells and bacteria in the urine. Following immunoglobulin administration and antibiotic therapy, clinical signs slowly resolved and the calf gained weight. The cow passed the fetal membranes during parturition, but the placenta was retained. Despite prophylactic systemic antibiotics and vaginal flushing, the cow became depressed and developed a leukocytosis and anemia. A mucopurulent vaginal discharge and ventral edema were noted on day 3, and milk production was minimal. Because decreased milk

production has been reported as a common sequel to retained placenta, efforts were focused on removing the placenta. Intermittent oxytocin therapy on days 2-14 did not result in expulsion of the placenta and produced only transient abdominal contractions and minimal increases in milk letdown. On day 15, 10 mg estradiol cypionate was administered i.m. followed by 200 IU oxytocin i.v. An additional 10 IU oxytocin was administered i.v. on day 16. The friable placenta was palpable within the vaginal vault on day 17. The remaining placenta was removed by gentle traction applied by a modified weighted pressure cuff. Once the placenta was removed, the cow's clinical problems slowly resolved and the calf continued to gain weight.

**Monitoring Parameters** -

1) Uterine contractions, status of cervix
2) Fetal monitoring if available and indicated

**Client Information** - Oxytocin should only be used by individuals able to adequately monitor its effects.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: Oxytocin products are approved for several species, including horses, dairy cattle, beef cattle, sheep, swine, cats and dogs. There is no milk or meat withdrawal times specified for oxytocin. Oxytocin is a prescription (Rx) drug.

Oxytocin for Injection 20 USP Units/ml in 10 ml, 30 ml, & 100 ml vials; available labeled generically from several manufacturers.

**Human-Approved Products**:

Oxytocin for Injection (Human-labeled) 10 Units/ml in 0.5 ml & 1 ml amps, 1 & 10 ml vials; 1 ml Tubex, 1 ml Steri-Dose syringe; *Pitocin*® (Parke-Davis); *Syntocinon*® (Sandoz); Oxytocin® (Wyeth); generic, (Rx)

Oxytocin, Synthetic, Nasal Spray (Human-labeled) 40 Units/ml in 2 and 5 ml squeeze bottles; *Syntocinon*® (Sandoz) (Rx)

**Paregoric - see Opiate Antidiarrheals**

## PENICILLAMINE

**Chemistry** - A monothiol chelating agent that is a degradation product of penicillins, penicillamine occurs as a white or practically white, crystalline powder with a characteristic odor. Penicillamine is freely soluble in water and slightly soluble in alcohol and has $pK_a$ values of 1.83, 8.03, and 10.83. Penicillamine may also be known as D-Penicillamine, beta,beta-Dimethylcysteine, or D-3-Mercaptovaline.

**Storage/Stability/Compatibility** - Penicillamine should be stored at room temperature (15-30°C). The capsules should be stored in tight containers and the tablets in well-closed containers.

**Pharmacology** - Penicillamine chelates a variety of metals, including copper, lead, iron, and mercury, forming stable water soluble complexes that are excreted by the kidneys.
Penicillamine also combines chemically with cystine to form a stable, soluble complex that can be readily excreted.

Penicillamine has antirheumatic activity. The exact mechanisms for this action are not understood, but the drug apparently improves lymphocyte function, decreases IgM rheumatoid factor and immune complexes in serum and synovial fluid.
Although penicillamine is a degradation product of penicillins, it has no antimicrobial activity.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - Penicillamine is used primarily for its chelating ability in veterinary medicine. It is the drug of choice for Copper storage-associated hepatopathies in dogs, and may be used for the long-term oral treatment of lead poisoning or in cystine urolithiasis.
Although the drug may be of benefit in chronic hepatitis, doses necessary for effective treatment may be too high to be tolerated.

**Pharmacokinetics** - Penicillamine is well absorbed after oral administration and peak serum levels occur about one hour (in humans) after dosing. The drug apparently crosses the placenta, but otherwise little information is known about its distribution. Penicillamine that is not complexed with either a metal or cystine is thought to be metabolized in the liver and excreted in the urine and feces.

**Contraindications/Precautions/Reproductive Safety** - Penicillamine is contraindicated in patients who have a history of penicillamine-related blood dyscrasias.
Penicillamine has been associated with the development of birth defects in offspring of rats given 10 times the recommended dose. There are also some reports of human teratogenicity.

**Adverse Effects/Warnings** - In dogs, the most prevalent adverse effect associated with penicillamine is nausea and vomiting. If vomiting is a problem, attempt to alleviate by giving smaller doses of the drug on a more frequent basis. Although food probably decreases the bioavailability of the drug, many clinicians recommend mixing the drug with food or giving at mealtimes if vomiting persists. Although thought to occur infrequently or rarely, fever, lymphadenopathy, skin hypersensitivity reactions, or immune-complex glomerulonephropathy may also potentially occur.

**Overdosage/Acute Toxicity** - No information located.

**Drug Interactions** - The amount of penicillamine absorbed from the GI tract may be reduced by the concurrent administration of **food, antacids, or iron salts**. Administration of penicillamine with **gold compounds, cytotoxic or other immunosuppressant agents (***e.g.,* **cyclophosphamide, azathioprine, but not corticosteroids), or phenylbutazone** may increase the risk of hematologic and/or renal adverse reactions. Concomitant administration with **4-aminoquinoline compounds (***e.g.,* **chloroquine, quinacrine)** may increase the risks of severe dermatologic adverse effects occurring. Penicillamine may cause **pyridoxine** deficiency in humans, but this is not believed to occur in dogs.

**Drug/Laboratory Interactions** - When using **technetium Tc 99m gluceptate** to visualize the kidneys, penicillamine may chelate this agent and form a compound which is excreted via the hepatobiliary system. This may result in gallbladder visualization which could confuse the results.

**Doses** -
**Dogs**:

For copper-associated hepatopathy:

a) 10 - 15 mg/kg PO *bid* on an empty stomach. Only effective for long-term use, not for acute copper toxicity. (Twedt and Whitney 1989)]
b) For Bedlington Terriers: Initially at 125 mg q12h PO. If anorexia and vomiting are significant problems, start dose at 125 mg daily and increase to 125 mg *bid* over several days. (Hardy 1989)
c) 125 - 250 mg PO 30 minutes prior to feeding. If vomiting occurs, divide daily dosage into *bid-tid*. (Cornelius and Bjorling 1988)

For cystine urolithiasis:

a) 15 mg/kg PO twice daily. If nausea and vomiting occur, mix with food or give at mealtime. Some dogs may need to have the dosage slowly increased to full dose in order to tolerate the drug. (Osborne, Hoppe, and O'Brien 1989)

To Drug Monograph Index To Ophthalmic Product Index

b) 15 mg/kg PO *bid* with food (Lage, Polzin, and Zenoble 1988)

For lead poisoning:

a) After initial therapy regimen with CaEDTA and if continued therapy is desired at home, may give penicillamine at 110 mg/kg/day PO divided q6-8h for 1-2 weeks. If vomiting, depression, and anorexia occur, may reduce dose to 33 - 55 mg/kg/day divided q6-8h which should be better tolerated. (Mount 1989)

b) As an alternate or adjunct to CaEDTA: 30 - 110 mg/kg/day divided *qid* for 7 days; may repeat after 7 days off therapy. If vomiting occurs, may give dimenhydrinate at 2 - 4 mg/kg PO 1/2 hour before penicillamine dose. (Grauer and Hjelle 1988b)

**Cats**:

For lead poisoning:

a) After initial therapy with CaEDTA and if blood lead is greater than 0.2 ppm at 3-4 weeks post-treatment, may repeat CaEDTA or give penicillamine at 125 mg q12h PO for 5 days. (Reid and Oehme 1989)

**Monitoring Parameters** - Monitoring of penicillamine therapy is dependent upon the reason for its use; refer to the references in the Dose section above for further discussion on the diseases and associated monitoring of therapy.

**Client Information** - This drug should preferably be given on an empty stomach, at least 30 minutes before feeding. If the animal develops problems with vomiting or anorexia, three remedies have been suggested. 1) Give same total daily dose, but divide into smaller individual doses and give more frequently. 2) Temporarily reduce the daily dose and gradually increase to recommended dosage. 3) Give with meals (will probably reduce amount of drug absorbed).

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Penicillamine Oral Titratable Tablets 250 mg (scored); *Depen*® (Wallace); (Rx)

Penicillamine Oral Capsules 125 mg, 250 mg; *Cuprimine*® (Merck) (Rx)

## PENICILLINS (GENERAL INFORMATION)

**Pharmacology** - Penicillins are usually bactericidal against susceptible bacteria and act by inhibiting mucopeptide synthesis in the cell wall resulting in a defective barrier and an osmotically unstable spheroplast. The exact mechanism for this effect has not been definitively determined, but beta-lactam antibiotics have been shown to bind to several enzymes (carboxypeptidases, transpeptidases, endopeptidases) within the bacterial cytoplasmic membrane that are involved with cell wall synthesis. The different affinities that various beta-lactam antibiotics have for these enzymes (also known as penicillin-binding proteins; PBPs) help explain the differences in spectrums of activity the drugs have that are not explained by the influence of beta-lactamases. Like other beta-lactam antibiotics, penicillins are generally considered to be more effective against actively growing bacteria.

The clinically available penicillins encompass several distinct classes of compounds with varying spectrums of activity: The so-called natural penicillins including penicillin G and V; the penicillinase-resistant penicillins including cloxacillin, dicloxacillin, oxacillin, nafcillin and methicillin; the aminopenicillins including ampicillin, amoxicillin, cyclacillin, hetacillin and bacampicillin; extended-spectrum penicillins including carbenicillin,

ticarcillin, piperacillin, azlocillin and mezlocillin; and the potentiated penicillins including amoxicillin-potassium clavulanate, ampicillin-sulbactam, and ticarcillin-potassium clavulanate.

The natural penicillins (G and K) have similar spectrums of activity, but penicillin G is slightly more active *in vitro* on a weight basis against many organisms. This class of penicillin has *in vitro* activity against most spirochetes and gram positive and gram negative aerobic cocci, but not penicillinase producing strains. They have activity against some aerobic and anaerobic gram positive bacilli such as *Bacillus anthracis*, *Clostridium sp*. (not *C. difficile*), *Fusobacterium* and *Actinomyces*. The natural penicillins are customarily inactive against most gram negative aerobic and anaerobic bacilli, and all *Rickettsia*, mycobacteria, fungi, *Mycoplasma* and viruses.

The penicillinase-resistant penicillins have a more narrow spectrum of activity than the natural penicillins. Their antimicrobial efficacy is aimed directly against penicillinase-producing strains of gram positive cocci, particularly *Staphylococcal* species and these drugs are sometimes called anti-staphylococcal penicillins. There are documented strains of *Staphylococcus* that are resistant to these drugs (so-called methicillin-resistant *Staph*), but these strains have not as yet been a major problem in veterinary species. While this class of penicillins do have activity against some other gram positive and gram negative aerobes and anaerobes, other antibiotics (penicillins and otherwise) are usually better choices. The penicillinase-resistant penicillins are inactive against *Rickettsia*, mycobacteria, fungi, *Mycoplasma*, and viruses.

The aminopenicillins, also called the “broad-spectrum” or ampicillin penicillins, have increased activity against many strains of gram negative aerobes not covered by either the natural penicillins or penicillinase-resistant penicillins, including some strains of *E. coli, Klebsiella,* and *Haemophilus*. Like the natural penicillins, they are susceptible to inactivation by beta-lactamase-producing bacteria (e.g *Staph aureus*). Although not as active as the natural penicillins, they do have activity against many anaerobic bacteria, including *Clostridial* organisms. Organisms that are generally not susceptible include *Pseudomonas aeruginosa*, *Serratia*, Indole-positive *Proteus* (*Proteus mirabilis* is susceptible), *Enterobacter*, *Citrobacter*, and *Acinetobacter*. The aminopenicillins also are inactive against *Rickettsia*, mycobacteria, fungi, *Mycoplasma*, and viruses.

The extended-spectrum penicillins, sometimes called anti-pseudomonal penicillins, include both alpha-carboxypenicillins (carbenicillin and ticarcillin) and acylaminopenicillins (piperacillin, azlocillin, and mezlocillin). These agents have similar spectrums of activity as the aminopenicillins but with additional activity against several gram negative organisms of the family Enterobacteriaceae, including many strains of *Pseudomonas aeruginosa*. Like the aminopenicillins, these agents are susceptible to inactivation by beta-lactamases.

In order to reduce the inactivation of penicillins by beta-lactamases, potassium clavulanate and sulbactam have been developed to inactivate these enzymes and thus extend the spectrum of those penicillins. When used with a penicillin, these combinations are often effective against many beta-lactamase-producing strains of otherwise resistant *E. coli, Pasturella spp, Staphylococcus spp, Klebsiella*, and *Proteus*. Type I beta-lactamases that are often associated with *E. coli, Enterobacter,* and *Pseudomonas* are not generally inhibited by clavulanic acid.

**Uses/Indications** - Penicillins have been used for a wide range of infections in various species. FDA-approved indications/species, as well as non-approved uses, are listed in the Uses/Indications and Dosage sections for each individual drug.

**Pharmacokinetics (General)** - The oral absorption characteristics of the penicillins are dependent upon its class. Penicillin G is the only available oral penicillin that is substantially affected by gastric pH and can be completely inactivated at pH’s of less than 2. The other orally available penicillins are resistant to acid degradation but bioavailability can be decreased by the presence of food (not amoxicillin). Of the orally

administered penicillins, penicillin V and amoxicillin tend to have the greatest bioavailability in their respective classes.

Penicillins are generally distributed widely throughout the body. Most drugs attain therapeutic levels in the kidneys, liver, heart, skin, lungs, intestines, bile, bone, prostate, and peritoneal, pleural and synovial fluids. Penetration into the CSF and eye only occur with inflammation and may not reach therapeutic levels. Penicillins are bound in varying degrees to plasma proteins and they cross the placenta.

Most penicillins are rapidly excreted largely unchanged by the kidneys into the urine via glomerular filtration and tubular secretion. Probenecid can prolong half-lives and increase serum levels by blocking the tubular secretion of penicillins. Eexcept for nafcillin and oxacillin, hepatic inactivation and biliary secretion is a minor route of excretion.

**Contraindications/Precautions/Reproductive Safety** - Penicillins are contraindicated in patients who have a history of hypersensitivity to them. Because there may be cross-reactivity, use penicillins cautiously in patients who are documented hypersensitive to other beta-lactam antibiotics (*e.g.*, cephalosporins, cefamycins, carbapenems).

Do not administer systemic antibiotics orally in patients with septicemia, shock, or other grave illnesses as absorption of the medication from the GI tract may be significantly delayed or diminished. Parenteral (preferably IV) routes should be used for these cases.

Penicillins have been shown to cross the placenta and safe use of them during pregnancy has not been firmly established, but neither have there been any documented teratogenic problems associated with these drugs. However, use only when the potential benefits outweigh the risks. Certain species (snakes, birds, turtles, Guinea pigs, and chinchillas) are reportedly sensitive to procaine penicillin G.

High doses of penicillin G sodium or potassium, particularly in small animals with a preexisting electrolyte abnormality, renal disease or congestive heart failure may cause electrolyte imbalances. Other injectable penicillins, such as ticarcillin, carbenicillin and ampicillin, have significant quantities of sodium per gram and may cause electrolyte imbalances when used in large dosages in susceptible patients.

**Adverse Effects/Warnings** - Adverse effects with the penicillins are usually not serious and have a relatively low frequency of occurrence.

Hypersensitivity reactions unrelated to dose can occur with these agents and can be manifested as rashes, fever, eosinophilia, neutropenia, agranulocytosis, thrombocytopenia, leukopenia, anemias, lymphadenopathy, or full blown anaphylaxis. In humans, it is estimated that up to 15% of patients hypersensitive to cephalosporins will also be hypersensitive to penicillins. The incidence of cross-reactivity in veterinary patients is unknown.

When given orally, penicillins may cause GI effects (anorexia, vomiting, diarrhea). Because the penicillins may also alter gut flora, antibiotic-associated diarrhea can occur, as well as selecting out resistant bacteria maintaining residence in the colon of the animal (superinfections).

High doses or very prolonged use has been associated with neurotoxicity (*e.g.,* ataxia in dogs). Although the penicillins are not considered to be hepatotoxic, elevated liver enzymes have been reported. Other effects reported in dogs include tachypnea, dyspnea, edema and tachycardia.

Some penicillins (ticarcillin, carbenicillin, azlocillin, mezlocillin, piperacillin and nafcillin) have been implicated in causing bleeding problems in humans. These drugs are infrequently used systemically in veterinary species at the present time and the veterinary ramifications of this effect is unclear.

To Drug Monograph Index  To Ophthalmic Product Index

**Overdosage/Acute Toxicity** - Acute oral penicillin overdoses are unlikely to cause significant problems other than GI distress, but other effects are possible (see Adverse effects). In humans, very high dosages of parenteral penicillins, especially in patients with renal disease, have induced CNS effects.

**Drug Interactions** - *In vitro* studies have demonstrated that penicillins can have synergistic or additive activity against certain bacteria when used with **aminoglycosides** or **cephalosporins**.
Use of **bacteriostatic antibiotics** (*e.g.,* **chloramphenicol, erythromycin, tetracyclines**) with penicillins is generally not recommended, particularly in acute infections where the organism is proliferating rapidly as penicillins tend to perform better on actively growing bacteria. In low concentrations, certain penicillins (*e.g.,* ampicillin, oxacillin or nafcillin) may have additive or synergistic effects against certain bacteria when used with **rifampin**, but there is apparent antagonism when the penicillin is present in high concentrations. **Probenecid** competitively blocks the tubular secretion of most penicillins, thereby increasing serum levels and serum half-lives. High dosages of certain penicillins (*e.g.,* ticarcillin, carbenicillin) have been associated with bleeding; they should be used cautiously in patients receiving **oral anticoagulants or heparin**.

**Drug/Laboratory Interactions** - Ampicillin may cause false-positive **urine glucose determinations** when using cupric sulfate solution (Benedict's Solution, *Clinitest*®). Tests utilizing glucose oxidase (*Tes-Tape*®, *Clinistix*®) are not affected by ampicillin. When using the Jaffe reaction to measure **serum or urine creatinine**, cephalosporins in high dosages (not ceftazidime or cefotaxime), may falsely cause elevated values. In humans, clavulanic acid and high dosages of piperacillin have caused a false-positive direct **Combs' test**.

As penicillins and other beta-lactams can inactivate **aminoglycosides** *in vitro* (and *in vivo* in patients in renal failure), serum concentrations of aminoglycosides may be falsely decreased if the patient is also receiving beta-lactam antibiotics and the serum is stored prior to analysis. It is recommended that if the assay is delayed, samples be frozen and, if possible, drawn at times when the beta-lactam antibiotic is at a trough.

**Monitoring Parameters** - Because penicillins usually have minimal toxicity associated with their use, monitoring for efficacy is usually all that is required unless toxic signs or symptoms develop. Serum levels and therapeutic drug monitoring are not routinely done with these agents.

**Client Information** - Owners should be instructed to give oral penicillins on an empty stomach, unless using amoxicillin or if GI effects (anorexia, vomiting) occur. Compliance with the therapeutic regimen should be stressed. Reconstituted oral suspensions should be kept refrigerated and discarded after 14 days.

## PENICILLIN G PK

For general information on the penicillins, including adverse effects, contraindications, overdosage, drug interactions and monitoring parameters, refer to the monograph: Penicillins, General Information.

**Chemistry** - Penicillin G is a natural penicillin and is obtained from cultures *Penicillium chrysogenum* and is available in several different salt forms. Penicillin G potassium (also known as benzylpenicillin potassium, aqueous or crystalline penicillin) occurs as colorless or white crystals, or white crystalline powder. It is very soluble in water and sparingly soluble in alcohol. Potency of penicillin G potassium is usually expressed in terms of Units. One mg of penicillin G potassium is equivalent to 1440-1680 USP Units (1355-1595 USP Units for the powder for injection). After reconstitution, penicillin G potassium powder for injection has a pH of 6-8.5, and contains 1.7 mEq of potassium per 1 million Units.

Penicillin G sodium (also known as benzylpenicillin sodium, aqueous or crystalline penicillin) occurs as colorless or white crystals, or white to slightly yellow, crystalline powder. Approximately 25 mg is soluble in

To Drug Monograph Index To Ophthalmic Product Index

1 ml of water. Potency of penicillin G sodium is usually expressed in terms of Units. One mg of penicillin G sodium is equivalent to 1500-1750 USP Units (1420-1667 USP Units for the powder for injection). After reconstitution, penicillin G sodium powder for injection has a pH of 6-7.5, and contains 2 mEq of sodium per 1 million Units.

Penicillin G procaine (also known as APPG, Aqueous Procaine Penicillin G, Benzylpenicillin Procaine, Procaine Penicillin G, Procaine Benzylpenicillin) is the procaine monohydrate salt of penicillin G. *In vivo* it is hydrolyzed to penicillin G and acts as a depot, or repository form of penicillin G. It occurs as white crystals or very fine, white crystalline powder. Approximately 4-4.5 mg are soluble in 1 ml of water and 3.3 mg are soluble in 1 ml of alcohol. Potency of penicillin G procaine is usually expressed in terms of Units. One mg of penicillin G procaine is equivalent to 900-1050 USP Units. The commercially available suspension for injection is buffered with sodium citrate and has a pH of 5-7.5. It is preserved with methylparaben and propylparaben.

Penicillin G Benzathine (also known as Benzathine Benzylpenicillin, Benzathine Penicillin G, Benzylpenicillin Benzathine, Dibenzylethylenediamine Benzylpenicillin) is the benzathine tetrahydrate salt of penicillin G. It is hydrolyzed *in vivo* to penicillin G and acts as a long-acting form of penicillin G. It occurs as an odorless, white, crystalline powder. Solubilities are 0.2-0.3 mg/ml of water and 15 mg/ml of alcohol. One mg of penicillin G benzathine is equivalent to 1090-1272 USP Units. The commercially available suspension for injection is buffered with sodium citrate and has a pH of 5-7.5. It is preserved with methylparaben and propylparaben.

**Storage/Stability/Compatibility** - Penicillin G sodium and potassium should be protected from moisture to prevent hydrolysis of the compounds. Penicillin G potassium tablets and powder for oral solution should be stored at room temperature in tight containers; avoid exposure to excessive heat. After reconstituting, the oral powder for solution should be stored from 2-8°C (refrigerated) and discarded after 14 days.

Penicillin G sodium and potassium powder for injection can be stored at room temperature (15-30°C). After reconstituting, the injectable solution is stable for 7 days when kept refrigerated (2-8°C) and for 24 hours at room temperature.

Penicillin G procaine should be stored at 2-8°C; avoid freezing. Benzathine penicillin G should be stored at 2-8°C.

All commonly used IV fluids (some Dextran products are incompatible) and the following drugs are reportedly **compatible** with **penicillin G potassium**: ascorbic acid injection, calcium chloride/gluconate, cephapirin sodium, chloramphenicol sodium succinate, cimetidine HCl, clindamycin phosphate, colistimethate sodium, corticotropin, dimenhydrinate, diphenhydramine HCl, ephedrine sulfate, erythromycin gluceptate/lactobionate, hydrocortisone sodium succinate, kanamycin sulfate, lidocaine HCl, methicillin sodium, methylprednisolone sodium succinate, metronidazole with sodium bicarbonate, nitrofurantoin sodium, polymyxin B sulfate, potassium chloride, prednisolone sodium phosphate, procaine HCl, prochlorperazine edisylate, sodium iodide, sulfisoxazole diolamine and verapamil HCl.

The following drugs/solutions are either **incompatible** or data conflicts regarding compatibility with **penicillin G potassium** injection: amikacin sulfate, aminophylline, cephalothin sodium, chlorpromazine HCl, dopamine HCl, heparin sodium, hydroxyzine HCl, lincomycin HCl, metoclopramide HCl, oxytetracycline HCl, pentobarbital sodium, prochlorperazine mesylate, promazine HCl, promethazine HCl, sodium bicarbonate, tetracycline HCl and vitamin B-complex with C.

The following drugs/solutions are reportedly **compatible** with **penicillin G sodium** injection: Dextran 40 10%, dextrose 5% (some degradation may occur if stored for 24 hours), sodium chloride 0.9% (some degradation may occur if stored for 24 hours), calcium chloride/gluconate, chloramphenicol sodium succinate, cimetidine HCl, clindamycin phosphate, colistimethate sodium, diphenhydramine HCl,

To Drug Monograph Index To Ophthalmic Product Index

erythromycin lactobionate, gentamicin sulfate, hydrocortisone sodium succinate, kanamycin sulfate, methicillin sodium, nitrofurantoin sodium, polymyxin B sulfate, prednisolone sodium phosphate, procaine HCl, verapamil HCl and vitamin B-complex with C.

The following drugs/solutions are either **incompatible** or data conflicts regarding compatibility with **penicillin G sodium** injection: amphotericin B, bleomycin sulfate, cephalothin sodium, chlorpromazine HCl, heparin sodium, hydroxyzine HCl, lincomycin HCl, methylprednisolone sodium succinate, oxytetracycline HCl, potassium chloride, prochlorperazine mesylate, promethazine HCl and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Uses/Indications** - Natural penicillins remain the drugs of choice for a variety of bacteria, including group A beta-hemolytic streptococci, many gram positive anaerobes, spirochetes, gram negative aerobic cocci, and some gram negative aerobic bacilli. Generally, if a bacteria is susceptible to a natural penicillin, either penicillin G or V is preferred for treating that infection as long as adequate penetration of the drug to the site of the infection occurs and the patient is not hypersensitive to penicillins.

**Pharmacokinetics (specific)** - Penicillin G potassium is poorly absorbed orally as a result of rapid acid-catalyzed hydrolysis. When administered on an empty (fasted) stomach, oral bioavailability is only about 15-30%. If given with food, absorption rate and extent will be decreased.

Penicillin G potassium and sodium salts are rapidly absorbed after IM injections and yield high peak levels usually within 20 minutes of administration. In horses, equivalent doses given either IV or IM demonstrated that IM dosing will provide serum levels above 0.5 micrograms/ml for about twice as long as IV administration [approx. 3-4 hours (IV) vs. 6-7 hours (IM)].
Procaine penicillin G is slowly hydrolyzed to penicillin G after IM injection. Peak levels are much lower than with parenterally administered aqueous penicillin G sodium or potassium, but serum levels are more prolonged.

Benzathine penicillin G is also very slowly absorbed after IM injections after being hydrolyzed to the parent compound. Serum levels can be very prolonged, but levels attained generally only exceed MIC's for the most susceptible *Streptococci*, and the use of benzathine penicillin G should be limited to these infections when other penicillin therapy is impractical.

After absorption, penicillin G is widely distributed throughout the body with the exception of the CSF, joints and milk. CSF levels are generally only 10% or less of those found in the serum when meninges are not inflamed. Levels in the CSF may be greater in patients with inflamed meninges or if probenecid is given concurrently. Binding to plasma proteins is approximately 50% in most species.

Penicillin G is principally excreted unchanged into the urine through renal mechanisms via both glomerular filtration and tubular secretion. Elimination half-lives are very rapid and are usually one hour or less in most species (if normal renal function exists).

**Doses -**
**Horses**:

For susceptible infections:

a) Penicillin G potassium: 5000 - 50,000 Units/kg IV *qid*
Penicillin G sodium: 5000 - 50,000 Units/kg IV *qid*
Penicillin G procaine: 5000 - 50,000 Units/kg IM *bid* (Robinson 1987)
b) Penicillin G sodium: 25,000 - 50,000 Units/kg IV, IM q6h
Penicillin G procaine: 20,000 - 100,000 Units/kg IM q12h
Penicillin G benzathine: 50,000 Units/kg IM q2 days (Upson 1988)

To Drug Monograph Index To Ophthalmic Product Index

c) Initially give Penicillin G (aqueous, sodium salt used in experiment) 10,000 IU/kg IM with procaine penicillin G at 15,000 IU/kg IM q12h. If infection is severe, penicillin G sodium at 10,000 IU/kg at the same time as the procaine penicillin G. (Love et al. 1983)
d) For treatment of botulism: Penicillin G sodium or potassium 22,000 - 44,000 IU/kg IV *qid* (do not use oral penicillin therapy). (Johnston and Whitlock 1987)
e) For preoperative antibiotic prophylaxis for colic: Penicillin G potassium 40,000 IU IV *qid* with gentamicin 2.2 mg/kg IV *tid*. (Stover 1987)
f) For respiratory infections (*Streptococci*): Initially, 20,000 - 40,000 U/kg of aqueous penicillin G (sodium/potassium) IM with 20,000 u/kg IM of procaine penicillin G which is then continued *bid*. (Beech 1987a)
g) For foals: Penicillin G Na or K: 25,000 - 50,000 U/kg IV q6-8h;
Procaine penicillin G 25,000 - 50,000 U/kg IM q12h. Use the longer dose interval or smaller dose in premature foals or those less than 7 days old. (Caprile and Short 1987)
h) Procaine penicillin G 25,000 Units/kg IM q12-24h
Penicillin G sodium: 15,000 - 20,000 U/kg IV or IM q6h (Baggot and Prescott 1987)
i) Penicillin G potassium: 12,500 - 100,000 Units/kg IV q4h
Penicillin G sodium: 12,500 - 100,000 Units/kg IV q4h
Penicillin G procaine: 20,000 - 50,000 Units/kg IM q12h (Brumbaugh 1987)

**Elephants:**

a) Procaine penicillin G (150,000 IU/ml) in combination with benzathine penicillin (150,000 IU / ml): 4,545 IU/kg q 96 hours for Bacillus anthracis, Corynebacterium diphtherae, Streptococci spp, Staphylococci (non- penicillinase producing).

Procaine penicillin G (150,000 IU/ml) in combination with benzathine penicillin (150,000 IU / ml): 2,273/kg q 48 h for Bacillus anthracis, Corynebacterium diphtherae, Streptococci spp, Staphylococci (non-penicillinase producing).

Procaine penicillin G (150,000 IU/ml) in combination with benzathine penicillin (150,000 IU / ml): 4,545 IU/kg q 36 h for Clostridia

Procaine penicillin G (150,000 IU/ml) in combination with benzathine penicillin (150,000 IU / ml): 4,545 IU/kg q 24 h for Pasteurella multocida (Schmidt, 1978).

a) Schmidt,M.J. 1978. **Penicillin and amoxicillin in elephants: A study comparing dose regimens administered with serum levels achieved in healthy elephants.** Journal of Zoo Animal Medicine 9:(4):127-136 **Abstract:** Several dose regimens of an aqueous suspension of benzathine penicillin G combined with procaine penicillin G, and an aqueous suspension of amoxicillin were administered to five healthy adult female Asian elephants. Blood samples were drawn and serum levels of the drugs were measured after each dose was administered. Based upon serum levels, suggestions are made for therapeutic dose regimens for clinical use of both penicillin and amoxicillin in elephants, based on comparable data available for other large domestic animals.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Penicillin G Procaine Injection 300,000 Units/ml in 100 ml and 250 ml bottles
*Crystacillin® 300 A.S. Veterinary* (Solvay); (OTC) Approved for use in cattle, sheep, horses, and swine. Do not exceed 7 days of treatment in non-lactating dairy cattle, beef cattle, swine or sheep, and 5 days in lactating dairy cattle. Milk withdrawal = 48 hours. Slaughter withdrawal: Calves (non-ruminating) 7 days; cattle 4 days; sheep 8 days; swine 6 days.

To Drug Monograph Index To Ophthalmic Product Index

Note: These withdrawal times are for the labeled dosage of 6,600 U/kg once daily which is rarely used clinically today. Actual withdrawal times may be longer. There are other generically labeled products available that may have different withdrawal times; refer to label for more information.

Note: There are several penicillin G procaine combination products available for the veterinary market. These products may contain dihydrostreptomycin, streptomycin or novobiocin, and be available in either intramammary or injectable dosage forms.

Penicillin G Benzathine 150,000 U/ml with Penicillin G Procaine Injection 150,000 Units/ml for Injection in 100 ml and 250 ml vials

*Flo-Cillin*® (Fort Dodge), *Pen BP-48*® (Pfizer), *Crystiben*® (Solvay), *Dual-Pen*® (TechAmerica), generic; (OTC) Approved (most products) in dogs, horses and beef cattle. Slaughter withdrawal: cattle=30 days. Actual species approvals and withdrawal times may vary with the actual product; refer to the label of the product you are using.

**Human-Approved Products**:

Penicillin G (aqueous) Potassium Powder for Injection 1,000,000 units in vials, 5,000,000 units in vials, 10,000,000 units in vials, 20,000,000 units/vial (Rx) *Penicillin G Potassium*® (Apothecon); *Pfizerpen*® (Roerig) (Rx)

Penicillin G (aqueous) Potassium Premixed Frozen Injection: 1,000,000 units, 2,000,000 units & 3,000,000 units in 50 mls *Penicillin G Potassium*® (Baxter) (Rx)

Penicillin G (aqueous) Sodium Powder for Injection 5 million Units/vial; *Penicillin G Sodium*® (Apothecon) (Rx)

Penicillin G Potassium Oral Tablets 200,000 Units, 250,000 Units, 400,000 Units, 500,000 Units, 800,000 Units; *Penicillin G Potassium*® (Rugby) (Rx); *Pentids '400'*® (Apothecon) (Rx); *Pentids '800'*® (Apothecon) (Rx); generic, (Rx)

Penicillin G Potassium Oral Powder for Suspension 400,000 Units/5 ml in 100 ml and 200 ml; *Pentids '400' for Syrup*® (Apothecon) (Rx)

Penicillin G (aqueous) Procaine for Injection 300,000 Units/ml in 10 ml vials, 500,000 Units/ml (600,00 units/1.2 ml) in 12 ml vials, 600,000 Units/unit dose in 1 ml Tubex, 1.2 million Units/unit dose in 2 ml Tubex &, 2.4 million Units/unit dose in 4 ml syringes; *Crysticillin 300 A.S.*® (Apothecon); *Pfizerpen-AS*® (Roerig); *Crysticillin 600 A.S.*® (Apothecon); *Wycillin*® (Wyeth-Ayerst); (Rx)

Penicillin G Benzathine for Injection 300,000 Units/ml in 10 ml vials; 600,000 unit/dose in 1 ml Tubex; 1,200,000 units/dose in 2 ml Tubex; 2,400,000 units/dose in 4 ml syringes; *Bicillin L-A*® (Wyeth-Ayerst); *Permapen*® (Roerig) (Rx)

Penicillin G Benzathine & Procaine Combined for Injection 300,000 units/ml (150,000 units each penicillin G benzathine & penicillin G procaine) in 10 ml vials; 600,000 units/dose (300,000 units each penicillin G benzathine & penicillin G procaine) in 1 ml Tubex; 1,200,000 units/dose in 2 ml Tubex; 2,400,000 units/dose in 4 ml syringe; 900,000 units penicillin G benzathine and 300,000 units penicillin G procaine per dose in 2 ml Tubex; *Bicillin C-R*® (Wyeth-Ayerst); *Bicillin C-R 900/300*® (Wyeth-Ayerst) (Rx)

## PENICILLIN V POTASSIUM

For general information on the penicillins, including adverse effects, contraindications, overdosage, drug interactions and monitoring parameters, refer to the monograph: Penicillins, General Information.

**Chemistry** - A natural penicillin, penicillin V is produced from *Penicillium chrysogenum* and is usually commercially available as the potassium salt. It may also be known as phenoxymethylpenicillin potassium. Penicillin V potassium occurs as an odorless, white, crystalline powder that is very soluble in water and

slightly soluble in alcohol. Potency of penicillin V potassium is usually expressed in terms of weight (in mg) of penicillin V, but penicillin V units may also be used. One mg of penicillin V potassium is equivalent to 1380-1610 USP Units of penicillin V. Manufacturers, however, generally state that 125 mg of penicillin V potassium is approximately equivalent to 200,000 USP units of penicillin V.

**Storage/Stability/Compatibility** - Penicillin V potassium tablets and powder for oral solution should be stored in tight containers at room temperature (15-30°C). After reconstitution, the oral solution should be stored at 2-8°C (refrigerated) and any unused portion discarded after 14 days.

**Pharmacology, Uses/Indications** - Penicillin V may be slightly less active than penicillin G against organisms susceptible to the natural penicillins, but its superior absorptive characteristics after oral administration make it a better choice against mild to moderately severe infections when oral administration is desired in monogastric animals. For more information on the types of organisms that penicillin V generally covers, refer to the general statement on penicillins and the penicillin G monograph.

**Pharmacokinetics (specific)** - The pharmacokinetics of penicillin V are very similar to penicillin G with the exception of oral bioavailability and the percent of the drug that is bound to plasma proteins. Penicillin V is significantly more resistant to acid-catalyzed inactivation in the gut and bioavailability after oral administration in humans is approximately 60-73%. In veterinary species, actual bioavailability measurements have been measured in calves (30%), but studies performed in horses and dogs have demonstrated that therapeutic serum levels can be achieved with the drug after oral administration. In dogs, it has been shown that food will decrease the rate and extent of absorption of the drug from the gut.

Distribution of penicillin V follows that of penicillin G but, at least in humans, the drug is bound to a larger extent to plasma proteins (approximately 80% with penicillin VK vs. 50% with penicillin G).

Like penicillin G, penicillin V is excreted rapidly in the urine via the kidney. Elimination half-lives are generally less than 1 hour in animals with normal renal function, but an elimination half-life of 3.65 hours has been reported after oral dosing in horses (Schwark et al. 1983).

**Doses -**

**Horses**:

For susceptible infections:

a) 66,000 U/kg (41.25 mg/kg) PO gives levels greater than 0.1 micrograms/ml for greater than 325 minutes which should be effective against *Streptococci*. (Beech 1987a) (Author's (Plumb) note: Because of the post-antibiotic effect phenomenon; dosing every 6-8 hours should be sufficient)
b) 110,000 U/kg (68.75 mg/kg) PO q8h (may yield supra-optimal levels against uncomplicated infections by sensitive organisms). (Schwark et al. 1983)
c) 110,000 U/kg PO q6-12h (Brumbaugh 1987)

**Client Information** - Unless otherwise instructed by the veterinarian, this drug should be given on an empty stomach, at least 1 hour before feeding or 2 hours after. Keep oral suspension in the refrigerator and discard any unused suspension after 14 days.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Penicillin V Potassium Oral Tablets 125 mg, 250 mg, 500 mg; (Rx)

Penicillin V Potassium Oral Powder for Suspension 125 mg/5 ml in 100 ml, 150 ml and 200 ml, 250 mg/5 ml in 100 ml, 150 ml and 200 ml; (Rx)

To Drug Monograph Index To Ophthalmic Product Index

There are a multitude of proprietary penicillin VK products, some more widely known include: *V-Cillin K*® (Lilly), *Pen-Vee K*® (Wyeth), *Veetids*® (Squibb), *Uticillin VK*® (Upjohn), *Beepen-VK*® (Beecham), *Ledercillin*® *VK* (Lederle)

## PENTAZOCINE

**Chemistry**- A synthetic partial opiate agonist, pentazocine is commercially available as two separate salts. The hydrochloride salt, which is found in oral dosage forms, occurs as a white, crystalline powder. It is soluble in water and freely soluble in alcohol. The commercial injection is prepared from pentazocine base with the assistance of lactic acid. This allows the drug to be soluble in water. The pH of this product is adjusted to a range of 4-5. Pentazocine is a weak base with an approximate $pK_a$ of 9.0.

**Storage/Stability/Compatibility** - The tablet preparations should be stored at room temperature and in tight, light-resistant containers. The injectable product should be kept at room temperature; avoid freezing.

The following agents have been reported to be **compatible** when mixed with pentazocine lactate: atropine sulfate, benzquinamide HCl, butorphanol tartrate, chlorpromazine HCl, dimenhydrinate, diphenhydramine HCl, droperidol, fentanyl citrate, hydromorphone, hydroxyzine HCl, meperidine HCl, metoclopramide, morphine sulfate, perphenazine, prochlorperazine edisylate, promazine HCl, promethazine HCl, and scopolamine HBr. The following agents have been reported to be **incompatible** when mixed with pentazocine lactate: aminophylline, amobarbital sodium, flunixin meglumine, glycopyrrolate, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, and sodium bicarbonate.

**Pharmacology** - While considered to be a partial opiate agonist, pentazocine exhibits many of the same characteristics as the true opiate agonists. It is reported to have an analgesic potency of approximately one-half that of morphine and five times that of meperidine. It is a very weak antagonist at the *mu* opioid receptor when compared to naloxone. It will not antagonize the respiratory depression caused by drugs like morphine, but may induce symptoms of withdrawal in human patients dependent to narcotic agents.

Besides its analgesic properties, pentazocine can cause respiratory depression, decreased GI motility, sedation, and it possesses antitussive effects. Pentazocine tends to have less sedative qualities in animals than other opiates and therefore is usually not used as a pre-operative medication.

In dogs, pentazocine has been demonstrated to cause a transient decrease in blood pressure. In man, pentazocine can cause increases in cardiac output, heart rate, and blood pressure.

**Pharmacokinetics** - Pentazocine is well absorbed following oral, IM, or SQ administration. Because of a high first-pass effect, only about 1/5$^{th}$ of an oral dose will enter the systemic circulation in patients with normal hepatic function.

After absorption, the drug is distributed widely into tissues. In the equine, it has been shown to be 80% bound to plasma proteins. Pentazocine will cross the placenta and neonatal serum levels have been measured at 60-65% of maternal levels at delivery. It is not clearly known if or how much pentazocine crosses into milk.

The drug is primarily metabolized in the liver with resultant excretion by the kidneys of the metabolites. In the horse, approximately 30% of a given dose is excreted as the glucuronide. Pentazocine and its metabolites have been detected in equine urine for up to 5 days following an injection. Apparently less than 15% of the drug is excreted by the kidneys in an unchanged form.

To Drug Monograph Index To Ophthalmic Product Index

Plasma half-lives have been reported for various species: Humans = 2-3 hrs; Ponies = 97 mins.; Dogs = 22 mins.; Cats = 84 mins.; Swine = 49 mins. Volumes of distribution range from a high of 5.09 L/kg in ponies to 2.78 L/kg in cats. In horses, the onset of action has been reported to be 2-3 minutes following IV dosing with a peak effect at 5-10 minutes.

**Uses/Indications** - Pentazocine is labeled for the symptomatic relief of pain of colic in horses and for the amelioration of pain accompanying postoperative recovery from fractures, trauma, and spinal disorders in dogs. It has also been used as an analgesic in cats (see adverse effects below) and in swine.

**Contraindications/Precautions** - All opiates should be used with caution in patients with hypothyroidism, severe renal insufficiency, adrenocortical insufficiency (Addison's), and in geriatric or severely debilitated patients.

Like other opiates, pentazocine must be used with extreme caution in patients with head trauma, increased CSF pressure or other CNS dysfunction (*e.g.,* coma). Pentazocine should not be used in place of appropriate therapy (medical &/or surgical) for equine colic, but only as adjunctive treatment for pain.

Because reproductive studies have not been done in dogs, the manufacturer does not recommend its use in pregnant bitches, or bitches intended for breeding. Studies performed in laboratory animals have not demonstrated any indications of teratogenicity.

The drug is contraindicated in patients having known hypersensitivity to it.

**Adverse Effects/Warnings** - In dogs, the most predominant adverse reaction following parenteral administration is salivation. Other potential side effects at usual doses include fine tremors, emesis, and swelling at the injection site. At very high doses (6 mg/kg) dogs have been noted to develop ataxia, fine tremors, convulsions, and swelling at the injection site.
Horses may develop transient ataxia, and symptoms of CNS excitement. Pulse and respiratory rates may be mildly elevated.

The use of pentazocine in cats is controversial. Some clinicians claim that the drug causes dysphoric reactions in cats which precludes its use in this species, while others disagree and state that drug may be safely used.

**Overdosage** - There is little information regarding acute overdose situations with pentazocine. For oral ingestions, the gut should be emptied if indicated and safe to do so. Symptoms should be managed by supportive treatment ($O_2$, pressor agents, IV fluids, mechanical ventilation) and respiratory depression can be treated with naloxone. Repeated doses of naloxone may be necessary.

**Drug Interactions** - When used with pentazocine, other **CNS depressants** (*e.g.,* anesthetic agents, antihistamines, phenothiazines, barbiturates, tranquilizers, alcohol, etc.) may cause increased CNS or respiratory depression; dosage may need to be decreased.

**Doses -**
**Horses**:

For analgesia:

a) 0.33 mg/kg slowly in jugular vein. In cases of severe pain, a second dose (0.33 mg/kg) be given IM 15 minutes later (Package Insert; *Talwin*®-*V* - Winthrop)
b) 0.33 - 0.66 mg/kg IV, IM or SQ (Jenkins 1987)
c) 0.4 - 0.8 mg/kg IV (Muir 1987)
d) 0.4 - 0.9 mg/kg IV (Thurmon and Benson 1987)

To Drug Monograph Index To Ophthalmic Product Index

Note: Duration of analgesia may last only 10-30 minutes following an IV dose.

**Monitoring Parameters** -

1) Analgesic efficacy
2) Respiratory rate/depth
3) Appetite/bowel function
4) CNS effects

**Client Information** - Clients should report any significant changes in behavior, appetite, bowel or urinary function in their animals.
It is not approved for use in food producing animals (including horses to be used for food). All pentazocine products are Class-IV controlled substances.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Pentazocine Lactate Injection: 30 mg/ml (as base) in 10 ml vials; *Talwin®-V* (Pharmacia & Upjohn); (Rx)
Pentazocine lactate injection is approved for use in horses and dogs.

**Human-Approved Products**:

Pentazocine Lactate Injection: 30 mg/ml in 10 ml vials and 1, 1.5, & 2 ml amps and pre-filled 2 ml carpuject syringes; *Talwin* ® (Sanofi Winthrop) (Rx)

Pentazocine HCl 50 mg & Naloxone HCl 0.5 mg Tablets (Scored); *Talwin NX®* (Sanofi Winthrop); *Pentazocine & Naloxone HCl®* (Royce) (Rx)

Pentazocine HCl 12.5 mg & Aspirin 325 mg Tablets; *Talwin Compound Caplets®* (Sanofi Winthrop) (Rx)

Pentazocine HCl 25 mg & Acetominophen 650 mg Tablets; *Talacen Caplets®* (Sanofi Winthrop) (Rx)

**Note**: All pentazocine products are **Class-IV controlled substances** and are prescription items only.

## PENTOBARBITAL SODIUM

(Note: Combinations of pentobarbital with other agents (*e.g.,* phenytoin) for euthanasia have a separate monograph listed under Euthanasia Agents)

**Chemistry** - Pentobarbital sodium occurs as odorless, slightly bitter tasting, white, crystalline powder or granules. It is very soluble in water and freely soluble in alcohol. The $pK_a$ of the drug has been reported to range from 7.85-8.03 and the pH of the injection is from 9-10.5. Alcohol or propylene glycol may be added to enhance the stability of the injectable product.

**Storage/Stability/Compatibility** - The injectable product should be stored at room temperature; the suppositories should be kept refrigerated. The aqueous solution is not very stable and should not be used if it contains a precipitate. Because precipitates may occur, pentobarbital sodium should not be added to acidic solutions.

The following solutions and drugs have been reported to be **compatible** with pentobarbital sodium: dextrose IV solutions, Ringer's injection, lactated Ringer's injection, Saline IV solutions, dextrose-saline combinations, dextrose-Ringer's combinations, dextrose-Ringer's lactate combinations, amikacin sulfate, aminophylline, atropine sulfate(for at least 15 minutes, not 24 hours), calcium chloride, cephapirin sodium,

chloramphenicol sodium succinate, hyaluronidase, hydromorphone HCl, lidocaine HCl, neostigmine methylsulfate, scopolamine HBr, sodium bicarbonate, sodium iodide, thiopental sodium, and verapamil HCl.

The following drugs have been reported to be **incompatible** with pentobarbital sodium: benzquinamide HCl, butorphanol tartrate, chlorpromazine HCl, cimetidine HCl, chlorpheniramine maleate, codeine phosphate, diphenhydramine HCl, droperidol, fentanyl citrate, glycopyrrolate, hydrocortisone sodium succinate, hydroxyzine HCl, insulin (regular), meperidine HCl, nalbuphine HCl, norepinephrine bitartrate, oxytetracycline HCl, penicillin G potassium, pentazocine lactate, phenytoin sodium, prochlorperazine edisylate, promazine HCl, promethazine HCl, and streptomycin sulfate. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references for more specific information.

**Pharmacology** -See the monograph: Barbiturates, Pharmacology of.

**Uses/Indications** - Once pentobarbital was the principal agent used for general anesthesia in small animals, but has been largely superceded by the inhalant anesthetic agents. It is still commonly used as an anesthetic in laboratory situations, for rodents and occasionally as a sedative agent in dogs and cats. Pentobarbital is considered to be a drug of choice in dogs and cats for treating intractable seizures secondary to convulsant agents (*e.g.,* strychnine) or as a result of CNS toxins (*e.g.,* tetanus). It should not be used to treat seizures caused by lidocaine intoxication.
Pentobarbital has been used as a sedative and anesthetic agent in horses, cattle, swine, sheep and goats. Often the drug is given after a preanesthetic agent to reduce pentobarbital dosages and side effects.

Pentobarbital is a major active ingredient in several euthanasia solutions. This indication is discussed later in this section in the monograph for pentobarbital euthanasia solutions.

**Pharmacokinetics** - Pentobarbital is absorbed quite rapidly from the gut after oral or rectal administration with peak plasma concentrations occurring between 30-60 minutes after oral dosing in humans. The onset of action usually occurs within 15-60 minutes after oral dosing and within 1 minute after IV administration.

Pentobarbital, like all barbiturates, distributes rapidly to all body tissues with highest concentrations found in the liver and brain. It is 35-45% bound to plasma proteins in humans. Although less lipophilic than the ultra-short acting barbiturates (*e.g.,* thiopental), pentobarbital is highly lipid soluble and patient fat content may alter the distributive qualities of the drug. All barbiturates cross the placenta and enter milk (at concentrations far below those of plasma).

Pentobarbital is metabolized in the liver principally by oxidation. Excretion of the drug is not appreciably enhanced by increasing urine flow or alkalinizing the urine. Ruminants (especially sheep and goats) metabolize pentobarbital at a very rapid rate. The elimination half-life in the goat has been reported to be approximately 0.9 hrs. Conversely, the half-life in dogs is approximately 8 hours and ranges from 15-50 hours in man.

**Contraindications/Precautions** - Use cautiously in patients who are hypovolemic, anemic, have borderline hypoadrenal function, or cardiac or respiratory disease. Large doses are contraindicated in patients with nephritis or severe respiratory dysfunction. Barbiturates are contraindicated in patients with severe liver disease or who have demonstrated previous hypersensitivity reactions to them.

When administering IV, give SLOWLY. It is not recommended to be used for cesarian section because of fetal respiratory depression. Cats tend to particularly sensitive to the respiratory depressant effects of barbiturates; use with caution in this species. Female cats are more susceptible to the effects of pentobarbital than male cats.

To Drug Monograph Index  To Ophthalmic Product Index

**Adverse Effects/Warnings** - Because of the respiratory depressant effects of pentobarbital, respiratory activity must be closely monitored and respiratory assistance must be readily available when using anesthetic dosages. Pentobarbital may cause excitement in dogs during recovery from anesthetic doses. Hypothermia may develop in animals receiving pentobarbital if exposed to temperatures below 27°C (80.6°F). The barbiturates can be very irritating when administered SQ or perivascularly; avoid these types of injections. Do not administer intra-arterially.

**Overdosage** - In dogs, the reported oral $LD_{50}$ is 85 mg/kg and IV $LD_{50}$ is 40 - 60 mg/kg. Fatalities from ingestion of meat from animals euthanized by pentobarbital have been reported in dogs. Treatment of pentobarbital overdose consists of removal of ingested product from the gut if appropriate and offering respiratory and cardiovascular support. Forced alkaline diuresis is of little benefit for this drug. Peritoneal or hemodialysis may be of benefit in severe intoxications.

**Drug Interactions** - Most clinically significant interactions have been documented in humans with phenobarbital, however, these intreactions may also be of significance in animals receiving pentobarbital, especially with chronic therapy.

The following drugs may increase the effect of pentobarbital: **Other CNS depressants (narcotics, phenothiazines, antihistamines, etc), valproic acid, and chloramphenicol.**
Pentobarbital may decrease the effect of the following drugs: **oral anticoagulants, corticosteroids,** beta**-Blockers (propranolol), quinidine, theophylline, metronidazole.**
Pentobarbital with **furosemide** may cause or increase postural hypotension. Barbiturates may effect the metabolism of **phenytoin**, monitoring of blood levels may be indicated.
Fatalities have been reported when dogs suffering from **lidocaine** induced seizures were treated with pentobarbital. Until this interaction is further clarified, it is suggested that lidocaine-induced seizures in dogs be treated initially with diazepam.

**Drug/Lab Interactions** - Barbiturates may cause increased retention of bromosulfopthalein (**BSP**; sulfobromopthalein) and give falsely elevated results. It is recommended that barbiturates not be administered within the 24 hours before BSP retention tests.

**Doses** - Note: In order to avoid possible confusion, doses used for euthanasia are listed separately under the monograph for pentobarbital euthanasia solutions.

**Horses**: Note: Pentobarbital is generally not considered an ideal agent for use in the adult horse due to possible development of excitement and injury when the animal is “knocked down”.

a) 3 - 15 mg/kg IV (Robinson 1987)
b) 15 - 18 mg/kg IV for light anesthesia (Schultz 1986)

**Monitoring Parameters** -

1) Levels of consciousness and/or seizure control
2) Respiratory and cardiac signs
3) Body temperature
4) If using chronically, routine blood counts and liver function tests should be performed.

**Client Information** - This drug is best used in an inpatient setting or with close professional supervision. If dosage forms are dispensed to clients, they must be in instructed to keep away from children and should be dispensed in child-resistant packaging.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Pentobarbital Sodium for Injection 64.8 mg/ml (1 grain/ml) 100 ml vials

To Drug Monograph Index To Ophthalmic Product Index

Generic; (Rx) Approved for use in dogs and cats.

**Human-Approved Products**:

Pentobarbital Sodium for Injection; 50 mg/ml in 1 & 2 ml syringes, 2 ml, 20 ml and 50 ml vials; (Rx)

Pentobarbital Sodium Oral Capsules; 50 mg, 100 mg capsules; (Rx)

Pentobarbital Sodium Rectal Suppositories; 30 mg, 60 mg, 120 mg, 200 mg in 12/pkg; (Rx)

A common trade name is *Nembutal Sodium*® (Abbott). May also be known as pentobarbitone sodium. Pentobarbital is a Class-II controlled substance and detailed records must be maintained with regard to its use and disbursement.

## PENTOXIFYLLINE

**Chemistry/Storage/Stability/Compatibility** - A synthetic xanthine derivative structurally related to caffeine and theophylline, pentoxifylline occurs as a white, odorless, bitter-tasting, crystalline powder. At room temperature, approximately 77 mg are soluble in one ml of water and 63 mg in one ml of alcohol.The commercially available tablets should be stored in well-closed containers, protected from light and at 15-30°C. Pentoxifylline is also known as oxpentifylline or BL-191.

**Pharmacology** - The mechanisms for pentoxifylline's actions are not fully understood. The drug increases erythrocyte flexibility probably by inhibiting erythrocyte phosphodiesterase and decreases blood viscosity by reducing plasma fibrinogen and increasing fibrinolytic activity.

Pentoxifylline is postulated to reduce negative endotoxic effects of cytokine mediators via its phosphodiesterase inhibition.

**Uses/Indications** - In horses, pentoxifylline has been used as adjunctive therapy for endotoxemia and in the treatment of navicular disease. At the time of writing, the drug is still under investigation to document both safety and efficacy for these purposes.

Pentoxifylline has been used in dogs to enhance healing and reduce inflammation caused by ulcerative dermatosis in Shelties and Collies and for other conditions where improved microcirculation may be of benefit.

Pentoxifylline's major indications for humans include symptomatic treatment of peripheral vascular disease (e.g., intermittent claudication, sickle cell disease, Raynaud's, etc.) and cerebrovascular diseases where blood flow may be impaired in the microvasculature.

**Pharmacokinetics** - A pharmacokinetic study done in horses showed high interpatient variability in absorption of oral dosage forms with peak levels occurring 1 - 10 hours after oral dosing. No significant difference in relative bioavailability was noted between whole and crushed extended-release tablets. The drug appears to rapidly eliminated (half life of about one hour after IV dosing). Because of the wide interpatient variability, the authors were unable to make dosing recommendations for clinical use.

In humans, pentoxifylline absorption from the gastrointestinal tract is rapid and almost complete, but a significant first-pass effect occurs. Food affects the rate, but not the extent of absorption. While the distributive characteristics have not been fully described, it is known that the drug enters maternal milk. Pentoxifylline is metabolized both in the liver and in erythrocytes and all identified metabolites appear to be active.

**Contraindications/Precautions/Reproductive Safety** - Pentoxifylline should be considered contraindicated in patients who have been intolerant to the drug or xanthines (e.g., theophylline, caffeine,

theobromine) in the past and those with cerebral hemorrhage or retinal hemorrhage. It should be used cautiously in patients with severe hepatic or renal impairment and those at risk for hemorrhage.

Although safety in pregnant, lactating or breeding animals has not been established, studies in pregnant rats and rabbits demonstrated no overt teratogenicity. As pentoxifylline and its metabolites enter maternal milk, benefits to the mother should be weighed against the risks to offspring.

**Adverse Effects/Warnings** - Most commonly reported adverse effects involve the GI tract (vomiting/inappetence). There are reports of dizziness and headache occurring in a small percentage of humans receiving the drug. Other adverse effects, primarily GI, CNS and cardiovascular related have been reported in people, but are considered to occur rarely. Note: Veterinary experience is limited with pentoxifylline and animal adverse effects may differ.

**Overdosage** - Humans overdosed with pentoxifylline have demonstrated signs of flushing, seizures, hypotension, unconsciousness, agitation, fever, somnolence, GI distress and ECG changes. One patient who ingested 80 mg/kg recovered completely. Overdoses should be treated using the usual methods of appropriate gut emptying and supportive therapies.

**Drug Interactions** - Use of non-steroidal antiinflammatory agents with pentoxifylline in horses is controversial. Some sources state that when used for endotoxemia in horses, pentoxyfilline's beneficial effects are negated by **NSAIDs**, but one study showed superior efficacy when flunixin and pentoxifylline were used together compared with either used alone. **Ciprofloxacin** (other quinolones too?) and **cimetidine** can increase pentoxifylline serum levels. Increased adverse effects of pentoxifylline may result. When pentoxifylline is used with **warfarin** or other anticoagulants, increased risk of bleeding may result. Use together with enhanced monitoring and caution. **Theophylline** blood levels may be increased when used concurrently with pentoxifylline.

**Doses** -
**Horses**:

a) To reduce the cytokine effects in endotoxemia: 8.5 mg/kg PO bid (considered to be experimental therapy) (Edens and Cargile 1997)
b) For treatment of navicular disease: 6 grams per day PO for 6 weeks (Livesay 1996)

**Monitoring Parameters** - Efficacy and adverse effects

**Client Information** - To reduce the GI effects of pentoxifylline, give with food. Clients should understand that veterinary experience with this medication is limited and that the risk versus benefit profile is not well defined.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Pentoxifylline 400 mg extended-release tablets (pink); *Trental*® Tablets (Hoechst Marion Roussel), Generic; (Rx)

## PERPHENAZINE ENANTHATE

To Drug Monograph Index To Ophthalmic Product Index

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

a) For transport of wild African elephants according to shoulder height: 1.0-1.49 m shoulder height (100-150 mg perphenazine); 1.5-1.99 m (150-200 mg); 2.0-2.49m (200-250 mg); 2.5-2.99 m (150-300mg). du Toit,J.G., 2001. **Veterinary Care of African Elephants.** Novartis, Pretoria, Republic of South Africa, 1-59 pp

b) During a translocation of 670 African elephants, 100-300 mg perphenazine was administered to keep the elephants calm after their release into bomas. (Coatsee, C. 1996. **Elephant Translocations.** Pachyderm 22: p.81.

c) Following transport of wild African elephants where confinement is to be continued at the destination: 100 mg IM for small calves < 1.6 m shoulder height and 200 mg IM for larger calves. Perphenazine has only been used on a small number of elephants but a positive effect has been noted. The optimal dose rate has not yet been established. Raath,J.P. 1993. **Chemical capture of the African elephant.** In: The Capture and care manual : capture, care, accommodation and transportation of wild African animals. Pretoria : Wildlife Decision Support Services : South African Veterinary Foundation, Pretoria pp. 484-511

d) Doses of 200-250 mg perphenazine were used to load semi-tame 13-15 year old African elephants; two aggressive young bulls (12-14 years) were calmed by the administration of 200 mg with a duration of effect of two weeks; an aggressive, adult bull in musth was calmed within a few hours by 300 mg of perphenazine. Ebedes,H. 1993. **The use of long-acting tranquilizers in captive wild animals.** In: The Capture and care manual : capture, care, accommodation and transportation of wild African animals. Pretoria : Wildlife Decision Support Services : South African Veterinary Foundation, Pretoria

e) Perphenazine has been given to a limited number of newly captured wild Asian elephants(n=4) weighing 1800-3800 kg at doses of 200-250 mg IM. All elephants exhibited a calming effect lasting about 2 weeks. (Mikota, personal experience, 2003).

## PHENOBARBITAL SODIUM

**Chemistry** - Phenobarbital, a barbiturate, occurs as white, glistening, odorless, small crystals or as a white, crystalline powder with a melting point of 174°-178°C and a $pK_a$ of 7.41. One gram is soluble in approximately 1000 ml of water, and 10 ml of alcohol. Compared to other barbiturates it has a low lipid solubility.

Phenobarbital sodium occurs as bitter-tasting, white, odorless, flaky crystals or crystalline granules or powder. It is very soluble in water, soluble in alcohol, and freely soluble in propylene glycol. The injectable product has a pH of 8.5-10.5.

**Storage/Stability/Compatibility** - Aqueous solutions of phenobarbital are not very stable. Propylene glycol is often used in injectable products to help stabilize the solution. Solutions of phenobarbital sodium should not be added to acidic solutions nor used if they contain a precipitate or are grossly discolored.

To Drug Monograph Index To Ophthalmic Product Index

The following solutions and drugs have been reported to be **compatible** with phenobarbital sodium: Dextrose IV solutions, Ringer's injection, lactated Ringer's injection, Saline IV solutions, dextrose-saline combinations, dextrose-Ringer's combinations, dextrose-Ringer's lactate combinations, amikacin sulfate, aminophylline, atropine sulfate (for at least 15 minutes, not 24 hours), calcium chloride and gluconate, cephapirin sodium, dimenhydrinate, polymyxin B sulfate, sodium bicarbonate, thiopental sodium, and verapamil HCl.

The following drugs have been reported to be **incompatible** with phenobarbital sodium: benzquinamide HCl, cephalothin sodium, chlorpromazine HCl, codeine phosphate, ephedrine sulfate, fentanyl citrate, glycopyrrolate, hydralazine HCl, hydrocortisone sodium succinate, hydroxyzine HCl, insulin (regular), meperidine HCl, morphine sulfate, nalbuphine HCl, norepinephrine bitartrate, oxytetracycline HCl, pentazocine lactate, procaine HCl, prochlorperazine edisylate, promazine HCl, promethazine HCl, and streptomycin sulfate. Compatibility is dependent upon factors such as pH, concentration, temperature, and diluents used and it is suggested to consult specialized references (*e.g.,* Trissel - see bibliography) for more specific information.

**Pharmacology** - See the monograph: Barbiturates, Pharmacology of.

**Uses/Indications** - Because of its favorable pharmacokinetic profile, relative safety and efficacy, low cost, and ability to treat epilepsy at sub-hypnotic doses, phenobarbital is generally considered to be the drug of first choice when treating idiopathic epilepsy in dogs and cats. It is also occasionally used as an oral sedative agent in these species. Because it has a slightly longer onset of action, it is used principally in the treatment of status epilepticus in dogs, cats and horses to prevent the recurrence of seizures after they have been halted with either a benzodiazepine or short-acting barbiturate.

In cattle, the microsomal enzyme stimulating properties of phenobarbital have been suggested for its use in speeding the detoxification of organochlorine (chlorinated hydrocarbon) insecticide poisoning. Additionally, phenobarbital has been used in the treatment and prevention of neonatal hyperbilirubinemia in human infants. It is unknown if hyperbilirubinemia is effectively treated in veterinary patients with phenobarbital.

**Pharmacokinetics** - The pharmacokinetics of phenobarbital have been thoroughly studied in humans and studied in a more limited fashion in dogs and horses. Phenobarbital is slowly absorbed from the GI tract. Bioavailabilities range from 70-90% in humans, approximately 90% in dogs and absorption is practically complete in adult horses. Peak levels occur in 4-8 hours after oral dosing in dogs, and in 8-12 hours in humans.

Phenobarbital is widely distributed throughout the body, but because of its lower lipid solubility it does not distribute as rapidly as most other barbiturates into the CNS. The amount of phenobarbital bound to plasma proteins has been reported to be 40-50%. The reported apparent volumes of distribution are approximately: Horse ≈ 0.8 L/kg; Foals ≈ 0.86 L/kg; Dogs ≈ 0.75 L/kg.

The drug is metabolized in the liver primarily by hydroxylated oxidation to *p*-hydroxyphenobarbital. Sulfate and glucuronide conjugates are also formed. The elimination half-lives reported in humans range from 2-6 days; in dogs from 37-75 hours with an average of approximately 2 days. Elimination half lives in horses are considerably shorter with values reported of approximately 13 hours in foals and 18 hours in adult horses. Phenobarbital will induce hepatic microsomal enzymes and it can be expected that elimination half-lives will decrease with time. Approximately 25% of a dose is excreted unchanged by the kidney. By alkalinizing the urine and/or substantially increasing urine flow, excretion rates can be increased. Anuric or oliguric patients may accumulate unmetabolized drug and dosage adjustments may need to be made in these patients.

**Contraindications/Precautions** - Use cautiously in patients who are hypovolemic, anemic, have borderline hypoadrenal function, or cardiac or respiratory disease. Large doses are contraindicated in patients with

nephritis or severe respiratory dysfunction. Barbiturates are contraindicated in patients with severe liver disease or who have demonstrated previous hypersensitivity reactions to them.

When administering IV, give slowly (not more than 60 mg/minute). Too rapid IV administration may cause respiratory depression. Commercially available injectable preparations (excluding the sterile powder) must not be administered subcutaneously or perivascularly as significant tissue irritation and possible necrosis may result. Applications of moist heat and local infiltration of 0.5% procaine HCl solution have been recommended to treat these reactions.

**Adverse Effects/Warnings** - Dogs may exhibit increased symptoms of anxiety and agitation when initiating therapy. These effects may be transitory in nature and often will resolve with small dosage increases. Occasionally dogs will exhibit profound depression at lower dosage ranges (and plasma levels). Polydipsia, polyuria, and polyphagia are also quite commonly displayed at moderate to high serum levels; these are best controlled by limiting intake of both food and water. Sedation and/or ataxia often become significant concerns as serum levels reach the higher ends of the therapeutic range. Increases in liver enzymes and anemias are more rare, but these potentially serious adverse effects have been reported in dogs. Cats may display a similar adverse reaction picture. Although there is much less information regarding its use in horses (and in particular foals), it would be generally expected that adverse effects would mirror those seen in other species.

**Overdosage** - Treatment of phenobarbital overdose consists of removal of ingested product from the gut if appropriate and offering respiratory and cardiovascular support. Activated charcoal has been demonstrated to be of considerable benefit in enhancing the clearance of phenobarbital, even when the drug was administered parenterally. Charcoal acts as a “sink” for the drug to diffuse from the vasculature back into the gut. Forced alkaline diuresis can also be of substantial benefit in augmenting the elimination of phenobarbital in patients with normal renal function. Peritoneal dialysis or hemodialysis may be helpful in severe intoxications or in anuric patients.

**Drug Interactions** - The following drugs may increase the effect of phenobarbital: **Other CNS depressants (narcotics, phenothiazines, antihistamines, etc), valproic acid, and chloramphenicol.** Phenobarbital may decrease the effect of the following drugs: **oral anticoagulants, chloramphenicol, corticosteroids, doxycycline,** beta**-Blockers (propranolol), quinidine, theophylline, metronidazole.** Pentobarbital with **furosemide** may cause or increase postural hypotension. Barbiturates may effect the metabolism of **phenytoin**; monitoring of blood levels may be indicated. **Rifampin** may induce hepatic microsomal enzymes and reduce the half-life and effect of phenobarbital. Phenobarbital may decrease the absorption of **griseofulvin** if given concurrently.

**Drug/Lab Interactions** - Barbiturates may cause increased retention of bromosulfopthalein (BSP; sulfobromopthalein) and give falsely elevated results. It is recommended that barbiturates not be administered within the 24 hours before **BSP retention tests**; or if they must, (*e.g.,* for seizure control) the results be interpreted accordingly.

**Doses -**
**Horses**:

a) 1 - 10 mg/kg IV (Robinson 1987)
b) Loading dose of 12 mg/kg IV over 20 minutes, then 6.65 mg/kg IV over 20 minutes every 12 hours (Duran et al. 1987)
c) 11 mg/kg PO q24 hours (Ravis et al. 1987)
d) Foals; for seizures: 20 mg/kg diluted with normal saline to a volume of 30-35 ml infused over 25-30 minutes IV, then 9 mg/kg diluted and infused as above q8h. Recommend monitoring serum levels if possible. (Spehar et al. 1984)

To Drug Monograph Index To Ophthalmic Product Index

**Monitoring Parameters** -

1) Anticonvulsant (or sedative) efficacy
2) Adverse effects (CNS related, PU/PD, weight gain)
3) Serum phenobarbital levels if lack of efficacy or adverse reactions noted. Although there is some disagreement among clinicians, therapeutic serum levels in dogs are thought to mirror those in people (15 - 40 micrograms/ml).
4) If used chronically, routine CBC's and liver enzymes at least every 6 months.

**Client Information** - Compliance with therapy must be stressed to clients for successful epilepsy treatment. Encourage client to give doses at the same time each day. Keep medications out of reach of children and stored in child-resistant packaging. Veterinarian should be contacted if animal develops significant adverse reactions (including symptoms of anemia and/or liver disease) or seizure control is unacceptable.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Phenobarbital Tablets 15 mg, 16 mg, 16.2 mg, 30 mg, 60 mg, 100 mg; Capsules 16 mg

Phenobarbital Elixir 15 mg/5ml in pt and UD 5, 10 & 20 ml, 20 mg/5ml in pt, gal, UD 5 and 7.5 ml

Phenobarbital Sodium for Injection 30 mg/ml, 60 mg/ml, 65 mg/ml, 130 mg/ml; in 1 ml amps, Tubex and vials

Also known as phenyethylmalonylurea or phenobarbitone. Other trade names may include: *Luminal*® (Winthrop-Breon), and *Barbita*® (Vortech). Phenobarbital is a **Class-IV controlled substance** and is available by prescription (Rx) only.

## PHENOXYBENZAMINE HCL

**Chemistry** - An alpha-adrenergic blocking agent, phenoxybenzamine HCl occurs as an odorless, white crystalline powder with a melting range of 136°-141° and a $pK_a$ of 4.4. Approximately 40 mg is soluble in 1 ml of water and 167 mg is soluble in 1 ml of alcohol.

**Storage/Stability/Compatibility** - Phenoxybenzamine capsules should be stored at room temperature in well-closed containers.

**Pharmacology** - Alpha-adrenergic response to circulating epinephrine or norepinepinephrine is noncompetitively blocked by phenoxybenzamine. The effects of phenoxybenzamine have been described as a "chemical sympathectomy". No effects on beta-adrenergic receptors or on the parasympathetic nervous system occur.

Phenoxybenzamine causes cutaneous blood flow to increase, but little effects are noted on skeletal or cerebral blood flow. Phenoxybenzamine can also block pupillary dilation, lid retraction, and nictitating membrane contraction. Both standing and supine blood pressures are decreased in humans.

**Uses/Indications -** Phenoxybenzamine is used in small animals primarily for its effect in reducing internal urethral sphincter tone in dogs and cats when urethral sphincter hypertonus is present. It can also be used to treat the hypertension associated with pheochromocytoma prior to surgery or as adjunctive therapy in endotoxicosis.

To Drug Monograph Index To Ophthalmic Product Index

In horses, phenoxybenzamine has been used for preventing or treating laminitis in its early stages and to treat secretory diarrheas.

**Pharmacokinetics** - No information was located on the pharmacokinetics of this agent in veterinary species. In humans, phenoxybenzamine is variably absorbed from the GI, with a bioavailability of 20-30%. Onset of action of the drug is slow (several hours) and increases over several days after regular dosing. Effects persist for 3-4 days after discontinuation of the drug.

Phenoxybenzamine is highly lipid soluble and may accumulate in body fat. It is unknown if phenoxybenzamine crosses the placenta or is excreted into milk. The serum half-life of phenoxybenzamine is approximately 24 hours in humans. It is metabolized (dealkylated) and excreted in both the urine and bile.

**Contraindications/Precautions** - Phenoxybenzamine is contraindicated in horses with symptoms of colic and in patients when symptoms of hypotension would be undesirable (*e.g.,* shock, unless fluid replacement is adequate). One author (Labato 1988) lists glaucoma and diabetes mellitus as contraindications for the use of phenoxybenzamine in dogs.

Phenoxybenzamine should be used with caution in patients with CHF or other heart disease as drug-induced tachycardia can occur. It should be used cautiously in patients with renal damage or cerebral/coronary arteriosclerosis.

**Adverse Effects/Warnings** - Adverse effects associated with alpha-adrenergic blockade include: hypotension, hypertension, miosis, increased intraocular pressure, tachycardia, inhibition of ejaculation and nasal congestion. Additionally, it can cause weakness/dizziness and GI effects (*e.g.,* nausea, vomiting). Constipation may occur in horses.

**Overdosage** - Overdosage of phenoxybenzamine may yield signs of postural hypotension (dizziness, syncope), tachycardia, vomiting, lethargy or shock.

Treatment should consist of emptying the gut if the ingestion was recent and there are no contraindications to those procedures. Hypotension can be treated with fluid support. Epinephrine is contraindicated (see Drug Interactions) and most vasopressor drugs are ineffective in reversing the effects of alpha-blockade. Intravenous norepinephrine (levarterenol) may be beneficial, however, if symptoms are severe.

**Drug Interactions** - Phenoxybenzamine will antagonize the effects of alpha-adrenergic sympathomimetic agents (*e.g.,* **phenylephrine**). If used with drugs that have both alpha□ and beta□adrenergic effects (*e.g.,* **epinephrine**), increased hypotension, vasodilatation or tachycardia may result.

**Doses** - **Note:**Because the only dosage form available is a 10 mg capsule, doses should be rounded to the nearest 2.5 mg dose when possible.
**Horses**:

a) 0.66 mg/kg in 500 ml saline IV (Robinson 1987)
b) 1.2 mg/kg PO, followed in 12 hours by 0.6 mg/kg PO for 2 doses (Schultz 1986)
c) 200 - 600 mg q12h for treatment of profuse, watery diarrhea. (Clark 1988)

**Monitoring Parameters** - 1) Clinical efficacy (adequate urination, etc.) 2) Blood pressure, if necessary/possible

**Client Information** - Contact veterinarian if animal has continuing problems with weakness, appears dizzy or collapses after standing, or has persistent vomiting. GI upset may be reduced if the drug is given with meals.

To Drug Monograph Index To Ophthalmic Product Index

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Phenoxybenzamine HCl 10 mg Capsules; *Dibenzyline*® (SKF); (Rx)

## PHENYLBUTAZONE * PK (ADVERSE EFFECT REPORTED)

**Chemistry** - A synthetic pyrazolone derivative related chemically to aminopyrine, phenylbutazone occurs as a white to off-white, odorless crystalline powder that has a $pK_a$ of 4.5. It is very slightly soluble in water and 1 gram will dissolve in 28 ml of alcohol. It is tasteless at first, but has a slightly bitter after-taste.

**Storage/Stability/Compatibility** - Oral products should be stored in tight, child-resistant containers if possible. The injectable product should be stored in a cool place (46 - 56° F) or kept refrigerated.

**Pharmacology** - Phenylbutazone has analgesic, anti-inflammatory, antipyrexic, and mild uricosuric properties. The proposed mechanism of action is by the inhibition of cyclooxygenase, thereby reducing prostaglandin synthesis. Other pharmacologic actions phenylbutazone may induce include reduced renal blood flow and decreased glomerular filtration rate, decreased platelet aggregation, and gastric mucosal damage.

**Pharmacokinetics** - Following oral administration, phenylbutazone is absorbed from both the stomach and small intestine. The drug is distributed throughout the body with highest levels attained in the liver, heart, lungs, kidneys, and blood. Plasma protein binding in horses exceeds 99%. Both phenylbutazone and oxyphenbutazone cross the placenta and are excreted into milk.

The serum half-life in the horse ranges from 3.5-6 hours, and like aspirin is dose-dependent. Therapeutic efficacy however, may last for more than 24 hours however, probably due to the irreversible binding of phenylbutazone to cyclooxygenase. In horses and other species, phenylbutazone is nearly completely metabolized, primarily to oxphenbutazone (active) and gamma-hydroxyphenylbutazone. Oxyphenbutazone has been detected in horse urine for up to 48 hours after a single dose. Phenylbutazone is more rapidly excreted into alkaline than into acidic urine .

Other serum half-lives reported for animals are: Cattle ≈ 40 - 55 hrs; Dogs ≈ 2.5 - 6 hrs; Swine ≈ 2 - 6 hrs.; Rabbits ≈ 3 hrs..

**Uses/Indications** - One manufacturer lists the following as the indications for phenylbutazone: “For the relief of inflammatory conditions associated with the musculoskeletal system in dogs and horses.” (Package Insert; *Butazolidin*® — Coopers). It has been used primarily for the treatment of lameness in horses and occasionally as an analgesic/anti-inflammatory, antipyrexic in dogs, cattle, and swine.

**Contraindications/Precautions** - Phenylbutazone is contraindicated in patients with a history of, or preexisting hematologic or bone marrow abnormalities, preexisting GI ulcers, and in food producing animals or lactating dairy cattle. Cautious use in both foals and ponies is recommended because of increased incidences of hypoproteinemia and GI ulceration. Foals with a heavy parasite burden or that are undernourished may be more susceptible to development of adverse effects.

Phenylbutazone may cause decreased renal blood flow and sodium and water retention, and should be used cautiously in animals with preexisting renal disease or CHF.

To Drug Monograph Index  To Ophthalmic Product Index

Because phenylbutazone may mask symptoms of lameness in horses for several days following therapy, it can be used by unethical individuals to disguise lameness for “soundness” exams. States may have different standards regarding the use of phenylbutazone in track animals. Complete elimination of phenylbutazone in horses may take 2 months and it can be detected in the urine for at least 7 days following administration.

Although phenylbutazone has shown no direct teratogenic effects, rodent studies have demonstrated reduced litter sizes, increased neonatal mortality, and increased stillbirth rates. Phenylbutazone should therefore be used in pregnancy only when the potential benefits of therapy outweigh the risks associated with it.

Phenylbutazone is contraindicated in patients demonstrating previous hypersensitivity reactions to it, and should be used very cautiously in patients that have a history of allergies to other drugs.

**Adverse Effects/Warnings** - The primary concerns with phenylbutazone therapy in humans include its bone marrow effects (agranulocytosis, aplastic anemia), renal and cardiovascular effects (fluid retention to acute renal failure), and GI effects (dyspepsia to perforated ulcers). Other serious concerns with phenylbutazone include, hypersensitivity reactions, neurologic, dermatologic, and hepatic toxicities.

While phenylbutazone is apparently a safer drug to use in horses and dogs than in people, serious adverse reactions can still occur. Toxic effects that have been reported in horses include oral and GI erosions and ulcers, hypoalbuminemia, diarrhea, anorexia, and renal effects (azotemia, renal papillary necrosis). Unlike humans, it does not appear that phenylbutazone causes much sodium and water retention in horses at usual doses, but edema has been reported. In dogs however, phenylbutazone may cause sodium and water retention, and diminished renal blood flow. Phenylbutazone-induced blood dyscrasias have also been reported in dogs.

Do not administer injectable preparation IM or SQ, as it is very irritating (swelling, to necrosis and sloughing). Intracarotid injections may cause CNS stimulation and seizures.

Therapy should be halted at first signs of any toxic reactions (*e.g.,* anorexia, oral lesions, depression, reduced plasma proteins, increased serum creatinine or BUN, leukopenia, or anemias). The use of sucralfate or the $H_2$ blockers (cimetidine, ranitidine) have been suggested for use in treating the GI effects. Misoprostol, a prostaglandin E analog, may also be useful in reducing the gastrointestinal effects of phenylbutazone.

**Overdosage** - Manifestations (human) of acute overdosage with phenylbutazone include, a prompt respiratory or metabolic acidosis with compensatory hyperventilation, seizures, coma, and acute hypotensive crisis. In an acute overdose, symptoms of renal failure (oliguric, with proteinuria and hematuria), liver injury (hepatomegaly and jaundice), bone marrow depression, and ulceration (and perforation) of the GI tract may develop. Other symptoms reported in humans include: nausea, vomiting, abdominal pain, diaphoresis, neurologic and psychiatric symptoms, edema, hypertension, respiratory depression, and cyanosis.

Standard overdose procedures should be followed (empty gut following oral ingestion, etc.). Supportive treatment should be instituted as necessary and intravenous diazepam used to help control seizures. Monitor fluid therapy carefully, as phenylbutazone may cause fluid retention.

**Drug Interactions** - Both phenylbutazone and the active metabolite oxyphenbutazone are highly bound to plasma proteins and may displace other highly bound drugs. This mechanism may affect serum levels and duration of actions of **phentoin, valproic acid, oral anticoagulants**, other **antiinflammatory agents,**

To Drug Monograph Index To Ophthalmic Product Index

**sulfonamides**, and the **sulfonylurea antidiabetic agents**. Phenylbutazone and oxyphenbutazone can induce hepatic microsomal enzymes and increase the metabolism of drugs affected by this system (*e.g.,* **digitoxin & phenytoin**). Conversely, other microsomal enzyme inducers (*e.g.,* **barbiturates, promethazine, rifampin, corticosteroids, or chlorpheniramine, diphenhydramine**) may decrease the plasma half-life of phenylbutazone. Phenylbutazone may increase the plasma half-life of **penicillin G or lithium**. Phenylbutazone administered concurrently with **hepatotoxic drugs** may increase the chances of hepatotoxicity developing. Phenylbutazone may antagonize the increased renal blood flow effects caused by **furosemide**. Concurrent use with **other NSAIDs** may increase the potential for adverse reactions developing, however many clinicians routinely use phenylbutazone concomitantly with flunixin in horses.

**Laboratory Test Interference** - Phenylbutazone and oxyphenbutazone may interfere with **thyroid function tests** by competing with thyroxine at protein binding sites or by inhibiting thyroid iodine uptake.

**Doses -**
**Horses**:

a) 4.4 - 8.8 mg/kg q24hrs PO or 3-6 mg/kg q12h IV (Do not exceed 8.8 mg/kg/day (Jenkins 1987)
b) 1 - 2 grams IV per 454 kg (1000 lb.) horse. Injection should be made slowly and with care. Limit IV administration to no more than 5 successive days of therapy. Follow with oral forms if necessary; or 2 - 4 grams PO per 454kg (1000 lb.) horse. Do not exceed 4 grams/day. Use high end of dosage range initially, then titrate to lowest effective dose. (Package Insert; *Butazolidin*® - Coopers)
c) 4.4 mg/kg PO twice on the first day, then 2.2 mg/kg PO *bid* for 4 days, then 2.2 mg/kg PO once daily or every other day. (Taylor et al. 1983)

**Elephants:**

a) Anecdotal doses of 1-2 mg/kg every 24 hours (route of administration not specified) have been reported. This is based on a survey of 20 zoo veterinarians in the U.S. The author cautions that phenylbutazone has potential for adverse effects and that the treatment interval reported by survey participants is much shorter than that predicted by metabolic scaling (2.5 mg every 40 hours).

a) Mortenson,J. and Sierra S. 1998. **Determining dosages for antibiotic and anti-inflammatory agents in elephants.** Proceedings of the First North American Conference on Elephant Foot care and Pathology. Pages: 50-55 **Abstract:** Clinical application of drug use in elephants for safe, reliable, and effective results necessitates the establishment of a treatment response curve or blood concentration profile for each drug and species (African vs. Asian). Because of the difficulty in obtaining accurate pharmacokinetic information, it is more common to select a drug dosage and frequency interval used in other species, specifically the cow and the horse. Where treatment monitoring with serum concentrations of the drug are difficult to obtain, extrapolation of treatment regimens between species of extraordinary size difference may be done by metabolic scaling to establish drug dosage rates and frequency intervals. The principle of metabolic scaling of pharmacokinetic parameters is based on the well established scaling of physiological processes across animals of various sizes. The goals of this paper are to cover what antibiotics are currently used now with Asian and African elephants by surveying North American zoos, reviewing standard equine doses, discussing metabolic scaling attempts, and reviewing pharmacokinetic studies done. Based on the survey, zoo veterinarians generally are not utilizing metabolic scaling formulas to determine antibiotic and anti-inflammatory drug dosages for elephants. It appears that several drugs are being dosed too frequently (amikacin, amoxicillin), and not frequent enough (trimethoprim-sulfamethoxazole) based on pharmacokinetic study results. Metabolic scaling dosages and treatment intervals do not correspond well with antibiotic pharmacokinetic studies done in both African and Asian elephants.

To Drug Monograph Index To Ophthalmic Product Index

a) Mortenson,J. 1998. **Determining dosages for anti-inflammatory agents in elephants.** Proceedings AAZV and AAWV Joint Conference. Pages: 477-479

a) Mortenson,J., 2001. **Determining dosages for antibiotics and anti-inflammatory agents.** In: Csuti,B., Sargent,E.L., and Bechert,U.S. (Editors), The Elephant's Foot. Iowa State University Press, Ames, Iowa, USA pp. 141-144

b) Two cases of segmental gangrene and sloughing of elephants' ears after intravenous injection of phenylbutazone have been reported (dose not specified). The author recommends that phenylbutazone be administered orally whenever possible. Miller,R.M. 1977. **Segmental gangrene and sloughing of elephants' ears after intravenous injection of phenylbutazone.** Veterinary Medicine Small Animal Clinician 72 (4): 633-637

**c) Pharmacokinetics of orally administered phenylbutazone in African and Asian elephants (Loxodonta africana and Elephas maximus).** U. Bechert, J. M. Christensen, C. Nguyen, R. Neelkant and E. Bendas. J. Zoo. Wildl. Med 2008 Vol. 39 Issue 2 Pages 188-200. http://www.ncbi.nlm.nih.gov/pubmed/18634209.

The pharmacokinetic parameters of phenylbutazone were determined in 18 elephants (Loxodonta africana and Elephas maximus) after single-dose oral administration of 2, 3, and 4 mg/kg phenylbutazone, as well as multiple-dose administrations with a 4-wk washout period between trials. After administration of 2 mg/kg phenylbutazone, mean serum concentrations peaked in approximately 7.5 hr at 4.3 +/- 2.02 microg/ml and 9.7 hr at 7.1 +/- 2.36 microg/ml for African and Asian elephants, respectively, while 3 mg/kg dosages resulted in peak serum concentrations of 7.2 +/- 4.06 microg/ml in 8.4 hr and 12.1 +/- 3.13 microg/ml in 14 hr. The harmonic mean half-life was long, ranging between 13 and 15 hr and 39 and 45 hr for African and Asian elephants, respectively. There was evidence of enterohepatic cycling of phenylbutazone in Asian elephants. Significant differences ($P < 0.0001$) in pharmacokinetic values occurred between African and Asian elephants for clearance (27.9 and 7.6 ml/hr/kg, respectively), terminal half-life (15.0 and 38.7 hr, respectively), and mean residence time (22.5 and 55.5 hr, respectively) using 2-mg/kg dosages as an example. This suggests that different treatment regimens for Asian and African elephants should be used. There were no apparent gender differences in these parameters for either elephant species.

**Monitoring Parameters** - 1) Analgesic/anti-inflammatory/antipyrexic effect 2) Regular complete blood counts with chronic therapy (especially in dogs). The manufacturer recommends weekly CBC's early in therapy, and biweekly with chronic therapy 3) Urinalysis &/or renal function parameters (serum creatinine/BUN) with chronic therapy 4) Plasma protein determinations, especially in ponies, foals, and debilitated animals.

**Client Information/FDA Approval Status** - Do not administer injectable preparation IM or SQ. Approved for use in dogs and horses not intended for food. While phenylbutazone is not approved for use in cattle, it is used. A general guideline for meat withdrawal times are: one dose=30 days, 2 doses=35 days, and 3 doses=40 days. Phenylbutazone is a veterinary prescription drug.

**Dosage Forms/Preparations (Veterinary)** -

Phenylbutazone Tablets 100 mg, 400 mg, 1 gram tablets; 2 gram boluses, 4 gram boluses *; Butazolidin*® (Schering); also available generically

Phenylbutazone Paste Oral syringes containing 6 grams or 12 grams/syringe; *Butazolidin*® *Paste* (Schering); *Phenylzone*® *Paste* (Luitpold)

Phenylbutazone Oral Gel: Each 30 grams of gel contains 4 grams phenylbutazone, 30 grams (of gel) per syringe; *Butatron*® (Rhone Merieux)

To Drug Monograph Index To Ophthalmic Product Index

Phenylbutazone Micro-encapsulated powder; *Equipalazone*® (Steri-Vet); 1 gm packets, 60's

Phenylbutazone Injection 200 mg/ml; 100 ml vials; *Butazolidin*® (Schering); generic

## PHENYLEPHRINE HCL

**Chemistry** - An alpha-adrenergic sympathomimetic amine, phenylephrine HCl occurs as bitter-tasting, odorless, white to nearly white crystals with a melting point of 145 - 146°C. It is freely soluble in water and alcohol. The pH of the commercially available injection is 3.0 - 6.5.

**Storage/Stability/Compatibility** - The injectable product should be stored protected from light. Do not use solutions if they are brown or contain a precipitate. Oxidation of the drug can occur without a color change. To protect against oxidation, the air in commercially available ampules for injection is replaced with nitrogen and a sulfite added.

Phenylephrine is reported to be **compatible** with all commonly used IV solutions and the following drugs: chloramphenicol sodium succinate, dobutamine HCl, lidocaine HCl, potassium chloride, and sodium bicarbonate. While stated to be incompatible with alkalies, it is stable with sodium bicarbonate solutions. Phenylephrine is reported to be **incompatible** with ferric salts, oxidizing agents, and metals.

**Pharmacology** - Phenylephrine has predominantly post-synaptic alpha-adrenergic effects at therapeutic doses. At usual doses it has negligible beta effects, but beta effects can occur at high doses.

Phenylephrine's primary effects, when given intravenously, include peripheral vasoconstriction with resultant increase in diastolic and systolic blood pressures, small decreases in cardiac output and an increase in circulation time. A reflex bradycardia (blocked by atropine) can occur. Most vascular beds are constricted (renal splanchnic, pulmonary, cutaneous), but coronary blood flow is increased. Its alpha effects can cause contraction of the pregnant uterus and constriction of uterine blood vessels.

**Uses/Indications** - Phenylephrine has been used to treat hypotension and shock (after adequate volume replacement), but many clinicians prefer to use an agent that also has cardiostimulatory properties. It may be of benefit, however, when cardiostimulation would be undesirable, such as during general anesthesia (halothane) or if the patient is also receiving other agents that sensitize the myocardium. Phenylephrine is recommended to be used to treat hypotension secondary to drug overdoses or idiosyncratic hypotensive reactions to drugs such as phenothiazines, adrenergic blocking agents, and ganglionic blockers. Its use to treat hypotension resulting from barbiturate or other CNS depressant agents is controversial. Phenylephrine has been used to increase blood pressure to terminate attacks of paroxysmal supraventricular tachycardia, particularly when the patient is also hypotensive. Phenylephrine has been used to treat both hypotension and to prolong the effects of spinal anesthesia.

Ophthalmic uses of phenylephrine include use for some diagnostic eye examinations, to reduce posterior synchiae formation and relieve pain associated with complicated uveitis. It has been applied intranasally in an attempt to reduce nasal congestion.

**Pharmacokinetics** - After oral administration, phenylephrine is rapidly metabolized in the GI tract and cardiovascular effects are generally unattainable via this route of administration. Following IV administration, pressor effects begin almost immediately and will persist for up to 20 minutes. The onset of pressor action after IM administration is usually within 10-15 minutes, and will last for approximately one hour.

It is unknown if phenylephrine is excreted into milk. It is metabolized by the liver, and the effects of the drug are also terminated by uptake into tissues.

To Drug Monograph Index  To Ophthalmic Product Index

**Contraindications/Precautions** - Phenylephrine is contraindicated in patients with severe hypertension, ventricular tachycardia or those who are hypersensitive to it. It should be used with extreme caution in geriatric patients, patients with hyperthyroidism, bradycardia, partial heart block or with other heart disease. Phenylephrine is not a replacement for adequate volume therapy in patients with shock.

**Adverse Effects/Warnings** - At usual doses, a reflex bradycardia, CNS effects (excitement, restlessness, headache) and, rarely, arrhythmias are seen. Blood pressure must be monitored to prevent hypertension.

Extravasation injuries with phenylephrine can be very serious (necrosis and sloughing of surrounding tissue). Patient's IV sites should be routinely monitored. Should extravasation occur, infiltrate the site (ischemic areas) with a solution of 5-10 mg phentolamine (Regitine®) in 10-15 ml of normal saline. A syringe with a fine needle should be used to infiltrate the site with many injections.

**Overdosage** - Overdosage of phenylephrine can cause hypertension, seizures, vomiting, paresthesias, ventricular extrasystoles and cerebral hemorrhage. Hypertension, if severe, can be treated by the administration of phentolamine (an alpha blocking agent). Should cardiac arrhythmias require treatment, use a beta-blocking drug such as propranolol.

**Drug Interactions** - Higher dosages of phenylephrine may be required to attain a pressor effect, if **phenothiazines** or an alpha-blocking agent (**phentolamine**) have been used prior to therapy. Phenylephrine may induce cardiac arrhythmias when used with **halothane** anesthesia or in **digitalized** patients. When used concurrently with **oxytocic agents,** pressor effects may be enhanced. **Atropine** will block the reflex bradycardia that phenylephrine causes. **Monoamine oxidase (MAO) inhibitors** should not be used with phenylephrine because of a pronounced pressor effect.

**Doses -**
**Horses**:

a) 5 mg IV (Enos and Keiser 1985)

**Monitoring Parameters** -

1) Cardiac rate/rhythm
2) Blood pressure, and blood gases if possible

**Client Information** - Parenteral phenylephrine should only be used by professionals in a setting where adequate monitoring is possible.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Phenylephrine HCl for Injection 10 mg/ml in ml amps; *Neo-Synephrine*® ((Sanofi Winthrop); generic; (Rx)
Phenylephrine is also available in ophthalmic and intranasal dosage forms and in combination with antihistamines, analgesics, decongestants, etc., for oral administration in humans.

## PHENYTOIN SODIUM

**Chemistry** - A hydantoin-derivative, phenytoin sodium occurs as a white, hygroscopic powder which is freely soluble in water and warm propylene glycol, and soluble in alcohol.

To Drug Monograph Index To Ophthalmic Product Index

Because phenytoin sodium slowly undergoes partial hydrolysis in aqueous solutions to phenytoin (base) with the resultant solution becoming turbid, the commercial injection contains 40% propylene glycol and 10% alcohol. The pH of the injectable solution is approximately 12.

Phenytoin sodium is used in the commercially available capsules (both extended and prompt) and the injectable preparations. Phenytoin (base) is used in the oral tablets and suspensions. Each 100 mg of phenytoin sodium contains 92 mg of the base.

**Storage/Stability/Compatibility** - Store capsules at room temperature (below 86°F) and protect from light and moisture. Store phenytoin sodium injection at room temperature and protect from freezing. If injection is frozen or refrigerated, a precipitate may form which should resolubilize when warmed. A slight yellowish color will not affect either potency or efficacy, but do not use precipitated solutions. Injectable solutions at less than a pH of 11.5 will precipitate. No problems with adsorption to plastic have been detected thus far.

Phenytoin sodium injection is generally incompatible with most IV solutions (upon standing) and drugs. It has been successfully mixed with sodium bicarbonate and verapamil HCl.

Because an infusion of phenytoin sodium is sometimes desirable, several studies have been performed to determine whether such a procedure can be safely done. The general conclusions and recommendations of these studies are: 1) use either normal saline or lactated Ringer's; 2) a concentration of 1 mg/ml phenytoin be used; 3) start infusion immediately and complete in a relatively short time; 4) use a 0.22 µm in-line IV filter; 5) watch the admixture carefully.

**Pharmacology** - The anticonvulsant actions of phenytoin are thought to be caused by the promotion of sodium efflux from neurons, thereby inhibiting the spread of seizure activity in the motor cortex. It is believed that excessive stimulation or environmental changes can alter the sodium gradient which may lower the threshold for seizure spread. Hydantoins tend to stabilize this threshold and limit seizure propagation from epileptogenic foci.

The cardiac electrophysiologic effects of phenytoin are similar (not identical) to that of lidocaine (Group 1B). It depresses phase O slightly and can shorten the action potential. Its principle cardiac use is in the treatment of digitalis-induced ventricular arrhythmias.
Phenytoin can inhibit insulin and vasopressin (ADH) secretion.

**Uses/Indications** - Because of its undesirable pharmacokinetic profiles in dogs and cats, the use of phenytoin as an anticonvulsant for long term treatment of epilepsy has diminished over the years. It remains however, as an alternative or adjunctive therapy in dogs who have not responded to, or have developed severe adverse reactions from either phenobarbital or primidone. Prerequisites for successful therapy include: a motivated client who will be compliant with multiple daily dosing and who is willing to assume the financial burden of high dose phenytoin therapy and therapeutic drug monitoring expenses.

Although not commonly used, phenytoin has been employed as an oral or IV antiarrhythmic agent in both dogs and cats. It has been described as the drug of choice for digitalis-induced ventricular arrhythmias in dogs.

It has been suggested that phenytoin be used as adjunctive treatment of hypoglycemia secondary to hyperinsulinism, but apparently little clinical benefit has resulted from this therapy.

**Pharmacokinetics** - After oral administration, phenytoin is nearly completely absorbed in humans, but in dogs, bioavailabilities may only be about 40%. Phenytoin is well distributed throughout the body and is about 78% bound to plasma proteins in dogs (vs. 95% in humans). Protein binding may be reduced in uremic patients. Small amounts of phenytoin may be excreted into the milk and it readily crosses the placenta.

To Drug Monograph Index  To Ophthalmic Product Index

The drug is metabolized in the liver and with much of the drug conjugated to a glucuronide form and then excreted by the kidneys. Phenytoin will induce hepatic microsomal enzymes which may enhance the metabolism of itself and other drugs. The serum half-life (elimination) differences between various species are striking. Phenytoin has reported half-lives of 2-8 hours in dogs, 8 hours in horses, 15-24 hours in humans, and 42-108 hours in cats. Because of the pronounced induction of hepatic enzymes in dogs, phenytoin metabolism is increased with shorter half-lives within 7-9 days after starting treatment. Puppies have a smaller volumes of distribution and shorter elimination half-lives (1.6 hours) than adult dogs.

**Contraindications/Precautions** - Some data suggest that additive hepatotoxicity may result if phenytoin is used with either primidone or phenobarbital. Weigh the potential risks versus the benefits before adding phenytoin to either of these drugs in dogs.

Phenytoin is contraindicated in patients known to be hypersensitive to it or other hydantoins. Intravenous use of the drug is contraindicated in patients with 2nd or 3rd degree heart block, sinoatrial block, Adams-Stokes syndrome, or sinus bradycardia. Safe use of this drug has not been established during pregnancy; weigh risks versus benefits.

**Adverse Effects/Warnings** - Adverse effects in dogs associated with high serum levels include anorexia and vomiting, ataxia, and sedation. Liver function tests should be monitored in patients on chronic therapy as hepatotoxicity (elevated serum ALT, decreased serum albumin, hepatocellular hypertrophy and necrosis, hepatic lipidosis, and extramedullary hematopoiesis) has been reported. Gingival hyperplasia has been reported in dogs receiving chronic therapy.
Oral absorption may be enhanced and GI upset decreased if given with food.

Cats exhibit ataxia, sedation, and anorexia secondary to accumulation of phenytoin and high serum levels. Cats have also been reported to develop a dermal atrophy syndrome secondary to phenytoin.

**Overdosage** - Symptoms of overdosage may include sedation, anorexia, and ataxia at lower levels, and coma, hypotension and respiratory depression at higher levels. Treatment of overdose symptoms in dogs is dependent on the severity of the symptoms since dogs so rapidly clear the drug. Severe intoxications should be handled supportively.

**Drug Interactions** - A case report of **chloramphenicol** increasing the serum half-life of phenytoin from 3 to 15 hours in a dogs has been reported. **Note**: the following interactions are from the human literature, because of the significant differences in pharmacokinetics in dogs and cats their veterinary significance will be variable. This list includes only agents used commonly in small animal medicine, many more agents have been implicated in the human literature: The following agents may increase the effects of phenytoin: **allopurinol, cimetidine, chloramphenicol, diazepam, ethanol, isoniazid, phenylbutazone, sulfonamides, trimethoprim, valproic acid, salicylates, and chlorpheniramine**. The following agents may decrease the pharmacologic activity of phenytoin: **barbiturates, diazoxide, folic acid, theophylline, antacids, antineoplastics, calcium (dietary and gluconate), enteral feedings, nitrofurantoin, and pyridoxine**. Phenytoin may decrease the pharmacologic activity of the following agents: **corticosteroids, disopyramide, doxycycline, estrogens, quinidine, dopamine, and furosemide**. Phenytoin may decrease the analgesic properties **meperidine**, but enhance its toxic effects. The toxicity of **lithium** may be enhanced. The pharmacologic effects of **primidone** may be altered. Some data suggest that additive hepatotoxicity may result if phenytoin is used with either **primidone** or **phenobarbital**. Weigh the potential risks versus the benefits before adding phenytoin to either of these drugs in dogs. **Pyridoxine (Vitamin $B_6$)** may reduce the serum levels of phenytoin.

**Doses -**
**Horses**:

To Drug Monograph Index To Ophthalmic Product Index

For seizures:

a) 2.83 - 16.43 mg/kg PO q8h to obtain serum levels from 5 - 10 micrograms/ml. Suggest monitoring serum levels to adjust dosage. (Kowalczyk and Beech 1983)

**Monitoring Parameters** -

1) Level of seizure control; sedation/ataxia
2) Body weight (anorexia)
3) Liver enzymes (if chronic therapy) & serum albumin
4) Serum drug levels if signs of toxicity or lack of seizure control

**Client Information** - Notify veterinarian if dog becomes anorexic, lethargic, ataxic, or if seizures are not adequately controlled. The importance of regular dosing is imperative for successful therapy.

**Dosage Forms/Preparations** -

**Veterinary-Approved Products**:

*Extended Phenytoin Sodium Capsules, USP*® (Fort Dodge) (Rx) 100 mg tablets. Approved for use in dogs.Note: This product may no longer be marketed.

**Human-Approved Products:**

Phenytoin Sodium, Extended Oral Capsules 30 mg, 100 mg; *Dilantin*® *Kapseals*® (Parke-Davis); generic, (Rx)

Phenytoin Oral Suspension 25 mg/ml in 8 oz. bottles; *Dilantin-125*® (Parke-Davis) (Rx)

Phenytoin Oral Tablets 50 mg; *Dilantin*® *Infa-Tabs*® (Parke-Davis) (Rx)

Phenytoin Sodium for Injection 50 mg/ml (46 mg/ml phenytoin) in 2 ml and 5 ml amps, syringes and vials; 150 mg (100 mg phenytoin sodium) in 2 ml vials; 750 mg (500 mg phenytoin sodium) in 10 ml vials (Rx)

Phenytoin may also be called diphenylhydantoin or DPH.

## PHYTONADIONE / VITAMIN $K_1$

**Chemistry** - A naphthoquinone derivative identical to naturally occurring vitamin $K_1$, phytonadione occurs as a clear, yellow to amber, viscous liquid. It is insoluble in water, slightly soluble in alcohol and soluble in lipids. Phytonadione may also be known as Vitamin $K_1$, phylloquinone, or phytomenadione.

**Storage/Stability/Compatibility** - Phytonadione should be protected from light at all times, as it is quite sensitive to light. If used as an intravenous infusion, the container should be wrapped with an opaque material. Tablets and capsules should be stored in well-closed, light-resistant containers.

Because most veterinary clinicians state that phytonadione is contraindicated for intravenous use, and since compatibility is dependent upon factors such as pH, concentration, temperature and diluents used, it is suggested to consult specialized references (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography) for more specific information on the compatibility of phytonadione with other drugs.

**Pharmacology** - Vitamin $K_1$ is necessary for the synthesis of blood coagulation factors II, VII, IX, and X in the liver. It is believed that Vitamin $K_1$ is involved in the carboxylation of the inactive precursors of these factors to form active compounds.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications -** The principal uses of exogenously administered phytonadione is in the treatment of anticoagulant rodenticide toxicity. It is also used for treating dicumarol toxicity associated with sweet clover ingestion in ruminants, sulfaquinoxaline toxicity, and in bleeding disorders associated with faulty formation of vitamin K-dependent coagulation factors.

**Pharmacokinetics** - Phytonadione is absorbed from the GI tract in monogastric animals via the intestinal lymphatics, but only in the presence of bile salts. Oral absorption of phytonadione may be significantly enhanced by administering with fatty foods. The relative bioavailability of the drug is increased 4-5 times in dogs given canned dog food with the dose. After oral administration, increases in clotting factors may not occur until 6-12 hours later.

Phytonadione may concentrate in the liver for a short period of time, but is not appreciably stored in the liver or other tissues. Only small amounts are distributed across the placenta in pregnant animals. Exogenously administered phytonadione enters milk. The elimination of Vitamin $K_1$ is not well understood.

**Contraindications/Precautions/Reproductive Safety** - Many veterinary clinicians state that the intravenous use of phytonadione is contraindicated because of increased risk of anaphylaxis development, but intravenous phytonadione is used in human medicine and several intravenous dosage regimens are outlined below in the Dosage section. Phytonadione is contraindicated in patients hypersensitive to it or any component of its formulation.

Vitamin K does not correct hypoprothrombinemia due to hepatocellular damage.
Phytonadione crosses the placenta only in small amounts, but its safety has not been documented in pregnant animals.

**Adverse Effects/Warnings** - Anaphylactoid reactions have been reported following IV administration of Vitamin $K_1$; use with extreme caution (See Contraindications above). Intramuscular administration may result in acute bleeding from the site of injection during the early stages of treatment. Small gauge needles are recommended for use when injecting SQ or IM. Subcutaneous injections or oral dosages may be slowly or poorly absorbed in animals that are hypovolemic.

Because 6-12 hours may be required for new clotting factors to be synthesized after phytonadione administration, emergency needs for clotting factors must be provided for by giving blood products.

**Overdosage/Acute Toxicity** - Phytonadione is relatively non-toxic, and it would be unlikely that toxic symptoms would result after a single overdosage. However, refer to the Adverse Effects section for more information.

**Drug Interactions** - As would be expected, phytonadione antagonizes the anticoagulant effects of **coumarin (***e.g.,* **warfarin) and indandione agents**. The following drugs may prolong or enhance the effects of anticoagulants and antagonize some of the therapeutic effects of phytonadione: **phenylbutazone, aspirin, chloramphenicol, sulfonamides (including trimethoprim-sulfa), diazoxide, allopurinol, cimetidine, metronidazole, anabolic steroids, erythromycin, ketoconazole, propranolol, and thyroid drugs.** Concomitant administration of **Mineral Oil** may reduce the absorption of oral vitamin K. Although chronic antibiotic therapy should have no significant effect on the absorption of phytonadione, these drugs may decrease the numbers of vitamin K producing bacteria in the gut.

**Doses -**
**Horses**:
For warfarin (or related compounds) toxicity:

To Drug Monograph Index To Ophthalmic Product Index

a) 500 mg SQ q4-6h until one-stage prothrombin time (OSPT) returns to normal control values. Whole blood or fresh plasma may also be necessary early in the course of treatment. (Byars 1987)
b) 0.5 - 2.5 mg/kg IM, if IV use is necessary (avoid if possible), dilute in saline or $D_5W$/saline and give very slowly (not to exceed 5 mg/minute). (Upson 1988)
c) For acute hypoprothrombinemia with hemorrhage: 0.5 - 2.5 mg/kg IV, not to exceed 10 mg/minute in mature animals and 5 mg/minute in newborn and very young animals.

For non-acute hypoprothrombinemia: 0.5 - 2.5 mg/kg IM or SQ (Label directions; *Veda-K1*®—Vedco)

**Monitoring Parameters** -
1) Clinical efficacy (lack of hemorrhage)
2) One-stage prothrombin time (OSPT)

**Client Information** - Because it may take several weeks to eliminate some of the anticoagulant rodenticides from the body, clients must be counseled on the importance of continuing to administer the drug (phytonadione) for as long as instructed or renewed bleeding may occur. Unless otherwise instructed, oral phytonadione should be administered with food, preferably foods high in fat content. During therapy, animals should be kept quiet whether at home or hospitalized.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Phytonadione Oral Capsules 25 mg; *Veta-K1*® (PVL; Vedco); (Rx) Approved for use in dogs and cats.

Phytonadione Aqueous Colloidal Solution for Injection 10 mg/ml in 30 ml and 100 ml vials; *Veda-K1*® (Vedco); (Rx) Approved for use dogs, cats, cattle, calves, horses, swine, sheep, and goats. No withdrawal times listed.

**Human-Approved Products**:

Phytonadione Oral Tablets 5 mg; *Mephyton*® (Merck); (Rx)

Phytonadione Injection 2 mg/ml (aqueous colloidal solution) in 0.5 ml amps and syringes and 10 mg/ml (aqueous dispersion) in 1 ml amps and 2.5 & 5 ml vials
*Aqua-Mephyton* (Merck); Generic (IMS); (Rx)

## PIPERAZINE

**Chemistry** - Piperazine occurs as a white, crystalline powder that may have a slight odor. It is soluble in water and alcohol. Piperazine is available commercially in a variety of salts, including citrate, adipate, phosphate, hexahydrate and dihydrochloride. Each salt contains a variable amount of piperazine (base): adipate (37%), chloride (48%), citrate (35%), dihydrochloride (50-53%), hexahydrate (44%), phosphate (42%) and sulfate (46%).

**Storage/Stability/Compatibility** - Unless otherwise specified by the manufacturer, piperazine products should be stored at room temperature (15-30°C).

**Pharmacology** - Piperazine is thought to exert “curare-like” effects on susceptible nematodes, thereby paralyzing or narcotizing the worm and allowing it to be passed out with the feces. The neuromuscular blocking effect is believed to be caused by blocking acetylcholine at the myoneural junction. In ascarids, succinic acid production is also inhibited.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - Piperazine is used for the treatment of ascarids in dogs, cats, horses, swine and poultry. Piperazine is considered to be safe to use in animals with concurrent gastroenteritis and during pregnancy.

**Pharmacokinetics** - Piperazine and its salts are reportedly readily absorbed from the proximal sections of the GI tract and the drug is metabolized and excreted by the kidneys. Absorptive, distribution and elimination kinetics on individual species were not located.

**Contraindications/Precautions** - Piperazine should be considered contraindicated in patients with chronic liver or kidney disease, and in patients with gastrointestinal hypomotility. There is some evidence in man, that piperazine may provoke seizures in patients with a seizure history or with renal disease when given in high dosages.

If used in horses with heavy infestations of *P. equorum*, rupture or blockage of intestines is possible due to the rapid death and detachment of the worm.

**Adverse Effects/Warnings** - Adverse effects are uncommon at recommended doses, but diarrhea, emesis and ataxia may be noted in dogs or cats. Horses and foals generally tolerate the drug quite well, even at high dosage rates, but a transient softening of the feces may be seen. Other adverse effects have been seen at toxic dosages, refer to the Overdosage section below for more information.

**Overdosage** - Acute massive overdosage can lead to paralysis and death, but the drug is generally considered to have a wide margin of safety. The oral $LD_{50}$ of piperazine adipate in mice is 11.4 g/kg.

In cats, adverse effects occur within 24 hours after a toxic dose is ingested. Emesis, weakness, dyspnea, muscular fasiculations of ears, whiskers, tail and eyes, rear limb ataxia, hypersalivation, depression, dehydration, head-pressing, positional nystagmus and slowed pupillary responses have all been described after a toxic ingestion. Many of these effects may also be seen in dogs after toxic piperazine ingestions.

Treatment is symptomatic and supportive. If ingestion was recent, use of activated charcoal and a cathartic has been suggested. Intravenous fluid therapy and keeping the animal in a quiet, dark place is also recommended. Recovery generally takes place within 3-4 days.

**Drug Interactions** - Although data conflicts, piperazine and **chlorpromazine** may precipitate seizures if used concomitantly. Piperazine and **pyrantel/morantel** have antagonistic modes of action and should generally not be used together. The use of **purgatives (laxatives)** with piperazine is not recommended as the drug may be eliminated before its full efficacy is established.

**Drug/Laboratory Interactions** - Piperazine can have an effect on **uric acid blood levels**, but references conflict with regard to the effect. Both falsely high and low values have been reported. Use results cautiously.

**Doses** - **Caution**: Piperazine is available in several salts that contain varying amounts of piperazine base (see Chemistry above). Many of the doses listed below do not specify what salt (if any) is used in the dosage calculations. If the dose is in question, refer to the actual product information for the product you are using.
**Horses:** There are combination products available for use in horses (see Dosage Forms/Preparations section) that contain piperazine that have increased efficacy against nematodes and other helminths. Refer to the individual products' package insert for more information.

a) 110 mg/kg (base) PO; repeat in 3-4 weeks. Retreating at 10 week intervals for *P. equorum* infections in young animals is recommended. (Roberson 1988b)

To Drug Monograph Index To Ophthalmic Product Index

b) 200 mg/kg PO. Maximum of 80 grams in adults, 60 grams in yearlings, and 30 grams in foals. (Brander, Pugh, and Bywater 1982)

**Monitoring Parameters** -1) Clinical and/or laboratory efficacy 2) Adverse effects

**Client Information** - Clients should be instructed to administer only the amount prescribed and to relate any serious adverse effects to the veterinarian.

**Dosage Forms/Preparations/Approval Status/Withdrawal Times** -

**Veterinary-Approved Products**:

Piperazine Dihydrochloride tablets equivalent to 50 mg, or 250 mg base. *Pipa-Tabs*® (Vet-A-Mix); (OTC) Approved for use in dogs and cats.

Additional products and combination products may be available for a variety of species.

**Human-Approved Products**: None

## POLYSULFATED GLYCOSAMINOGLYCAN

**Chemistry** - Polysulfated glycosaminoglycan (PSGAG) is chemically similar to natural mucopolysaccharides found in cartilaginous tissues. PSGAG is reportedly an analog of heparin.

**Storage/Stability/Compatibility** - Commercial products should be stored in a cool place 8-15°C (46-59°F). The manufacturer recommends discarding the unused portion from a vial or ampule and does not recommend mixing with any other drug or chemical.

**Pharmacology** - In joint tissue, PSGAG inhibits proteolytic enzymes that can degrade proteoglycans (including naturally occurring glycosaminoglycans), thereby preventing or reducing decreased connective tissue flexibility, resistance to compression and resiliency. By acting as a precursor, PSGAG also increases the synthesis of proteoglycans. PSGAG also reduces inflammation by reducing concentrations of prostaglandin $E_2$ (released in response to joint injury) and increases hyaluronate concentrations in the joint, thereby restoring synovial fluid viscosity.

**Uses/Indications** - PSGAG administered either IM or IA is indicated for the treatment of non-infectious and/or traumatic joint dysfunction and associated lameness of the carpal joints in horses. Some studies have indicated that PSGAG is much less effective in joints where there has been acute trauma but without the presence of degradative enzymes.
It is also approved for the control of signs associated with non-infectious degenerative and/or traumatic arthritis in dogs.

**Pharmacokinetics** - PSGAG is deposited in all layers of articular cartilage and is preferentially taken up by osteoarthritic cartilage. When administered IM, articular levels will with time exceed those found in the serum. Peak joint levels are reached 48 hours after IM injection, and persist for up to 96 hours after injection.

**Contraindications/Precautions/Reproductive Safety** - PSGAG is contraindicated for intra-articular administration in patients hypersensitive to it. While the manufacturer states there are no contraindications for IM use of the drug, the drug should not be used in place of other therapies in cases where infection is present or suspected, or in place of surgery or joint immobilization in cases where indicated.

To Drug Monograph Index To Ophthalmic Product Index

Some clinicians feel that PSGAG should not be used within one week of arthrotomy in the dog, because it may cause increased bleeding. This effect apparently has not been confirmed in the literature however.

Reproductive studies have apparently not been performed; use with caution during pregnancy or in breeding animals (the manufacturer does not recommend use in breeding animals).

**Adverse Effects/Warnings** - Adverse effects are unlikely when using the IM route. Intraarticular administration may cause a post-injection inflammation (joint pain, effusion, swelling and associated lameness) secondary to sensitivity reactions, traumatic injection technique, overdosage, number or frequency of injections. Treatment consisting of anti-inflammatory drugs, cold hydrotherapy, and rest is recommended. Although rare, joint sepsis secondary to injection is also potentially possible; strict aseptic technique should be employed to minimize its occurrence. In dogs, a dose-related inhibition of coagulation/hemostasis has been described.

**Overdosage/Acute Toxicity** - Doses five times those recommended (2.5 grams) given IM to horses twice weekly for 6 weeks revealed no untoward toxic effects. Approximately 2% of horses receiving overdoses (up to 1250 mg) IA showed transient symptoms associated with joint inflammation.

**Drug Interactions** - While specific drug interactions have not been detailed to date, using this product in conjunction with either steroids or non-steroidal antiinflammatory agents could mask the signs and symptoms associated with septic joints.

There is some concern that since PSGAG is a heparin analog that it should not be used in conjunction with **other NSAID's** or **other anticoagulants**. Clinical significance is unclear, but use together with caution.

**Doses** -
**Horses**:

a) For IM administration: 500 mg IM (of IM product) every 4 days for 28 days. Thoroughly cleanse injection site before injecting. Do not mix with other drugs or chemicals. (Package Insert- Adequan® I.M.)

For intra-articular administration: 250 mg (of IA product) IA once a week for 5 weeks. Joint area should be shaved, and cleansed as if a surgical procedure, prior to injecting. Do not mix with other drugs or chemicals. (Package Insert- Adequan® I.M.)

b) For IM injection: 500 mg IM every 3-4 days for a minimum of 4 and preferably, 7 treatments.

For intra-articular injection: As above; author recommends adding 125 mg of amikacin for injection into the A injection to reduce potential for infection. (Nixon 1992)

**Monitoring Parameters** - Efficacy and joint inflammation/infection if administered IA.

**Client Information** - The IA product must be administered by veterinary professionals; the IM product could, with proper instruction be administered by the owner.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Polysulfated glycosaminoglycan for Intra-Articular Injection 250 mg/ml in 1 ml glass ampules or 1 ml single use vials, boxes of 6; *Adequan® I.A.* (Luitpold); (Rx) Approved for use in horses (not in those intended for food).

Polysulfated glycosaminoglycan for Intra-Muscular Injection 100 mg/ml in 5 ml glass ampules or 5 ml vials, boxes of 4; *Adequan® I.M.* (Luitpold); (Rx) Approved for use in horses (not in those intended for food).

To Drug Monograph Index To Ophthalmic Product Index

Polysulfated glycosaminoglycan for IM Injection 100 mg/ml; *Adequan*® *Canine* (Luitpold); (Rx) Approved for use in Dogs.

**Human-Approved Products**: None

**Potassium Bromide - see Bromide Salts**

## POTASSIUM CHLORIDE
## POTASSIUM GLUCONATE

**Chemistry** - Potassium chloride occurs as either white, granular powder or as colorless, elongated, prismatic or cubical crystals. It is odorless and has a saline taste. One gram is soluble in about 3 ml of water and is insoluble in alcohol. The pH of the injection ranges from 4-8. One gram of potassium chloride contains 13.4 mEq of potassium. A 2 mEq/ml solution has an osmolarity of 4000 mOsm/L. Potassium chloride may also be known as KCl.

Potassium gluconate occurs as white to yellowish white, crystalline powder or granules. It is odorless and has a slightly bitter taste and is freely soluble in water. One gram of potassium gluconate contains 4.3 mEq of potassium.

**Storage/Stability/Compatibility** - Potassium gluconate oral products should be stored in tight, light resistant containers at room temperature (15-30°C), unless otherwise instructed by the manufacturer. Unless otherwise directed by the manufacturer, potassium chloride products should be stored in tight, containers at room temperature (15-30°C); protect from freezing.

Potassium chloride for injection is reportedly **compatible** with the following intravenous solutions and drugs (as an additive): All commonly used intravenous replacement fluids (not 10% fat emulsion), aminophylline, amiodarone HCl, bretylium tosylate, calcium gluconate, carbenicillin disodium, cephalothin sodium, cephapirin sodium, chloramphenicol sodium succinate, cimetidine HCl, clindamycin phosphate, corticotropin (ACTH), cytarabine, dimenhydrinate, dopamine HCl, erythromycin gluceptate/lactobionate, heparin sodium, hydrocortisone sodium succinate, isoproterenol HCl, lidocaine HCl, metaraminol bitartrate, methicillin sodium, methyldopate HCl, metoclopramide HCl, nafcillin sodium, norepinephrine bitartrate, oxacillin sodium, oxytetracycline HCl, penicillin G potassium, phenylephrine HCl, piperacillin sodium, sodium bicarbonate, tetracycline HCl, thiopental sodium, vancomycin HCl, verapamil HCl, and vitamin B-complex with C.

Potassium chloride for injection **compatibility information conflicts** or is dependent on diluent or concentration factors with the following drugs or solutions: fat emulsion 10%, amikacin sulfate, dobutamine HCl, methylprednisolone sodium succinate (at Y-site), penicillin G sodium, and promethazine HCl (at Y-site). Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography) for more specific information.
Potassium chloride for injection is reportedly **incompatible** with the following solutions or drugs: amphotericin B, diazepam (at Y-site), and phenytoin sodium (at Y-site).

**Pharmacology** - Potassium is the principal intracellular cation in the body. It is essential in maintaining cellular tonicity; nerve impulse transmission; smooth, skeletal and cardiac muscle contraction; and maintenance of normal renal function. Potassium is also used in carbohydrate utilization and in protein synthesis.

To Drug Monograph Index  To Ophthalmic Product Index

**Uses/Indications** - Potassium supplementation is used to prevent or treat potassium deficits. When feasible and appropriate, oral or nutritional therapy is generally preferred over parenteral potassium administration, because it is generally safer.

**Pharmacokinetics** - Potassium is primarily (80-90%) excreted via the kidneys with the majority of the remainder excreted in the feces. Very small amounts may be excreted in perspiration (in animals with sweat glands).

**Contraindications/Precautions** - Potassium salts are contraindicated in patients with hyperkalemia, renal failure or severe renal impairment, severe hemolytic reactions, untreated Addison's disease, and acute dehydration. Solid oral dosage forms should not be used in patients where GI motility is impaired. Use cautiously in digitalized patients (see Drug Interactions).

Because potassium is primarily an intracellular electrolyte, serum levels may not adequately reflect the total body stores of potassium. Acid-base balance may also mask the actual potassium picture. Patients with systemic acidosis conditions may appear to have hyperkalemia when in fact they may be significantly low in total body potassium. Conversely, alkalosis may cause a falsely low serum potassium value. Assess renal and cardiac function prior to therapy and closely monitor serum potassium levels. Supplementation should generally occur over 3-5 days to allow equilibration to occur between extracellular and intracellular fluids. Some clinicians feel that if acidosis is present, use potassium acetate, citrate or bicarbonate; and if alkalosis is present, use potassium chloride.

**Adverse Effects/Warnings** - The major problem associated with potassium supplementation is the development of hyperkalemia. Symptoms associated with hyperkalemia can range from muscular weakness and/or GI disturbances to cardiac conduction disturbances. Clinical symptoms can be exacerbated by concomitant hypocalcemia, hyponatremia, or acidosis. Intravenous potassium salts must be diluted before administering and given slowly (see Doses).
Oral therapy can cause GI distress and IV therapy may be irritating to veins.

**Overdosage/Acute Toxicity** - Fatal hyperkalemia may develop if potassium salts are administered too rapidly IV or if potassium renal excretory mechanisms are impaired. Symptoms associated with hyperkalemia are noted in the Adverse Effects section above. Treatment of hyperkalemia is dependent upon the cause and/or severity of the condition and can consist of: discontinuation of the drug with ECG, acid/base and electrolyte monitoring, glucose/insulin infusions, sodium bicarbonate, calcium therapy, and polystyrene sulfonate resin. It is suggested to refer to other references appropriate for the species being treated for specific protocols for treatment of hyperkalemia.

**Drug Interactions** - Potassium retention may occur when potassium is given with **angiotensin converting enzyme inhibitors (***e.g.,* **captopril, enalapril)** or with **potassium-sparing diuretics (***e.g.,* **spironolactone)**. In patients with severe or complete heart block who are receiving **digitalis** therapy, potassium salts are not recommended to be used. Oral potassium given with **non-steroidal antiinflammatory agents, or anticholinergic agents** may increase the risk of gastrointestinal adverse effects occurring. **Glucocorticoids, mineralocorticoids, or ACTH** may cause increased renal losses of potassium.

**Doses** -
**Dogs & Cats**:

For hypokalemia:

a) Intravenous replacement: If animal has normal renal function, IV KCl not to exceed 0.5 mEq/kg/hr. Use IV replacement very cautiously in animals with impaired renal function or in those receiving potassium-sparing diuretics.

Subcutaneous replacement: If IV use is unfeasible or rapid correction is unnecessary, may add KCl to SQ fluids; do not exceed 30 mEq of potassium per liter.

To Drug Monograph Index To Ophthalmic Product Index

Oral replacement: Potassium gluconate PO at a rate of 2.2 mEq per 100 calories of required energy intake or potassium gluconate elixir (20 mEq/ml) for dogs at 5 ml q8-12h PO. (Bell and Osborne 1986)

**Ruminants**:

For hypokalemia in "downer" cows:

a) 80 g sodium chloride and 20 g potassium chloride in 10 liters of water PO via stomach tube. Provide a bucket containing similar solution for cow to drink and another containing fresh water. (Caple 1986)

For hypokalemia:

a) 50 grams PO daily; 1 mEq/kg/hr IV drip. (Howard 1986)

**Monitoring Parameters** - Level and frequency of monitoring associated with potassium therapy is dependent upon the cause and/or severity of hypokalemia, acid/base abnormalities, renal function, and concomitant drugs administered or disease states and can include: 1) Serum potassium ; 2) Other electrolytes; 3) Acid/base status; 4) Glucose; 5) ECG; 6) CBC; 7) Urinalyses

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

There are several products for parenteral use that contain potassium; refer to the tables at the end of this section or individual proprietary veterinary products (*e.g., Cal-Dextro® K*—Fort Dodge) for additional information.

Oral Products:

Potassium Gluconate Oral Powder Each 0.65 gram 4 oz (1/4 teaspoonful) contains 2 mEq of potassium; in 4 oz. containers *Tumil-K* ® (Daniels) (Rx)

*Tumil-KCaplets*® (Daniels); (Rx) Approved for use in dogs and cats.

*Tumil-K Gel*® (Daniels) (Rx) 5 oz/tube

**Human-Approved Products**: Not a complete list.

Parenteral Products:

Potassium Chloride for Injection 2 mEq/ml in 250 & 500 ml; 10 mEq in 10 & 20 ml vials, syringes, & amps; 30 mEq in 14, 20, 30 & 100 ml vials and 20 ml syringes; 40 mEq in 20, 30, 50 & 100 ml vials, 20 ml amps and syringes; 60 mEq & 90 mEq in 30 ml vials. Must be diluted before administering. (Rx)

Potassium acetate for injection and potassium phosphate for injection (see previous monograph) are also available.

There are a multitude of human-labeled potassium salts for oral use available in several dosage forms; refer to human drug references for more information on these products.

## PRALIDOXIME CHLORIDE

**Chemistry** - A quaternary ammonium oxime cholinesterase reactivator, pralidoxime chloride occurs as a white to pale yellow, crystalline powder with a $pK_a$ of 7.8-8. It is freely soluble in water. The commercially available injection has a pH of 3.5-4.5 after reconstitution. Pralidoxime may also be known as 2-PAM Chloride, or 2-Pyridine Aldoxime Methochloride.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, pralidoxime chloride powder for injection should be stored at room temperature. After reconstituting with sterile water for injection, the solution should be used within a few hours. Do not use sterile water with preservatives added.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Pralidoxime reactivates cholinesterase that has been inactivated by phosphorylation secondary to certain organophosphates. Via nucleophilic attack, the drug removes and binds the offending phosphoryl group attached to the enzyme and is then excreted.

**Uses/Indications** - Pralidoxime is used in the treatment of organophosphate poisoning, often in conjunction with atropine and supportive therapy.

**Pharmacokinetics** - Pralidoxime is only marginally absorbed after oral dosing and oral dosage forms are no longer available in the United States. It is distributed primarily throughout the extracellular water. Because of its quaternary ammonium structure, it is not believed to enter the CNS in significant quantities, but recent studies and clinical responses have led some to question this. Pralidoxime is thought to be metabolized in the liver and excreted as both metabolite(s) and unchanged drug in the urine.

**Contraindications/Precautions/Reproductive Safety** - Pralidoxime is contraindicated in patients hypersensitive to it. Pralidoxime is generally not recommended to be used in instances of carbamate poisoning because inhibition is rapidly reversible, but there is some controversy regarding this issue.

Pralidoxime should be used with caution in patients receiving anticholinesterase agents for the treatment of myasthenia gravis as it may precipitate a myasthenic crisis. It should also be used cautiously and at a reduced dosage rate in patients with renal impairment.

**Adverse Effects/Warnings** - At usual doses, pralidoxime generally is safe and free of significant adverse effects. Rapid IV injection may cause tachycardia, muscle rigidity, transient neuromuscular blockade, and laryngospasm.

Pralidoxime must generally be given within 24 hours of exposure to be effective, but some benefits may occur, particularly in large exposures, if given within 36-48 hours.

**Overdosage/Acute Toxicity** - The acute $LD_{50}$ of pralidoxime in dogs is 190 mg/kg and, at high dosages, exhibits symptoms of its own anticholinesterase activity. Symptoms of toxicity in dogs may be exhibited as muscle weakness, ataxia, vomiting, hyperventilation, seizures, respiratory arrest and death.

**Drug Interactions** - Anticholinesterases can potentiate the action of **barbiturates**; use with caution.
**Cimetidine** may potentiate the action of organophosphates by slowing its metabolism.
Use of **succinylcholine, theophylline/aminophylline, reserpine, and respiratory depressant drugs (***e.g.,* **narcotics, phenothiazines)** should be avoided in patients with organophosphate toxicity.

**Doses** - Note: often used in conjunction with atropine; refer to that monograph and/or the references below for more information.

**Cattle**:

For organophosphate poisoning:

a) 25 - 50 mg/kg as a 20% solution IV over 6 minutes; or as a maximum of 100 mg/kg/day as an IV drip. (Smith 1986)

**Horses**:

For organophosphate poisoning:

a) 20 mg/kg (may require up to 35 mg/kg) IV and repeat q4-6h. (Oehme 1987c)

**Monitoring Parameters** - Monitoring of pralidoxime therapy is basically by monitoring the signs and symptoms associated with organophosphate poisoning. For more information, refer to one of the references outlined noted below.

To Drug Monograph Index To Ophthalmic Product Index

**Client Information** - This agent should only be used with close professional supervision.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:
Pralidoxime Chloride 1 gram cake in containers of six 20 ml vials without diluent or syringes; 600 mg in one 2 ml auto-injector; *Protopam Chloride*® (Wyeth-Ayerst); (Rx); Pralidoxime Chloride® (Survival Technology) (Rx)

## PRAZIQUANTEL

**Chemistry** - A prazinoisoquinoline derivative anthelmintic, praziquantel occurs as a white to practically white, hygroscopic, bitter tasting, crystalline powder, either odorless or having a faint odor. It is very slightly soluble in water and freely soluble in alcohol.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, praziquantel tablets should be stored in tight containers at room temperature. Protect from light.

**Pharmacology** - Praziquantel's exact mechanism of action against cestodes has not been determined. At low concentrations *in vitro*, the drug appears to impair the function of their suckers and stimulates the worm's motility. At higher concentrations *in vitro*, praziquantel increases the contraction (irreversibly at very high concentrations) of the worm's strobilla (chain of proglottids). Also, praziquantel causes irreversible focal vacuolization with subsequent cestodal disintegration at specific sites of the cestodal integument.

In schistosomes and trematodes, praziquantel directly kills the parasite, possibly by increasing calcium ion flux into the worm. Focal vacuolization of the integument follows and the parasite is phagocytized.

**Uses/Indications** - Praziquantel is indicated for (approved labeling) for the treatment of *Dipylidium caninum*, *Taenia pisiformis* and *Echinococcus granulosis* in dogs, and *Dipylidium caninum* and *Taenia taeniaeformis* in cats. Fasting is not required nor is it recommended before dosing. A single dose is usually effective, but measures should be taken to prevent reinfection, particularly against *D. caninum*.

Praziquantel has been used in birds and other animals, but it is usually not economically feasible to use in large animals. In humans, praziquantel is used for schistosomiasis, other trematodes (lung, liver, intestinal flukes) and tapeworms. It is not routinely effective in treating *F. hepatica* infections in humans.

**Pharmacokinetics** - Praziquantel is rapidly and nearly completely absorbed after oral administration, but there is a significant first-pass effect after oral administration. Peak serum levels are achieved after 30-120 minutes in dogs.
Praziquantel is distributed throughout the body and crosses the blood-brain barrier into the CNS and across the intestinal wall.

Praziquantel is metabolized by the liver to metabolites of unknown activity. It is excreted primarily in the urine and the elimination half-life is approximately 3 hours in the dog.

**Contraindications/Precautions/Reproductive Safety** - The manufacturer recommends not using praziquantel in puppies less than 4 weeks old or in kittens less than 6 weeks old. However, a combination product containing praziquantel and febantel from the same manufacturer is approved for use in puppies and kittens of all ages. No other contraindications are listed for this compound by the manufacturer. In

humans, praziquantel is contraindicated in patients hypersensitive to the drug. Praziquantel is considered to be safe to use in pregnant dogs or cats.

**Adverse Effects/Warnings** - When used orally, praziquantel can cause anorexia, vomiting, lethargy or diarrhea in dogs, but the incidence of these effects is less than 5%. In cats, adverse effects were quite rare (<2%) in field trials using oral praziquantel with salivation and diarrhea being reported.

An increased incidence of adverse effects have been reported after using the injectable product. In dogs, pain at the injection site, vomiting, drowsiness and/or a staggering gait were reported from field trials with the drug. Some cats (9.4%) showed symptoms of diarrhea, weakness, vomiting, salivation, sleepiness, transient anorexia and/or pain at the injection site.

**Overdosage/Acute Toxicity** - Praziquantel has a wide margin of safety. In rats and mice the oral $LD_{50}$ is at least 2 g/kg. An oral $LD_{50}$ could not be determined in dogs, as at doses greater than 200 mg/kg, the drug induced vomiting. Parenteral doses of 50 - 100 mg/kg in cats caused transient ataxia and depression. Injected doses at 200 mg/kg were lethal in cats.

**Drug Interactions** - Reportedly in humans, synergistic activity occurs with praziquantel and **oxamniquine** in the treatment of schistosomiasis. The clinical implications of this synergism in veterinary patients is not clear.

**Doses** -

**Sheep & Goats**:
For all species of *Moniezia*, *Stilesia*, or *Avitellina*:
a) 10 - 15 mg/kg (Roberson 1988a)

**Llamas**:
For susceptible parasites:
a) 5 mg/kg PO. (Fowler 1989)

**Elephants:**

a) 2.5-4.0 mg/kg orally for cestodiasis
Chandrasekharan,K. 2002. **Specific diseases of Asian elephants**. Journal of Indian Veterinary Association Kerala 7:(3):31-34

Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T., 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference to Kerala.** In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-449

**Monitoring Parameters** -
1) Clinical efficacy

**Client Information** - Fasting is not required nor is it recommended before dosing. A single dose is usually effective, but measures should be taken to prevent reinfection, particularly against *D. caninum*. Tablets may be crushed or mixed with food. Because tapeworms are often digested, worm fragments may not be seen in the feces after using.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

To Drug Monograph Index To Ophthalmic Product Index

Praziquantel 23 mg (feline), 34 mg (canine) Tablets; *Droncit® Tablets* (Bayer); (Rx) Approved for use in cats and dogs.

Praziquantel Injection 56.8 mg/ml in 10 ml vials; *Droncit® Injection* (Bayer); (Rx) Approved for use in cats and dogs.

Praziquantel/pyrantel pamoate; *Drontal Tablets®* (Bayer) (Rx) Approved for use in cats

Praziquantel/pyrantel pamoate plus febantel; *Drontal Plus Tablets®* (Bayer) (Rx) small, medium and large dog sizes

**Human-Approved Products**:

Praziquantel Tablets 600 mg; *Biltricide®* (Bayer) (Rx)

## PREDNISOLONE

## PREDNISOLONE SODIUM SUCCINATE
## PREDNISOLONE ACETATE
## PREDNISONE

For more information refer to the monograph: Glucocorticoids, General Information or to the manufacturer's product information for veterinary labeled products.

Note: Although separate entities, prednisone is rapidly converted by the liver *in vivo* to prednisolone. Except for patients in frank hepatic failure, the drugs can, for all intents, be considered equivalent.

**Chemistry** - Prednisolone and prednisone are synthetic glucocorticoids. Prednisolone and prednisolone acetate occur as odorless, white to practically white, crystalline powders. Prednisolone is very slightly soluble in water and slightly soluble in alcohol. The acetate ester is practically insoluble in water and slightly soluble in alcohol. The sodium succinate ester is highly water soluble. Prednisolone is also known as deltahydrocortisone or metacortandralone.

Prednisone occurs as an odorless, white to practically white, crystalline powder. Prednisone is very slightly soluble in water and slightly soluble in alcohol. Prednisone is also known as deltacortisone or deltadehydrocortisone.

**Storage/Stability/Compatibility** - Prednisolone and prednisone tablets should be stored in well-closed containers. All prednisone and prednisolone products should be stored at temperatures less than 40°, and preferably between 15-30°C; avoid freezing liquid products. Do not autoclave. Oral liquid preparations of prednisone should be stored in tight containers.

Prednisolone sodium succinate should be stored at room temperature and protected from light (store in carton). After reconstitution, the product is recommended to be used immediately and not stored.

Little data appears to be available regarding the compatibility of prednisolone sodium succinate injection (*Solu-Delta Cortef®* — Upjohn) with other products. A related compound, prednisolone sodium phosphate is reportedly **compatible** with the following drugs/solutions: ascorbic acid injection, cephalothin sodium, cytarabine, erythromycin lactobionate, fluorouracil, heparin sodium, methicillin sodium, penicillin G potassium/sodium, tetracycline HCl and vitamin B-Complex with C. It is reportedly **incompatible** with: calcium gluconate/gluceptate, dimenhydrinate, metaraminol bitartrate, methotrexate sodium, prochlorperazine edisylate, polymyxin B sulfate, promazine HCl, and promethazine. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

To Drug Monograph Index  To Ophthalmic Product Index

**Doses -**
**Horses**:

For adjunctive therapy of COPD:

a) Prednisolone: Initially, 600 - 800 mg IM or PO in a 450 kg horse. May be possible to decrease dose and go to alternate day dosing. Doses as low as 200 mg every other day may be effective. (Beech 1987a)

For glucocorticoid effects:

a) Prednisolone sodium succinate: 0.25 - 1 mg/kg IV, Predniso(lo)ne tablets 0.25 - 1 mg/kg PO; Prednisolone acetate: 0.25 - 1.0 mg/kg IM or 10 - 25 mg subconjunctivally. (Robinson 1987)

**Elephants:**

**a) For treatment of heatstroke: 1mg / 3 kg body weight.** Schmidt,M.J., 1986. **Proboscidea (Elephants)**. In: Fowler,M.E. (Editor), Zoo and wild animal medicine. W.B. Saunders, Philadelphia,PA, USA pp. 884-923

**Dosage Forms/Preparations/Approval Status/Withdrawal Times**-

**Veterinary-Approved Products:**
A zero tolerance of residues in milk for these compounds have been established for dairy cattle. All these agents require a prescription (Rx). Known approved-veterinary products are indicated below.

Prednisolone Tablets 5 mg. 20 mg

*Delta-Cortef*® (Upjohn), *Prednis-Tab*® (Vet-A-Mix); generic (Rx). Approved for use in dogs.

Prednisolone Acetate Suspension for Injection 25 mg/ml, 50 mg/ml, 100 mg/ml
Available under several trade names and generically.

Prednisolone Sodium Succinate for Injection (Veterinary) 20 mg/ml in 50 ml vials

*Solu-Delta Cortef*® (Upjohn), *Sterisol-20*® (Anthony), generic; (Rx) Approved for dogs, cats, and horses. Refer to the package insert for more information on dosage and preparation of the solution before using.

Prednisolone Sodium Phosphate for Injection (Veterinary) 100 mg/vial, 500 mg/vial

*Cortisate-20*® (Schering). Approved for IV use in dogs. Refer to the package insert for more information on dosage, etc.

Prednisone Suspension for Injection (Veterinary) 10 mg/ml, 40 mg/ml; *Meticorten*® (Schering) Approved for dogs, cats, and horses.

**Human-Approved Products:**

Prednisolone Tablets: 5 mg *Delta-Cortef*® (Upjohn); generic, (Rx)
Prednisone Tablets: 1 mg, 2.5 mg, 5 mg, 10 mg, 20, mg, 50 mg (Rx)

Prednisolone Syrup: 15 mg/5 ml in 240 ml; *Prelone*® (Muro) (Rx)
Prednisone Oral Solution/Syrup: 1 mg/ml in 30 ml, 120 ml, 240 ml and 500 ml (Rx)

Prednisolone Acetate Injection: 25 mg/ml, 50 mg/ml in 10 & 30 ml vials; *Key-Pred 25*® (Hyrex) (Rx); *Predalone 50*® (Forest) (Rx); *Predcor-50*® (Hauck) (Rx); generic

## PROCAINAMIDE HCL

**Chemistry** - Structurally related to procaine, procainamide is used as an antiarrhythmic agent. Procainamide HCl differs from procaine by the substitution of an amide group for the ester group found on

procaine. It occurs as an odorless, white to tan, hygroscopic, crystalline powder with a $pK_a$ of 9.23 and a melting range from 165°-169°C. It is very soluble in water and soluble in alcohol. The pH of the injectable product ranges from 4 - 6.

**Storage/Stability/Compatibility** - Oxidation due to the injection of air into the vial may cause discoloration of the injectable solution. The solution may be used if the color is no darker than a light amber. Refrigeration may retard the development of oxidation, but the solution may be stored at room temperature.

The injectable product is reportedly **compatible** with sodium chloride 0.9% injection, and water for injection. Procainamide is also compatible with dobutamine HCl, lidocaine HCl, and verapamil HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - A class 1A antiarrhythmic agent, procainamide exhibits cardiac actions similar to that of quinidine. Procainamide prolongs the refractory times in both the atria and ventricles, decreases myocardial excitability, and depresses automaticity and conduction velocity. It has anticholinergic properties which may contribute to its effects. Procainamide's effects on heart rate are unpredictable, but it usually causes only slight increases or no change in heart rate. It may exhibit negative inotropic actions on the heart, although cardiac outputs are generally not affected.

On ECG, QRS widening, and prolonged PR & QT intervals can be seen. The QRS complex and T wave may occasionally show some slight decreases in voltage.

**Uses/Indications** - Procainamide is indicated for the treatment of ventricular premature complexes (VPC's), ventricular tachycardia, or supraventricular tachycardia associated with Wolff-Parkinson-White (WPW) syndrome with wide QRS complexes. Higher doses may be beneficial in the treatment of supraventricular tachycardias, although procainamide cannot be considered a first-line agent for this dysrhythmia.

**Pharmacokinetics** - After IM or IV administration, the onset of action is practically immediate. After oral administration in humans, approximately 75-95% of a dose is absorbed in the intestine, but some patients absorb less than 50% of a dose. Food, delayed gastric emptying or decreased stomach pH may delay oral absorption. In dogs, it has been reported that the oral bioavailability is approximately 85% and the absorption half-life is 0.5 hours. However, there is an apparent large degree of variability in both bioavailability and half-life of absorption.

Distribution of procainamide is highest into the CSF, liver, spleen, kidneys, lungs, heart and muscles. The volume of distribution in dogs is approximately 1.4 - 3 L/kg. It is only approximately 20% protein bound in humans and 15% in dogs. Procainamide can cross the placenta and is excreted into milk.

The elimination half-life in dogs has been reported to be variable, most studies report values between 2-3 hours. In humans, procainamide is metabolized to *N*-acetyl-procainamide (NAPA), an active metabolite. It appears, however, that dogs do not form appreciable amounts of NAPA from procainamide. In the dog, approximately 90% (50-70% unchanged) of an intravenous dose is excreted in the urine as procainamide and metabolites within 24 hours after dosing.

**Contraindications/Precautions** - Procainamide may be contraindicated in patients with myasthenia gravis (see Drug Interactions). Procainamide is contraindicated in patients hypersensitive to it, procaine or other chemically related drugs. In humans, procainamide is contraindicated in patients with systemic lupus erythematosis (SLE), but it is unknown if it adversely affects dogs with this condition. Procainamide should not be used in patients with torsade de pointes, or with 2nd or 3rd degree heart block (unless artificially paced).

To Drug Monograph Index  To Ophthalmic Product Index

Procainamide should be used with extreme caution, if at all, in patients with cardiac glycoside intoxication. It should be used with caution in patients with significant hepatic or renal disease or with congestive heart failure.

**Adverse Effects/Warnings** - Adverse effects are generally dosage (blood level) related in the dog. Gastrointestinal effects may include anorexia, vomiting, or diarrhea. Effects related to the cardiovascular system can include weakness, hypotension, negative inotropism, widened QRS complex and QT intervals, AV block, multiform ventricular tachycardias. Fevers and leukopenias are a possibility. Profound hypotension can occur if injected too rapidly IV. In humans, an SLE syndrome can occur, but its incidence has not been established in the dog. Dosages should usually be reduced in patients with renal failure, congestive heart failure or those who are critically ill.

**Overdosage** - Symptoms of overdosage can include hypotension, lethargy, confusion, nausea, vomiting, and oliguria. Cardiac signs may include widening of the QRS complex, junctional tachycardia, ventricular fibrillation, or intraventricular conduction delays.

If an oral ingestion, emptying of the gut and charcoal administration may be beneficial to remove any unabsorbed drug. IV fluids, plus dopamine, phenylephrine, or norepinephrine could be considered to treat hypotensive effects. A 1/6 molar intravenous infusion of sodium lactate may be used in an attempt to reduce the cardiotoxic effects of procainamide. Forced diuresis using fluids and diuretics along with reduction of urinary pH, can enhance the renal excretion of the drug. Temporary cardiac pacing may be necessary should severe AV block occur.

**Drug Interactions** - Use with caution with **other antidysrhythmic agents**, as additive cardiotoxic or other toxic effects may result. Procainamide may antagonize the effects of **pyridostigmine, neostigmine,** or other anticholinesterases in patients with myasthenia gravis.
Procainamide may potentiate the effects of other **drugs having hypotensive effects**.
Procainamide should only be used in patients with **digitalis** intoxication when treatment with potassium, lidocaine or phenytoin is ineffective. **Cimetidine** may decrease the renal clearance of procainamide with a resultant increase in serum level of procainamide. Procainamide may potentiate or prolong the neuromuscular blocking activity of muscle relaxants such as **succinylcholine** or other agents (*e.g.,* **aminoglycosides**) having neuromuscular blocking activity.

**Doses -**
**Horses**:

a) Intravenous: 0.5 mg/kg every 10 minutes until resolution or until a total of 2 - 4 mg/kg has been given. (Muir and McGuirk 1987a)

**Monitoring Parameters** -

1) ECG; continuously with IV dosing
2) Blood pressure if possible, during IV administration
3) Symptoms of toxicity (see Adverse Reactions/Overdosage)
4) Serum levels
   Because of the variability in pharmacokinetics reported in the dog, it is encouraged to monitor therapy using serum drug levels. Because dogs apparently do not form the active metabolite NAPA in appreciable quantities, the therapeutic range for procainamide is controversial. Therapeutic ranges from 3 - 8 micrograms/ml to 8 - 20 micrograms/ml have been suggested. This author would suggest using the lower range as a guideline to initiate therapy, but not to hesitate increasing doses to attain the higher values if efficacy is not achieved and toxicity is not a problem. Digitalis-induced ventricular arrhythmias may require substantially higher blood levels for control. Trough levels are usually specified when monitoring oral therapy. Because NAPA is routinely

monitored with procainamide in human medicine, it may be necessary to request to your laboratory that NAPA values need not be automatically run for canine patients.

**Client Information** - Oral products should be administered at evenly spaced intervals throughout the day/night. Unless otherwise directed, give the medication on an empty stomach at least 1/2 hour before feeding. Notify veterinarian if animal's condition deteriorates or symptoms of toxicity (*e.g.,* vomiting, diarrhea, weakness, etc.) occur.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Procainamide HCl for injection 100 mg/ml in 10 ml vials & 500 mg/ml in 2 ml vials and 2 & 4 ml syringes; *Pronestyl*® (Princeton Pharm.); Generic; (Rx)

Procainamide HCl Tablets or Capsules 250 mg, 375 mg, 500 mg; *Pronestyl*® (Princeton Pharm.); Generic; (Rx)

Procainamide HCl Sustained-Release Tablets 250 mg, 500 mg, 1000 mg (Extended release only) (Note: These products are not recommended for initial therapy and have not been extensively used in veterinary medicine.); *Pronestyl*® *SR* (Princeton Pharm.), *Procanbid*® (Parke-Davis), Generic; (Rx)

Forest) (Rx); *Predcor-50*® (Hauck) (Rx); generic

## PROMAZINE HCL * (ADVERSE EFFECT REPORTED)

**Chemistry** - A propylamino phenothiazine derivative, promazine is structurally identical to chlorpromazine, but lacks the chlorine atom at the 2 position of the phenothiazine nucleus. It occurs as a bitter tasting, practically odorless, white to slight yellow crystalline powder. Promazine is freely soluble in alcohol and 333 mg are soluble in 1 ml of water at 25°C. The commercial injection has a pH from 4-4.5 and is dissolved in a solution of sterile water for injection.

**Storage/Stability/Compatibility** - Protect from prolonged exposure to air, protect from light, and store from 15-30°C. Avoid freezing the injectable product.
Upon prolonged exposure to air, promazine will oxidize and change to a pink or blue color. Do not use the injectable product if color changes (a slight yellowish tint is OK), or a precipitate forms.

The following products have been reported to be **compatible** when mixed with promazine injection: All usual intravenous fluids (except Ionosol B with Dextrose 5% or isotonic sodium bicarbonate), atropine sulfate, chlorpromazine HCl, chloramphenicol sodium succinate, diphenhydramine, droperidol, fentanyl citrate, glycopyrrolate, heparin sodium, hydroxyzine HCl, lidocaine HCl, meperidine, metoclopramide, metaraminol bitartrate, morphine sulfate, pentazocine lactate, promethazine, scopolamine HBr, & tetracycline HCl.

The following products have been reported as being **incompatible** when mixed with promazine: Ionosol B with dextrose 5%, aminophylline, chlorothiazide sodium, dimenhydrinate, fibrinogen, fibrinolysin (human), methohexital sodium, nafcillin sodium, penicillin g potassium, pentobarbital sodium, phenobarbital sodium, sodium bicarbonate (is reportedly compatible when 100 mg/l of promazine mixed with 2.4 mEq/l of bicarb in $D_5W$), thiopental sodium, and warfarin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Promazine has pharmacologic actions similar to acepromazine; refer to that monograph for a more detailed discussion of phenothiazine actions in animals.

**Uses/Indications** - Used basically for the same purposes as acepromazine; refer to that monograph for more information. Promazine is approved for use in dogs, cats, and horses.

**Pharmacokinetics** - Promazine is absorbed when given orally to non-ruminants; the drug is also apparently absorbed to some extent in ruminants when oral granules are used as they have some efficacy. In the dog, the onset of action following an IV dose is usually within 5 minutes, and following an IM dose within 30 minutes. Onsets of action reportedly are slightly longer in large animal species after parenteral administration. In horses, the onset of action after the oral granules have been consumed average around 45 minutes. The duration of action of promazine has been described as being dose-dependent, but generally ranges between 4-6 hours.

Promazine is metabolized in the liver primarily to glucuronide conjugates and these are excreted by the kidneys. In the horse, promazine metabolites are not detectable in the urine 72 hours after the last dose.

**Contraindications/Precautions** - Refer to the monograph for acepromazine for more information. Additionally, there are reports of horses being unusually sensitive to noise and reacting violently to sudden stimulation.

**Adverse Effects/Warnings** - Refer to the monograph for acepromazine for more information.

**Overdosage** - Refer to the monograph for acepromazine for more information.

**Drug Interactions** - Refer to the monograph for acepromazine for more information.

**Doses -**

**Horses**:

a)1.1 mg/kg IV as a tranquilizer (Lumb and Jones 1984)
b) 0.4 - 1.0 mg/kg IV (Robinson 1987)
c) 0.99 - 1.98 mg/kg PO (equivalent to 1.63 - 3.26 grams/100 lbs of body weight) One level capful of promazine granules (Fort Dodge) will treat 300 lbs of horse at a dosage of approximately 1.45 mg/kg. Onset of action generally starts in 45 minutes and lasts for 4-6 hours. (Package Insert - Promazine Granules, Fort Dodge)

**Elephants:**

a) A 200 kg bull calf became excited and repeatedly charged after the intramuscular administration of 70 mg promazine. An hour later, the calf was intubated and halothane anesthesia initiated. The calf stopped breathing and died within 2-3 minutes. No lesions were found at necropsy. Fowler,M.E. 1981. **Problems with immobilizing and anesthetizing elephants.** Proceedings of the American Association of Zoo Veterinarians 87-91

**Monitoring Parameters** -

1) Cardiac rate/rhythm/blood pressure if indicated and possible to measure
2) Degree of tranquilization
3) Body temperature (especially if ambient temperature is very hot or cold)

**Client Information** - May discolor the urine to a pink or red-brown color; this is not abnormal.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

To Drug Monograph Index To Ophthalmic Product Index

**Veterinary-Approved Products**:

Promazine HCl Granules (Veterinary); 10.25 oz containers containing 8 grams of promazine HCl; each gram of granules contains 27.5 mg. of promazine HCl; (Fort Dodge); (Rx) Approved for use in horses.

**Human-Approved Products**:

Promazine HCl for Injection 2 mg/ml in 10 ml vials; 5 mg/ml in 2 ml, 10 ml, &100 ml vials; *Sparine*® (Wyeth-Ayerst), generic; (Rx)

Promazine HCl tablets 25 mg, 50 mg, 100 mg; *Sparine*® (Wyeth-Ayerst); *Prozine-50*® (Hauck); generic, (Rx)

Promazine HCl Oral Syrup 2 mg/ml in 120 ml bottles; *Sparine*® (Wyeth); (Rx)

## PROPANTHELINE BROMIDE

**Chemistry** - A quaternary ammonium antimuscarinic agent, propantheline bromide occurs as bitter-tasting, odorless, white or practically white crystals, with a melting range of 156-162° (with decomposition). It is very soluble in both water and alcohol.

**Storage/Stability/Compatibility** - Propantheline bromide tablets should be stored at room temperature in tight containers.

**Pharmacology** - An antimuscarinic with similar actions as atropine, propantheline is a quaternary ammonium compound, however, and does not cross appreciably into the CNS. It, therefore, should not exhibit the same extent of CNS adverse effects that atropine possesses. For further information, refer to the atropine monograph.

**Uses/Indications -** In small animal medicine propantheline bromide has been used for its antispasmodic/antisecretory effects in the treatment of diarrhea. It is also employed in the treatment of hyperreflexic detrusor or urge incontinence and as oral treatment in anticholinergic responsive bradycardias. In horses, propantheline has been used intravenously to reduce colonic peristalsis and to relax the rectum to allow easier rectal examination and perform surgical procedures to the rectum.

**Pharmacokinetics** - Quaternary anticholinergic agents are not completely absorbed after oral administration because it is completely ionized. In humans, peak levels occur about 2 hours after oral administration. Food apparently decreases the amount of drug absorbed.

The distribution of propantheline has not been extensively studied, but like other quaternary antimuscarinics, propantheline is poorly lipid soluble and does not extensively penetrate into the CNS or eye.

Propantheline is believed to be prevalently metabolized in the GI and/or liver; less than 5% of an oral dose is excreted unchanged in the urine.

**Contraindications/Precautions** - Use of propantheline should be considered contraindicated if the patient has a history of hypersensitivity to anticholinergic drugs, tachycardias secondary to thyrotoxicosis or cardiac insufficiency, myocardial ischemia, unstable cardiac status during acute hemorrhage, GI obstructive disease, paralytic ileus, severe ulcerative colitis, obstructive uropathy or myasthenia gravis (unless used to reverse adverse muscarinic effects secondary to therapy).

To Drug Monograph Index To Ophthalmic Product Index

Antimuscarinic agents should be used with extreme caution in patients with known or suspected GI infections. Propantheline or other antimuscarinic agents can decrease GI motility and prolong retention of the causative agent(s) or toxin(s) resulting in prolonged symptoms. Antimuscarinic agents must also be used with extreme caution in patients with autonomic neuropathy.

Antimuscarinic agents should be used with caution in patients with hepatic disease, renal disease, hyperthyroidism, hypertension, CHF, tachyarrhythmias, prostatic hypertrophy, esophogeal reflux, and geriatric or pediatric patients.

**Adverse Effects/Warnings** - With the exception of fewer effects on the eye and the CNS, propantheline can be expected to have a similar adverse reaction profile as atropine (dry mouth, dry eyes, urinary hesitancy, tachycardia, constipation, etc.). High doses may lead to the development of ileus with resultant bacterial overgrowth in susceptible animals. For more information refer to the atropine monograph.

**Overdosage** - Because of its quaternary structure, it would be expected that minimal CNS effects would occur after an overdose of propantheline when compared to atropine. See the information listed in the atropine monograph for more information on the symptoms and signs that may be see following an overdose.

If a recent oral ingestion, emptying of gut contents and administration of activated charcoal and saline cathartics may be warranted. Treat symptoms supportively and symptomatically. Do not use phenothiazines as they may contribute to the anticholinergic effects. Fluid therapy and standard treatments for shock may be instituted.

The use of physostigmine is controversial and should probably be reserved for cases where the patient exhibits either extreme agitation and is at risk for injuring themselves or others, or for cases where supraventricular tachycardias and sinus tachycardias are severe or life-threatening. The usual dose for physostigmine (human) is 2 mg IV slowly (for average sized adult); if no response may repeat every 20 minutes until reversal of toxic antimuscarinic effects or cholinergic effects takes place. The human pediatric dose is 0.02 mg/kg slow IV (repeat q10 minutes as above) and may be a reasonable choice for treatment of small animals. Physostigmine adverse effects (bronchoconstriction, bradycardia, seizures) may be treated with small doses of IV atropine.

**Drug Interactions** - The following drugs may enhance the activity of propantheline and its derivatives: **antihistamines, procainamide, quinidine, meperidine, benzodiazepines, phenothiazines**. The following drugs may potentiate the adverse effects of propantheline and its derivatives: **primidone, disopyramide, nitrates, long-term corticosteroid use** (may increase intraocular pressure). Propantheline and its derivatives may enhance the actions of **nitrofurantoin, thiazide diuretics, sympathomimetics**. Propantheline delays the absorption, but increases the peak serum level of **ranitidine**. The relative bioavailability of ranitidine may be increased by 23% when propantheline is administered concomitantly with ranitidine.
Propantheline may decrease the absorption of **cimetidine**.

**Doses -**
**Horses**:

a) 0.014 mg/kg IV (Robinson 1987)
b) 30 mg IV to inhibit peristalsis for 2 hours during rectal surgery (Merkt et al. 1979)

Note: There is no commercially available injectable product available in the U.S.A.. Should a preparation be made from oral tablets, it should be freshly prepared and filtered through a 0.22 micron filter before administering. Use with caution.

**Monitoring Parameters** - Dependent of reason for use

To Drug Monograph Index To Ophthalmic Product Index

1) Clinical efficacy
2) Heart rate and rhythm if indicated
3) Adverse effects

**Client Information** - Dry mouth may be relieved by applying small amounts of water to animal's tongue for 10-15 minutes. Protracted vomiting and diarrhea can be serious; contact veterinarian if symptoms are not alleviated.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Propantheline Bromide Tablets 7.5 mg, 15 mg; *Pro-Banthine*® (Schiapparelli Searle); Generic; (Rx)

## PROPOFOL

**Chemistry** - Propofol is an alkylphenol derivative (2,6 - diisopropylphenol). The commercially available injection is an emulsion containing 100 mg/ml of soybean oil, 22.5 mg/ml of glycerol, and 12 mg/ml of egg lecithin. The emulsion has a pH of 7-8.5. Propofol may also be known as disoprofol.

**Storage/Stability/Compatibility** - Store propofol injection below 22°C (72°F), but not below 4°C (40°F.); do not refrigerate or freeze. Protect from light. Shake well before using. Do not use if the emulsion has separated. The manufacturer recommends discarding any unused portion at the end of the anesthetic procedure or after 6 hours, whichever occurs sooner.

Compatibility with other agents has not been well established. Propofol is compatible with the commonly used IV solutions (*e.g.,* LRS, $D_5W$) when injected into a running IV line.

**Pharmacology** - Propofol is a short acting hypnotic unrelated to other general anesthetic agents. Its mechanism of action is not well understood.

In dogs, propofol produces rapid, yet smooth and excitement-free anesthesia induction (in 30-60 seconds) when given slowly IV. Sub-anesthetic dosages will produce sedation, restraint and an unawareness of surroundings. Anesthetic dosages produces unconsciousness.

Propofol's cardiovascular effects include arterial hypotension, bradycardia, (especially in combination with opiate premedicants) and negative inotropism. It causes significant respiratory depression, particularly with rapid administration or very high dosages. Propofol also decreases intraocular pressure, increases appetite and has antiemetic properties. It does not appear to precipitate malignant hyperthermia and it has little or no analgesic properties.

**Uses/Indications** - In appropriate patients, propofol may be useful as an induction agent (especially before endotracheal intubation or an inhalant anesthetic); as an anesthetic for outpatient diagnostic or minor procedures (*e.g.,* laceration repair, radiologic procedures, minor dentistry, minor biopsies, endoscopy, etc.). Propofol may be of particular usefulness for use in Greyhounds and in patients with preexisting cardiac dysrhythmias.

To Drug Monograph Index To Ophthalmic Product Index

In dogs, propofol's labeled indications are: 1) for induction of anesthesia; 2) for maintenance of anesthesia for up to 20 minutes; 3) for induction of general anesthesia where maintenance is provided inhalant anesthetics.

**Pharmacokinetics** - After IV administration, propofol rapidly crosses the blood brain barrier and has an onset of action usually within one minute. Duration of action after a single bolus lasts about 2-5 minutes. It is highly bound to plasma proteins (95-99%), crosses the placenta, is highly lipophilic and reportedly enters maternal milk.

Propofol's short duration of action is principally due to its rapid redistribution from the CNS to other tissues. It is rapidly biotransformed in the liver via glucuronide conjugation to inactive metabolites which are then excreted primarily by the kidneys. Because cat's do not glucuronidate as well as dogs or humans, this may help explain their problems with consecutive day administration (see Adverse Effects below).

There are limited data available on propofol's pharmacokinetic parameters in dogs. The steady state volume of distribution is >3L/kg, elimination half life is about 1.4 hours and clearance is about 50 ml/kg/min.

**Contraindications/Precautions/Reproductive Safety** - Propofol is contraindicated in patients hypersensitive to it or any of component of the product. It should not be used in patients where general anesthesia or sedation are contraindicated. Propofol should only be used in facilities where sufficient monitoring and patient-support capabilities are available.

Because patients who are in shock, under severe stress or have undergone trauma may be overly sensitive to the cardiovascular and respiratory depressant effects of propofol, it should be used with caution in these patients. Adequate perfusion should be maintained before and during propofol anesthesia and dosage adjustments may be necessary.

Because propofol is so highly bound to plasma proteins, patients with hypoproteinemia may be susceptible to untoward effects. Other general anesthetic agents may be a safer choice in these patients.

The benefits of propofol should be weighed against its risks in patients with a history of hyperlipidemia, seizures or anaphylactic reactions. Cat's with preexisting liver disease may be susceptible to longer recovery times.

Propofol crosses the placenta and its safe use during pregnancy has not been established. High dosages (6 times those recommended) in laboratory animals caused increased maternal death and decreased offspring survival rates after birth.

**Adverse Effects/Warnings** - Because there is a high incidence of apnea with resultant cyanosis if propofol is given too rapidly, it should be given slowly (25% of the calculated dose every 30 seconds until desired effect).

Propofol has been documented to cause histamine release in some patients and anaphylactoid reactions (rare) have been noted in humans. Propofol has direct myocardial depressant properties and resultant arterial hypotension has been reported.

Occasionally, dogs may exhibit seizure-like symptoms (paddling, opisthotonus, myoclonic twitching) during induction, which if persist, may be treated with intravenous diazepam. Propofol may have both anticonvulsant and seizure-causing properties. It should be used with caution in patients with a history of, or active seizure disorders. However, some clinicians believe that propofol is actually better-suited to use in seizure patients or in high seizure-risk procedures (*e.g.*, myelography) than is thiopental.

To Drug Monograph Index  To Ophthalmic Product Index

While propofol is not inexpensive, it should be used in a single-use fashion as it is a good growth medium (contains no preservative) for bacteria.

When used repeatedly (once daily) in cats, increased Heinz body production, slowed recoveries, anorexia, lethargy, malaise, and diarrhea have been noted. Heinz body formation is due to oxidative injury to RBC's and has been documented in cats with other phenolic compounds as well. Consecutive use in dogs appears to be safe.

Pain upon injection has been reported in humans, but does not appear to be of major significance for dogs or cats. Extravasation of injection is not irritating nor does it cause tissue sloughing.

**Overdosage/Acute Toxicity** - Overdosages are likely to cause significant respiratory depression and potentially cardiovascular depression. Treatment should consist of propofol discontinuation, artificial ventilation with oxygen, and if necessary, symptomatic and supportive treatment for cardiovascular depression (*e.g.*, intravenous fluids, pressors, anticholinergics, etc.).

**Drug Interactions** - Propofol used in conjunction with **preanesthetic agents** (*e.g.*, **acepromazine, opiates**) may cause increased vasodilation and negative cardiac inotropy. This may be of particular concern in animals with preexisting cardiopulmonary disease, in shock, or suffering from trauma. Propofol-induced bradycardia may be exacerbated in animals receiving **opiate premedicants**, particularly when anticholinergic agents (*e.g.*, atropine) are not given concurrently. As would be logically expected, increased CNS depressant effects and recovery times may be noted in patients receiving other **CNS depressant medications** with propofol.
**Drugs that inhibit the hepatic P-450 enzyme system (*e.g.*, chloramphenicol, cimetidine**) or **other basic lipophilic drugs (*e.g.*, fentanyl, halothane)** may potentially increase the recovery times associated with propofol. Clinical significance is unclear, but in cats it may be of significance.

**Doses** -
**Dogs & Cats**:

a) As a single injection (25% of the calculated dose every 30 seconds until desired effect):
For healthy, unpremedicated animal: 6 mg/kg IV
For healthy, premedicated animal: After tranquilizer (*e.g.,* acepromazine) = 4 mg/kg IV; After sedative (*e.g.*, xylazine, opioids) = 3 mg/kg IV

As a constant infusion:
For sedation only: 0.1 mg/kg/minute
For minor surgery: 0.6 mg/kg/min, or 1 ml (10 mg) per minute per 12-25 kg of body weight (Robinson, Sanderson et al. 1993)

b) 4 - 8 mg/kg IV (Hubbell 1994)

c) 6 mg/kg IV; in healthy animals 25% of the calculated dose is administered every 30 seconds until intubation is possible. After induction, duration of anesthesia is only 2.5 - 9.4 minutes. Maintenance anesthesia obtained using either inhalational agents or a continuous infusion of propofol at approximately 0.4 mg/kg/minute. If anesthesia appears inadequate, a small bolus of 1 mg/kg followed by an increase in the infusion rate by 25%. If infusion is too deep, discontinue infusion until suitable anesthesia level is achieved. An infusion dose of 0.1 mg/kg/min appears to be suitable dose for sedation in the dog. (Ilkiw 1992)

d) As an induction agent for halothane or isoflurane anesthesia: 6.6 mg/kg IV given over 60 seconds to unpredmedicated dogs. Best achieved by early intubation and administration of the inhalant following propofol induction. (Bufalari, Miller et al. 1998)

**Monitoring Parameters** - 1) Level of anesthesia/CNS effects; 2) Respiratory depression; 3) Cardiovascular status (cardiac rate/rhythm; blood pressure)

To Drug Monograph Index  To Ophthalmic Product Index

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Propofol Injectable 10 mg/ml in 20 ml (single use) amps & vials; *Rapinovet*® (Schering); *PropoFlo*® (Abbott) (Rx). Approved for use in dogs.

**Human-Approved Products**:

Propofol Injection 10 mg/ml in 20 ml ampules and 50 & 100 ml vials for infusion; *Diprivan*® (Zeneca); (Rx)

## PROPRANOLOL HCL

**Chemistry** - A non-specific beta-adrenergic blocking agent, propranolol HCl occurs as a bitter-tasting, odorless, white to almost white powder with a $pK_a$ of 9.45 and a melting point of about 161°C. One gram of propranolol is soluble in about 20 ml of water or alcohol. At a pH from 4-5, solutions of propranolol will fluoresce. The commercially available injectable solutions are adjusted with citric acid to a pH 2.8 - 3.5.

**Storage/Stability/Compatibility** - All propranolol preparations should be stored at room temperature (15-30°C) and protected from light. Propranolol solutions will decompose rapidly at alkaline pH. Propranolol injection is reported to be compatible with D5W, 0.9% sodium chloride, or lactated Ringer's injection. It is also physically compatible with dobutamine HCl, verapamil HCl and benzquinamide HCl.

**Pharmacology** - Propranolol blocks both $beta_1$ and $beta_2$ adrenergic receptors in the myocardium, bronchi, and vascular smooth muscle. Propranolol does not have any intrinsic sympathomimetic activity (ISA). Additionally, propranolol possesses membrane-stabilizing effects (quinidine-like) affecting the cardiac action potential and direct myocardial depressant effects. Cardiovascular effects secondary to propranolol include: decreased sinus heart rate, depressed AV conduction, diminished cardiac output at rest and during exercise, decreased myocardial oxygen demand, decrease hepatic and renal blood flow, reduced blood pressure, and inhibition of isoproterenol-induced tachycardia. Electrophysiologic effects on the heart include decreased automaticity, increased or no effect on effective refractory period, and no effect on conduction velocity.

Additional pharmacologic effects of propranolol, include increased airway resistance (especially in patients with bronchoconstrictive disease), prevention of migraine headaches, increased uterine activity (more so in the non-pregnant uterus), decreased platelet aggregability, inhibited glycogenolysis in cardiac and skeletal muscle and increased numbers of circulating eosinophils.

**Uses/Indications** - While propranolol is used for hypertension, migraine headache prophylaxis and angina in human patients, it is used primarily in veterinary medicine for its antiarrhythmic effects. Dysrhythmias treated with propranolol include, atrial premature complexes, ventricular premature complexes, supraventricular premature complexes and tachyarrhythmias, ventricular or atrial tachyarrhythmias secondary to digitalis, atrial tachycardia secondary to WPW with normal QRS complexes, and atrial fibrillation (generally in combination with digoxin). Propranolol reportedly improves cardiac performance in animals with hypertrophic cardiomyopathy. It has been used to treat systemic hypertension and symptoms associated with thyrotoxicosis and pheochromocytoma.

**Pharmacokinetics** - Propranolol is well absorbed after oral administration, but a rapid first-pass effect through the liver reduces systemic bioavailability to approximately 2-27% in dogs, thereby explaining the significant difference between oral and intravenous dosages. These values reportedly increase with chronic dosing.

To Drug Monograph Index To Ophthalmic Product Index

Propranolol is highly lipid soluble and readily crosses the blood-brain barrier. The apparent volume of distribution has been reported to 3.3 - 11 L/kg in the dog. Propranolol will cross the placenta and enters milk (at very low levels). In humans, propranolol is approximately 90% bound to plasma proteins.

Propranolol is principally metabolized by the liver. An active metabolite, 4-hydroxypropranolol, has been identified after oral administration in humans. Less than 1% of a dose is excreted unchanged into the urine. The half-life in dogs has been reported to range from 0.77 - 2 hours, and in horses, less than 2 hours.

**Contraindications/Precautions** - Propranolol is contraindicated in patients with overt heart failure, hypersensitivity to this class of agents, greater than 1st degree heart block, or sinus bradycardia. Non-specific beta-blockers are generally contraindicated in patients with CHF unless secondary to a tachyarrhythmia responsive to beta-blocker therapy. They are also relatively contraindicated in patients with bronchospastic lung disease.

Propranolol should be used cautiously in patients with significant renal or hepatic insufficiency. It should also be used cautiously in patients with sinus node dysfunction.

Propranolol can mask the symptoms associated with hypoglycemia. It can also cause hypoglycemia or hyperglycemia and, therefore, should be used cautiously in labile diabetic patients.

Propranolol can mask the symptoms associated with thyrotoxicosis, but it has been used clinically to treat the symptoms associated with this condition.
Use propranolol cautiously with digitalis or in digitalis intoxicated patients; severe bradycardias may result.

**Adverse Effects/Warnings** - It is reported that adverse effects most commonly occur in geriatric animals or those that have acute decompensating heart disease. Adverse effects considered to be clinically relevant include: bradycardia, lethargy and depression, impaired AV conduction, CHF or worsening of heart failure, hypotension, hypoglycemia, and bronchoconstriction. Syncope and diarrhea have also been reported in canine patients.

Exacerbation of symptoms have been reported following abrupt cessation of beta-blockers in humans. It is recommended to withdraw therapy gradually in patients who have been receiving the drug chronically.

**Overdosage** - The most predominant symptoms expected would be hypotension and bradycardia. Other possible effects could include: CNS (depressed consciousness to seizures), bronchospasm, hypoglycemia, hyperkalemia, respiratory depression, pulmonary edema, other arrhythmias (especially AV block), or asystole.

If overdose is secondary to a recent oral ingestion, emptying the gut and charcoal administration may be considered. Monitor ECG, blood glucose, potassium, and, if possible, blood pressure. Treatment of the cardiovascular and CNS effects are symptomatic. Use fluids, and pressor agents to treat hypotension. Bradycardia may be treated with atropine. If atropine fails, isoproterenol given cautiously has been recommended. Use of a transvenous pacemaker may be necessary. Cardiac failure can be treated with a digitalis glycosides, diuretics, oxygen and, if necessary, IV aminophylline. Glucagon (5-10 mg IV - Human dose) may increase heart rate and blood pressure and reduce the cardiodepressant effects of propranolol. Seizures generally will respond to IV diazepam.

**Drug Interactions** - **Sympathomimetics** (metaproterenol, terbutaline, beta□effects of epinephrine, phenylpropanolamine, etc.) may have their actions blocked by propranolol. Additive myocardial depression may occur with the concurrent use of propranolol and myocardial depressant **anesthetic agents**. **Phenothiazines** given with propranolol may exhibit enhanced hypotensive effects. **Thyroid hormones** may decrease the effect of beta blocking agents. Propranolol doses may need to be decreased when initiating

**methimazole or propylthiouracil** therapy. **Cimetidine** may decrease the metabolism of propranolol and increase blood levels. **Furosemide and hydralazine** may increase the effects of propranolol. Effects of **tubocurarine and succinylcholine** may be enhanced with propranolol therapy. Hepatic enzyme induction by **phenobarbital, rifampin or phenytoin** may increase the metabolism of propranolol. Unopposed alpha effects of **epinephrine** may lead to rapid increases in blood pressure and decrease in heart rate when given with propranolol. Propranolol may prolong the hypoglycemic effects of **insulin** therapy. **Lidocaine** clearance may be impaired by propranolol. Effects of **theophylline** (bronchodilitation) may be blocked by propranolol. Concurrent use of beta□blockers with **calcium channel blockers** (or other negative inotropes should be done with caution; particularly in patients with preexisting cardiomyopathy or CHF.

**Doses -**
**Horses**:

a) 0.1 - 0.3 mg/kg twice a day IV administered over 1 minute (Muir and McGuirk 1987a)
b) Oral: Days 1 & 2: 175 mg *tid*; Days 3 & 4: 275 mg *tid*; Days 5 & 6: 350 mg *tid*.
Intravenous: Days 1 & 2: 25 mg *bid*; Days 3 & 4: 50 mg *bid*; Days 5 & 6: 75 mg *bid* (Hilwig 1987)

**Monitoring Parameters** -

1) ECG
2) Toxicity (see Adverse Effects/Overdosage)
3) Blood pressure if administering IV

**Client Information** - To be effective, the animal must receive all doses as prescribed. Notify veterinarian if animal becomes lethargic or becomes exercise intolerant, begins wheezing, has shortness of breath or cough, or develops a change in behavior or attitude.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Propranolol HCl Tablets 10 mg, 20 mg, 40 mg, 60 mg, 80 mg, 90 mg; *Inderal*® (Wyeth-Ayerst), Generic; (Rx)

Propranolol HCl Extended/Sustained-Release capsules 60 mg, 80 mg, 120 mg, 160 mg; *Inderal*® *LA* (Wyeth-Ayerst); *Betachron E-R*® (Inwood); generic, (Rx)

Propranolol for Injection 1 mg/ml in 1 ml amps or vials; *Inderal*® (Wyeth-Ayerst) (Rx), Generic; (Rx)

Propranolol Oral Solution 4 mg/ml, 8 mg/ml, 80 mg/ml concentrate in 30 ml; *Propranolol Intensol*® (Roxane); *Propranolol HCl*® (Roxane) (Rx)

Also, fixed dose combination products containing propranolol and hydrochlorothiazide are available to treat hypertension in humans.

**Prostaglandin F2 alpha - see Dinoprost**

## PSYLLIUM HYDROPHILIC MUCILLOID

**Chemistry** - Psyllium is obtained from the ripe seeds of varieties of *Plantago* species. The seed coating is high in content of hemicellulose mucillages which absorb and swell in the presence of water.

**Storage/Stability/Compatibility** - Store psyllium products in tightly closed containers; protect from excess moisture or humidity.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - By swelling after absorbing water, psyllium increases bulk in the intestine and is believed to induce peristalsis and decrease intestinal transit time. In the treatment of sand colic in horses, psyllium is thought to help collect sand and to help lubricate its passage through the GI tract.

**Uses/Indications -** Bulk forming laxatives are used in patients where constipation is a result a too little fiber in their diets or when straining to defecate may be deleterious. Psyllium is considered to be the laxative of choice in the treatment and prevention of sand colic in horses.

Psyllium has also been used to increase stool consistency in patients with chronic, watery diarrhea. The total amount of water in the stool remains unchanged.

**Pharmacokinetics** - Psyllium is not absorbed when administered orally. Laxative action may take up to 72 hours to occur.

**Contraindications/Precautions** - Bulk-forming laxatives should not be used in cases where prompt intestinal evacuation is required, or when fecal impaction (no feces being passed) or intestinal obstruction is present.

**Adverse Effects/Warnings** - With the exception of increased flatulence, psyllium very rarely produces any adverse reactions if adequate water is given or is available to the patient. If insufficient liquid is given, there is an increased possibility of esophogeal or bowel obstruction occurring.

**Overdosage** - If administered with sufficient liquid, psyllium overdose should cause only an increased amount of soft or loose stools.

**Drug Interactions** - Because the potential exists for bulk-forming laxatives to bind **digoxin, salicylates and nitrofurantoin**, it is recommended that bulk-forming laxatives be administered at least 3 hours apart from these drugs.

**Doses** -
**Horses**:

For treatment of sand colic:

a) 0.5 kg in 6-8 L (1 pound in 1.5-2 gallons) of water via stomach tube. Mix with water just before administration; simultaneously mixing water with psyllium as mixture is being pumped is ideal. May repeat as necessary as long as horse continues to pass feces and fluid does not accumulate in stomach. After initial treatment, may add up to 125 gm with each feeding; best if mixed with grain or sweet feed. Water must be available. (Calahan 1987)
b) 0.25 kg mixed in 8 L of warm water *bid*. After obstruction is resolved may add to grain ration; may require 2-3 weeks of therapy to eliminate the majority of sand. (Clark and Becht 1987)

**Monitoring Parameters** -

1) Stool consistency, frequency

**Client Information** - Contact veterinarian if patient begins vomiting. Be sure animal has free access to water.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

*Equi-Psyllium*® (Equine Healthcare) is a product labeled for use in horses. It is available in 5 lb. jars.

To Drug Monograph Index To Ophthalmic Product Index

**Human-Approved Products**: There are many human-approved products containing psyllium, most products contain approximately 3.4 grams of psyllium per rounded teaspoonful. Commonly known products include: *Metamucil*® (Procter & Gamble), *Hydrocil*® *Instant* (Reid-Rowell), *Correctol*® *Powder* (Plough), *Konsyl*® (Lafayette), *Serutan* (Beecham), *Effer-syllium*® (Stuart), *Perdiem*® *Plain* (Rorer), and *Siblin*® (Warner-Lambert). These products are all OTC.

## PYRANTEL PAMOATE
## PYRANTEL TARTRATE

**Chemistry** - A pyrimidine-derivative anthelmintic, pyrantel pamoate occurs as yellow to tan solid and is practically insoluble in water and alcohol. Pyrantel tartrate is more water soluble than is the pamoate salt. Each gram of pyrantel pamoate is approximately equivalent to 347 mg (34.7%) of the base. Pyrantel pamoate may also be known as pyrantel embonate.

**Storage/Stability/Compatibility** - Pyrantel pamoate products should be stored in tight, light-resistant containers at room temperature (15-30°C) unless otherwise directed by the manufacturer.

**Pharmacology** - Pyrantel acts as a depolarizing neuromuscular blocking agent in susceptible parasites, thereby paralyzing the organism. The drug possesses nicotine-like properties and acts similarly to acetylcholine. It also inhibits cholinesterase.

**Uses/Indications** - Pyrantel has been used for the removal of the following parasites in **dogs**: ascarids (*Toxocara canis, T. leonina*), hookworms *(Ancylostoma caninum, Uncinaria stenocephala)* and stomach worm *(Physaloptera).* Although not approved for use in **cats**, it is useful for similar parasites and is considered to be safe to use.

Pyrantel is indicated (labeled) for the removal of the following parasites in **horses**: *Strongylus vulgaris* and *equinus., Parasacaris equorum,* and *Probstymayria vivapara.* It has variable activity against *Oxyuris equi.*, *S. edentatus* and small strongyles. Pyrantel is active against ileocecal tapeworm (*A. perfoliata*) when used at twice the recommended dose.

Although there are apparently no pyrantel products approved for use in **cattle**, **sheep**, or **goats**, the drug is effective (as the tartrate) for the removal of the following parasites: *Haemonchus spp., Ostertagia spp., Trichostrongylus spp., Nematodirus spp., Chabertia spp., Cooperia spp. and Oesophagostomum spp.*.

Pyrantel tartrate is indicated (labeled) for the removal or prevention of the following parasites in **swine**: large roundworms (*Ascaris suum*) and *Oesophagostomum spp.*. The drug also has activity against the swine stomach worm (*Hyostrongylus rubidus*).

Although not approved, pyrantel has been used in **pet birds** and **llamas**. See the Dosage section for more information.

**Pharmacokinetics** - Pyrantel pamoate is poorly absorbed from the GI tract, thereby allowing it to reach the lower GI in dogs, cats and equines. Pyrantel tartrate is absorbed more readily than the pamoate salt. Pigs and dogs absorb pyrantel tartrate more so than do ruminants, with peak plasma levels occurring 2-3 hours after administration. Peak plasma levels occur at highly variable times in ruminants. Absorbed drug is rapidly metabolized and excreted into the urine and feces.

To Drug Monograph Index  To Ophthalmic Product Index

**Contraindications/Precautions/Usage in Pregnancy** - Use with caution in severely debilitated animals. The manufacturers usually recommend not administering the drug to severely debilitated animals. Pyrantel is considered to be safe to use during pregnancy and in nursing animals.

**Adverse Effects/Warnings** - When administered at recommended doses, adverse effects are unlikely. Emesis may occur however, in small animals receiving pyrantel pamoate.

**Overdosage/Acute Toxicity** - Pyrantel has a moderate margin of safety. Dosages up to approximately 7 times recommended generally result in no toxic reactions. In horses, doses of 20 times those recommended yielded no adverse effects. The $LD_{50}$ in mice and rats for pyrantel tartrate is 170 mg/kg and is >690 mg/kg for pyrantel pamoate in dogs.

Chronic dosing of pyrantel pamoate in dogs resulted in symptoms when given at 50 mg/kg/day, but not at 20 mg/kg/day over 3 months. Symptoms of toxicity that could possibly be seen include increased respiratory rates, profuse sweating (in animals able to do so), ataxia or other cholinergic effects.

**Drug Interactions** - Because of similar mechanisms of action (and toxicity), pyrantel is recommended not to be used concurrently with **morantel** or **levamisole**. Observation for adverse effects should be intensified if used concomitantly with an **organophosphate** or **diethylcarbamazine**. **Piperazine** and pyrantel have antagonistic mechanisms of action; do not use together.

**Doses** -
All doses are for pyrantel pamoate unless otherwise noted. **Caution**: Listed dosages are often not specified as to whether using the salt or base.
**Horses**:

For susceptible parasites:

a) 6.6 mg (as base)/kg PO; 13.2 mg (as base)/kg for cestodes. (Robinson 1987), (Roberson 1988b)
b) 19 mg/kg PO (Brander, Pugh, and Bywater 1982)
c) Pyrantel tartrate: 12.5 mg/kg PO (Roberson 1988b)

**Client Information** - Shake suspensions well before administering

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Pyrantel Pamoate Tablets 22.7 mg (of base), 113.5 mg (of base); *Nemex® Tabs* (Pfizer); (OTC) Approved for use in dogs.

Pyrantel Pamoate Oral Suspension; 2.27 mg/ml (as base)(for dogs only), 4.54 mg/ml (of base); *Nemex®-2* (Pfizer); RFD Liquid Wormer® (Pfizer) (OTC) Approved for use in dogs & cats.

Pyrantel Pamoate Oral Suspension 50 mg/ml (of base); *Strongid® T* (Pfizer); (OTC) Approved for use in horses not intended for food.

Pyrantel Pamoate Oral Paste 43.9% w/w pyrantel base in 23.6 g (20 ml) paste (180 mg pyrantel base/ml); *Strongid® Paste* (Pfizer); (OTC) Approved for use in horses not intended for food.

**Human-Approved Products**:

Pyrantel Pamoate Oral Suspension or liquid 50 mg/ml (base) in 30 & 60 ml; *Antiminth®* (Pfizer) (OTC); *Reese's Pinworm®* (Reese) (OTC); *Pin-Rid®* (Apothecary) (OTC);*Pin-X®* (Effcon) (OTC)

Pyrantel Capsules 180 mg (equivalent to 62.5 mg pyrantel base); *Pin-Rid®* (Apothecary) (OTC); Reese's Pinworm® (Reese) (OTC)

To Drug Monograph Index To Ophthalmic Product Index

## PYRAZINAMIDE * PK ADVERSE EFFECT REPORTED

The following section was authored by Joel Maslow MD PhD MBA

**Chemistry** - Pyrazinamide (PZA) is a synthetic analog of nicotinamide and occurs as a white crystalline powder. It is only slightly soluble in water or alcohol. PZA has a pKa of 0.5.

**Storage/Stability/Compatibility** –PZA is stable at room temperature (15-30ºC) in tablet and powder form.

**Mechanism of action** – The mechanism of action of PZA is unknown; its action may be through inhibition of cell wall biosynthesis.

**Uses/Indications** – PZA is indicated for the treatment of *M. tuberculosis* infection; *M. bovis* is inherently resistant to PZA since it does not express a pyrazinamidase and cannot activate PZA to its active form. It is bacteriocidal against these organisms. PZA should only be used in conjunction with other anti-mycobacterial agents to avoid the development of bacterial resistance.

**Pharmacokinetics** –

PZA is only available for oral administration. It is absorbed well from the gastrointestinal tract in humans with >98% bioavailability. Serum concentrations range between 30-50 mcg/ml with doses of 20-25 mg/kg. Peak serum concentrations occur at approximately 2 hr with a half life of 7 hrs. PZA reaches CSF concentrations equivalent to serum levels with inflamed meninges. PZA has excellent intracellular penetration and is active at an acid pH (5.5) of the phagosome.

PZA is metabolized by the liver. PZA and metabolites are excreted by the kidneys requiring dose adjustments in renal failure.

PZA is well absorbed orally and rectally (via enema) in elephants (Maslow JN, unpublished observations). PZA administered rectally at a dose of 25-30 mg/kg achieved serum concentrations of 5.5-17.1 mcg/ml. Peak serum concentrations and serum half life were 1.5-2 hrs and 7 hrs, respectively. PZA given as an oral bolus yielded serum concentrations of 18.1-29.1 mcg/ml with similar absorption and elimination kinetics. Administration of PZA with food decreased bioavailability with Cmax between 2.3-19.9 mcg/ml and increased absportion kinetics with a Tmax of 4.5 hrs. Elimination also appeared to be altered and was decreased to 4.5 hrs.

PZA has been successfully administered orally and subcutaneously to bongo antelope (Auclair, 2002). A single oral dose of 50 mg/kg yielded a 5.9 mcg/ml (CV%, 62.3) and Tmax of 5 hrs. A single s.c. dose of 50 mg/kg yielded a Cmax of 16.8 mcg/ml (CV%, 12.5) with a Tmax of 3.5 hrs and a serum half-life of 2.85 hrs.

**Contraindications/Precautions/Reproductive Safety** – Teratogenic studies have not been performed for PZA. The CDC recommends that PZA be used in pregnancy when the benefits outweigh the potential risks. PZA is distributed in breast milk.

**Pediatric use** – although PZA is not approved for use in children, it is generally accepted that the drug is well tolerated in children.

**Adverse Effects/Warnings** – PZA may cause gastrointestinal upset in humans. Hepatotoxicity is common in humans at high dose (50 mg/kg) but uncommon at doses typically used (20-35 mg/kg). PZA can

To Drug Monograph Index To Ophthalmic Product Index

decrease urate excretion with the possibility of hyperuricemia and gouty arthritis. PZA has also caused photosensitive rashes in humans.

PZA has been well tolerated in bongo antelope **Population pharmacokinetics of antituberculous drugs and treatment of *Mycobacterium bovis* infection in Bongo Antelope (*Tragelaphus eurycrus isaaci* ).** B. Auclair, S. Mikota, C. A. Peloquin, R. Aguilar and J. N. Maslow. Journal of Zoo and Wildlife Medicine 2002 Vol. 33 Issue 3 Pages 193-203.

**Drug Interactions** – There are no known drug interactions with PZA.

**Doses** –
**Human dosing**:
The initial human dose of ethambutol is 20-35 mg/kg per day given as a single daily dose. PZA is typically included as initial treatment of *M. tuberculosis* as part of 3 and 4-drug regimens. PZA serum concentrations of 20-60 mcg/ml are associated with successful treatment of *M. tuberculosis* in humans (Peloquin, 1997). After a 2-month induction period of treatment of susceptible strains, PZA is eliminated from the regimen.

**Bongo antelope:**
An initial dose of 50 mg/kg given subcutaneously is recommended. While PZA can be administered to bongo antelope, doses approaching 150 mg/kg may be necessary to achieve target concentrations. Serum concentrations should be determined at 2 hrs after administration.

**Monitoring –** In general serum concentrations should be monitored at 2 hrs after oral or subcutaneous administration to bongo antelope and 2 hrs after oral bolus and rectal enema dosing to elephants. Serum concentrations should be determined at 3-4 hrs after oral dosing to elephants when PZA is administered with food. Based on studies in humans, a serum concentration of 20-60 mcg/ml is associated with therapeutic success (Peloquin, 1997).

**Elephants:**

**a) Adverse effect:** In one elephant under treatment for tuberculosis, a low grade anemia was observed when INH and pyrazinamide were administered rectally 4 times weekly. The anemia resolved when the INH dose was decreased from 3.75 to 2.5 mg/kg and the PZA dose was decreased from 35 to 25 mg/kg (Mikota et.al. 2001). Author's (Mikota) note: It is likely that the anemia was caused by the INH rather than by pyrazinamide. Mikota,S.K., Peddie,L., Peddie,J., Isaza,R., Dunker,F., West,G., Lindsay,W., Larsen,R.S., Salman,M.D., Chatterjee,D., Payeur,J., Whipple,D., Thoen,C., Davis,D.S., Sedgwick,C., Montali,R.J., Ziccardi,M., and Maslow,J. 2001. **Epidemiology and diagnosis of Mycobacterium tuberculosis in captive Asian elephants (Elephas maximus)**. Journal of Zoo and Wildlife Medicine 32:(1):1-16

b) An initial dose of 25 mg/kg given orally as a freshly suspended powder achieves serum concentrations considered therapeutic (see below). Rectal enema dosing and oral administration with food may require doses of 100 mg/kg to achieve serum concentrations considered therapeutic. Drug levels should be determined 2 hrs after oral bolus and rectal enema dosing and 3-4 hrs following oral dosing with food.

**Population pharmacokinetics of pyrazinamide in elephants. 2005.** M. Zhu, J. N. Maslow, S. K. Mikota, R. Isaza, F. Dunker, H. Riddle, et al. J. Vet. Pharmacol. Ther Vol. 28 Issue 5 Pages 403-409. DOI: JVP670 [pii];10.1111/j.1365-2885.2005.00670.x [doi]

Full article here: https://d1wqtxts1xzle7.cloudfront.net/49414258/j.1365-2885.2005.00670.x20161006-982-iwa68z-libre.pdf?1475805024=&response-content-disposition=inline%3B+filename%3DPopulation_pharmacokinetics_of_pyrazinam.pdf&Expires=1693239256

To Drug Monograph Index To Ophthalmic Product Index

&Signature=a6DmzAdSZXYrK~hG~3rpASlZYOePOEl8xG3hWSGuFUevqDMXTjM5LErKLKmuRAwQbOzQ~Whr-dnF~igt9CzQBkU8sdewoQcOXOswCGBEljgJBicQaoh~toqr1pKCuIUT--0n3-eoVlhaiYaazw8Qno3BcVuNXOI3cpg~zLSU9kl4yEgNt9uipTO0Ydy0cuqauMdQlvKfqOdnGNtZ0A~GAe9hS6Y5NFf3SgaKw1ZOzujdtOfQuVY7EdgYflV7S2Kujk6HAwg0GecykeXaK5p1HOA54Rn7sm3DRFtETGGOxXvfV6y35G3YoIq2wkwYl1exvBxFHC~-b967HgeCMOqoSA__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA

This study was undertaken to characterize the population pharmacokinetics (PK), therapeutic dose, and preferred route of administration for pyrazinamide (PZA) in elephants. Twenty-three African (Loxodonta africana) and Asian (Elephas maximus) elephants infected with or in contact with others culture positive for Mycobacterium tuberculosis were dosed under treatment conditions. PZA was dosed daily at 20-30 mg/kg via oral (fasting or nonfasting state) or rectal (enema or suppository) administration. Blood samples were collected 0-24 h postdose. Population PK was estimated using nonlinear mixed effect modeling. Drug absorption was rapid with T(max) at or before 2 h regardless of the method of drug administration. C(max) at a mean dose of 25.6 (+/-4.6) mg/kg was 19.6 (+/-9.5 microg/mL) for PZA given orally under fasting conditions. Under nonfasting conditions at a mean dose of 26.1 +/- 4.2 mg/kg, C(max) was 25% (4.87 +/- 4.89 microg/mL) and area under concentration curve (AUC) was 30% of the values observed under fasting conditions. Mean rectal dose of 32.6 +/- 15.2 mg/kg yielded C(max) of 12.3 +/- 6.3 microg/mL, but comparable AUC to PZA administered orally while fasting. Both oral and rectal administration of PZA appeared to be acceptable and oral dosing is preferred because of the higher C(max) and lower inter-subject variability. A starting dose of 30 mg/kg is recommended with drug monitoring between 1 and 2 h postdose. Higher doses may be required if the achieved C(max) values are below the recommended 20-50 microg/mL range.

**c) The pharmacokinetics of a single oral or rectal dose of concurrently administered isoniazid, rifampin, pyrazinamide, and ethambutol in Asian elephants (Elephas maximus).**
2014. A. P. Brock, R. Isaza, E. F. Egelund, R. P. Hunter and C. A. Peloquin. Journal of Veterinary Pharmacology and Therapeutics Vol. 37 Issue 5 Pages 472-479.
Accession Number: WOS:000342801400007 DOI: 10.1111/jvp.12119

Tuberculosis, caused by Mycobacterium tuberculosis, is a disease of concern in captive Asian elephants (Elephas maximus). Treatment for tuberculosis in elephants utilizes multidrug protocols combining isoniazid, rifampin, pyrazinamide, and/or ethambutol. In this study, a single, coformulated dose of isoniazid 5mg/kg, rifampin 10mg/kg, pyrazinamide 30mg/kg, and ethambutol 30mg/kg was administered orally to six Asian elephants, and rectally to five elephants using a cross-over design. Blood samples were collected serially over 24h. Pyrazinamide and ethambutol concentrations were determined using validated gas chromatography assays. Isoniazid and rifampin concentrations were determined using validated high-performance liquid chromatography assays. Rectal isoniazid produced an earlier T-max compared with oral administration. Oral isoniazid resulted in a comparatively lower C-max, but higher AUC values compared with rectal isoniazid. Oral rifampin and oral ethambutol were well absorbed while rectal rifampin was not. Oral pyrazinamide produced comparatively higher C-max and AUC values compared with rectal pyrazinamide. Results of this study indicate that currently recommended therapeutic monitoring sample collection times for rectal isoniazid and oral rifampin do not provide an accurate assessment of exposure for these drugs. This study demonstrates notable individual variability, indicating that dosing of these medications requires individual monitoring and provides additional information to guide the clinician when treating elephants.

**d) Serum concentrations of antimycobacterial drugs in Asian Elephants (Elephas maximus).** 2016. L. Young, S. Scott, M. Salfinger and E. Ramsay. Proc. AAZV / EAZWV / IZW Joint Conference 2016

Mycobacterium tuberculosis is an important disease of captive Asian elephants (Elephas maximus.) In this study six adult Asian elephants which had Mycobacterium tuberculosis cultured from trunk wash samples or had reactive DPP/MAPIA serologic responses were treated, concurrently, with one to three

To Drug Monograph Index To Ophthalmic Product Index

antimycobacterial drugs. Enrofloxacin hydrochloride, 2.5 mg/kg p.o., s.i.d., was administered to all animals in various foodstuffs for 9-15 mo. Serum enrofloxacin concentrations ranged from 230-2380 µg/ml (targeted concentrations = 125-1000 µg/ml).1 Pyrazinamide (PZA), 30 mg/kg p.o., s.i.d., was administered to five elephants in various foodstuffs for 9-12 mo. Serum PZA concentrations ranged from 26-57 µg/ml (targeted concentrations = 20- 60 µg/ml).2 Ethambutol (EMB), 30 mg/kg p.o., s.i.d., was administered to one elephant for 12 mo. A serum EMB concentration of 4.07 µg/ml was achieved (targeted concentration = 2-6 µg/ml).2 Rifampin (RIF), 10 mg/kg p.o., s.i.d., was administered to one elephant for 9 mo. A serum RIF concentration of 16 µg/ml was achieved (targeted concentration = 8-24 µg/ml). All elephants were monitored for adverse clinical effects throughout treatments. Notable side effects were limited to excess, foamy lacrimation, believed to have occurred secondary to PZA administration. Clinical chemistries and complete blood counts were monitored in all animals and values remained within reference intervals throughout treatments. This study shows antimycobacterial drug dosages may require individuation, but concurrent, long-term, multidrug regimens for the treatment of Mycobacterium tuberculosis in Asian elephants can achieve appropriate therapeutic levels with minimal detrimental side effects.

Also see:
Using therapeutic drug monitoring to dose the antimycobacterial drugs. C. Peloquin.
Clinics in Chest Medicine 1997 Vol. 18 Pages 79-97

Clinical pharmacology of the anti-tuberculoisis drugs. C. A. Peloquin.In: Clinical Tuberculosis, edited by P. D. O. Davies. Arnold Publishers 2003

Tuberculosis treatment protocols and complications for elephants. G. Dumonceaux and S. Mikota. Proceedings International Elephant Conservation and Research Symposium 2006 Pages 84-85. Request full paper from smikota@elephantcare.org.

## PYRILAMINE MALEATE

**Chemistry** - An ethylenediamine antihistamine, pyrilamine maleate occurs as a white, crystalline powder with a melting range of 99-103°. One gram is soluble in approximately 0.5 ml of water or 3 ml alcohol.

**Storage/Stability/Compatibility** - Avoid freezing the injectable product.

**Pharmacology** - Antihistamines ($H_1$-receptor antagonists) competitively inhibit histamine at $H_1$ receptor sites. They do not inactivate, nor prevent the release of histamine, but can prevent histamine's action on the cell. Besides their antihistaminic activity, these agents also have varying degrees of anticholinergic and CNS activity (sedation). Pyrilamine is considered to be less sedating and have much less anticholinergic effects when compared to most other antihistamines.

**Uses/Indications** - Antihistamines are used in veterinary medicine to reduce or help prevent histamine mediated adverse effects.

**Pharmacokinetics** - The pharmacokinetics of this agent have apparently not been extensively studied.

**Contraindications/Precautions** - The manufacturer indicates that the use of this product "should not supercede the use of other emergency drugs and procedures."

**Adverse Effects/Warnings** - Adverse effects in horses can include CNS stimulation (nervousness, insomnia, convulsions, tremors, ataxia), palpitation, GI disturbances, CNS depression (sedation), muscular weakness, anorexia, lassitude and incoordination.

To Drug Monograph Index  To Ophthalmic Product Index

**Overdosage** - Treatment of overdosage is basically supportive and symptomatic. The manufacturer (Schering - *Histavet-P*®) suggests using "careful titration" of barbiturates to treat convulsions, and analeptics (caffeine, ephedrine, or amphetamines) to treat CNS depression. Most toxicologists however, recommend avoiding the use of CNS stimulants in the treatment of CNS depressant overdoses. Phenytoin (IV) is recommended in the treatment of seizures caused by antihistamine overdose in humans; barbiturates and diazepam are to be avoided.

**Drug Interactions** - Increased sedation can occur if diphenhydramine is combined with **other CNS depressant drugs**. Antihistamines may partially counteract the anticoagulation effects of **heparin** or **warfarin**. Pyrilamine may enhance the effects of **epinephrine**.

**Laboratory Interactions** - Antihistamines can decrease the wheal and flare response to **antigen skin testing**. In humans, it is suggested that antihistamines be discontinued at least 4 days before testing.

**Doses -**
**Horses**:

a) 0.88 - 1.32 mg/kg (2-3 mls of 20 mg/ml solution per 100 lbs body weight) IV (slowly), IM or SQ; may repeat in 6-12 hours if necessary. Foals: 0.44 mg/kg (1 ml of 20 mg/ml solution per 100 lbs. body weight) IV (slowly), IM or SQ; may repeat in 6-12 hours if necessary. (Package Insert; *Histavet-P*® - Schering)
b) 1 mg/kg IV, IM or SQ (Robinson 1987)
c) 0.5 -1.5 grams IM (Swinyard 1975)

**Monitoring Parameters** -

1) Clinical efficacy and adverse effects

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Pyrilamine Maleate Injection 20 mg/ml; 100 ml vial; *Histavet-P*® (Schering); (Rx) Approved for use in horses not intended for food only.

**Human-Approved Products**:

Pyrilamine Maleate Tablets 25 mg; Generic; (Rx/OTC)

## PYRIMETHAMINE

**Chemistry** - An aminpyrimidine agent structurally related to trimethoprim, pyrimethamine occurs as an odorless, white, or almost white, crystalline powder or crystals. It is practically insoluble in water and slightly soluble in alcohol.

**Storage/Stability/Compatibility** - Pyrimethamine tablets should be stored in tight, light-resistant containers. Pyrimethamine tablets may be crushed to make oral suspensions of the drug. Although stable in an aqueous solution, sugars tend to adversely affect the stability of pyrimethamine. If cherry syrup, corn syrup, or sucrose-containing liquids are used in the preparation of the suspension, it is recommended to store the suspension at room temperature and discard after 7 days.

**Pharmacology** - Pyrimethamine is a folic acid antagonist similar to trimethoprim. It acts by inhibiting the enzyme, dihydrofolate reductase that catalyzes the conversion of dihydrofolic acid to tetrahydrofolic acid.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - In veterinary medicine, pyrimethamine is used to treat (often in combination with sulfonamides) toxoplasmosis in small animals. In horses, it is used to treat equine protozoal myeloencephalitis, sometimes called equine toxoplasmosis.

In humans, pyrimethamine is used for the treatment of toxoplasmosis and as a prophylactic agent for malaria.

**Pharmacokinetics** - No pharmacokinetic data was located for veterinary species. In humans, pyrimethamine is well absorbed from the gut after oral administration. It is distributed primarily to the kidneys, liver, spleen and lungs, but does cross the blood-brain barrier. It has a volume of distribution of about 3 L/kg and is 80% bound to plasma proteins. Pyrimethamine enters milk in levels greater than those found in serum and is detected in milk for up to 48 hours after dosing.

In humans, the plasma half-life is approximately 3-5 days. It is unknown how or where the drug is metabolized, but metabolites are found in the urine.

**Contraindications/Precautions/Reproductive Safety** - Pyrimethamine is contraindicated in patients hypersensitive to it and should be used cautiously in patients with preexisting hematologic disorders. Pyrimethamine has been demonstrated to be teratogenic in rats. However, it has been used in treating women with toxoplasmosis during pregnancy. Clearly, the risks associated with therapy must be weighed against the potential for toxicity, the severity of the disease, and any alternative therapies available (*e.g.,* clindamycin in small animals). Concomitant administration of folinic acid has been recommended if the drug is to be used during pregnancy.

**Adverse Effects/Warnings** - In small animals, anorexia, malaise, vomiting, depression and bone marrow depression (anemia, thrombocytopenia, leukopenia) have been seen. Adverse effects may be more prominent in cats and may be noted 4-6 days after starting combination therapy. Hematologic effects can develop rapidly and frequent monitoring is recommended, particularly if therapy persists longer than 2 weeks. Oral administration of folinic acid at 1 mg/kg PO, folic acid 5 mg/day, or Brewer's yeast 100 mg/kg/day have been suggested to alleviate adverse effects.

The drug is unpalatable to cats when mixed with food and the 25 mg tablet dosage size makes successful dosing a challenge.

In horses, pyrimethamine when used in combination with sulfonamides has caused leukopenias, thrombocytopenia and anemias. Baker's yeast or folinic acid have been suggested to be used to antagonize these adverse effects.

**Overdosage/Acute Toxicity** - Reports of acute overdosage of pyrimethamine in animals was not located. In humans, vomiting, nausea, anorexia, CNS stimulation (including seizures) and hematologic effects can be seen. Recommendations for treatment include: standard procedures in emptying the gut or preventing absorption, parenteral barbiturates for seizures, folinic acid for hematologic effects and long-term monitoring (at least 1 month) of renal and hematopoietic systems.

**Drug Interactions** - Pyrimethamine is synergistic with **sulfonamides** in activity against toxoplasmosis (and malaria). ***p*-aminobenzoic acid (PABA)** is reportedly antagonistic towards the activity of pyrimethamine; clinical significance is unclear. Use of pyrimethamine with **trimethoprim/sulfa** is not recommended (in humans) as adverse effects may be additive, but this combination has been used clinically in horses.

**Doses -**
**Horses**:
For equine protozoal myeloencephalitis:

To Drug Monograph Index To Ophthalmic Product Index

a) Pyrimethamine 0.1 - 0.2 mg/kg PO once daily, with trimethoprim/sulfadiazine 15 mg/kg PO *bid*. Dosage may be continued for up to 2 months. Reinstitute therapy if animal is stressed; long-term intermittent therapy may be rational. Guarded prognosis; relapses are not uncommon. (Brewer 1987) (**NOTE**: Since this reference was published, pyrimethamine dosage is now more commonly given at 1 mg/kg PO once daily—Plumb; March 1999)

**Monitoring Parameters** -
1)See adverse effects; CBC with platelet count 2)Clinical efficacy

**Client Information** - Clients should he instructed to monitor for symptoms of abnormal bleeding, lassitude, etc. that may signal development of hematologic disorders. Accurate dosing of the tablets in cats may be very difficult as only 25 mg tablets are commercially available. Preferably, custom prepared capsules containing the accurate dosage should be prepared.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**
Pyrimethamine Tablets 25 mg; *Daraprim*® (Glaxo Wellcome); (Rx)

## QUINIDINE GLUCONATE
## QUINIDINE POLYGALACTURONATE
## QUINIDINE SULFATE

**Chemistry** - Used as an antiarrhythmic agent, quinidine is an alkaloid obtained from *cinchona* or related plants, or is prepared from quinine. It is available commercially in three separate salts: gluconate, polygalcturonate, or sulfate. Quinidine gluconate occurs as a very bitter tasting, odorless, white powder. It is freely soluble in water and slightly soluble in alcohol. The injectable form has a pH of 5.5-7. Quinidine polygalcturonate occurs as a bitter tasting, creamy white, amorphous powder. It is sparingly soluble in water and freely soluble in hot 40% alcohol.
Quinidine sulfate occurs as very bitter tasting, odorless, fine, needle-like, white crystals that may cohere in masses. One gram is soluble in approximately 100 ml of water or 10 ml of alcohol.

**Storage/Stability/Compatibility** - All quinidine salts darken upon exposure to light (acquire a brownish tint) and should be stored in light-resistant, well-closed containers. Use only colorless, clear solutions of quinidine gluconate for injection.

Quinidine gluconate injection is usually administered intramuscularly, but may be given very slowly (1 ml/minute) intravenously. It may be diluted by adding 10 to 40 ml of $D_5W$. Quinidine gluconate is reported to be **compatible** with bretylium tosylate, cimetidine HCl, and verapamil HCl. It is reportedly **incompatible** with alkalies and iodides.

**Pharmacology** - A class IA antiarrhythmic, quinidine has effects similar to that of procainamide. It depresses myocardial excitability, conduction velocity and contractility. Quinidine will prolong the effective refractory period, which prevents the reentry phenomenon and increases conduction times. Quinidine also possesses anticholinergic activity which decreases vagal tone and may facilitate AV conduction.

**Uses/Indications** - Quinidine is indicated in small animal or equine medicine for the treatment of ventricular arrhythmias (VPC's, ventricular tachycardia), refractory supraventricular tachycardias, supraventricular

arrhythmias associated with anomalous conduction in Wolff-Parkinson-White (WPW) syndrome, and acute atrial fibrillation. Oral therapy is generally not used in cats.

**Pharmacokinetics** - After oral administration, quinidine salts are nearly completely absorbed from the GI. However, the actual amount that reaches the systemic circulation will be reduced due to the hepatic first-pass effect. The extended-release formulations of quinidine sulfate and gluconate, as well as the polygalacturonate tablets, are more slowly absorbed than the conventional tablets or capsules.

Quinidine is distributed rapidly to all body tissues except the brain. Protein binding varies from 82-92%. The reported volumes of distribution in various species are: horses ≈ 15.1 L/kg, cattle ≈ 3.8 L/kg; dogs ≈ 2.9 L/kg; cats ≈ 2.2 L/kg. Quinidine is distributed into milk and crosses the placenta.

Quinidine is metabolized in the liver, primarily by hydroxylation. Approximately 20% of a dose may be excreted unchanged in the urine within 24 hours after dosing. Serum half-lives reported in various species are: horses ≈ 8.1 hours; cattle ≈ 2.3 hours; dogs ≈ 5.6 hours; cats ≈ 1.9 hours; swine ≈ 5.5 hours; goats ≈ 0.9 hours. Acidic urine (pH < 6) can increase renal excretion of quinidine and decrease its serum half-life.

**Contraindications/Precautions** - Quinidine is generally contraindicated in patients who have demonstrated previous hypersensitivity reactions to it; myasthenia gravis; complete AV block with an AV junctional or idioventricular pacemaker; intraventricular conduction defects (especially with pronounced QRS widening); digitalis intoxication with associated arrhythmias or AV conduction disorders; aberrant ectopic impulses; or abnormal rhythms secondary to escape mechanisms. It should be used with extreme caution, if at all, in any form of AV block or if any symptoms of digitalis toxicity are exhibited.

Quinidine should be used with caution in patients with uncorrected hypokalemia, hypoxia, and disorders or acid-base balance. Use cautiously in patients with hepatic or renal insufficiency as accumulation of the drug may result.

**Adverse Effects/Warnings** - In dogs, gastrointestinal effects may include anorexia, vomiting, or diarrhea. Effects related to the cardiovascular system can include weakness, hypotension (especially with too rapid IV administration), negative inotropism, widened QRS complex and QT intervals, AV block, and multiform ventricular tachycardias hypotension.

Horses may exhibit swelling of the nasal mucosa, laminitis, GI distress, and the development of urticarial wheals. Horses may also develop cardiac arrhythmias including AV block, circulatory collapse and sudden death.

Patients exhibiting signs of toxicity or lack of response may be candidates for therapeutic serum monitoring. The therapeutic range is thought to be 2.5 - 5.0 micrograms/ml in dogs. Toxic effects usually are not seen unless levels are >10 micrograms/ml.

**Overdosage** - Symptoms of overdosage can include depression, hypotension, lethargy, confusion, seizures, vomiting, diarrhea and oliguria. Cardiac signs may include depressed automaticity and conduction, or tachyarrhythmias. The CNS effects are often delayed after the onset of cardiovascular effects but may persist after the cardiovascular effects have begun to resolve.

If a recent oral ingestion, emptying of the gut and charcoal administration may be beneficial to remove any unabsorbed drug. IV fluids, plus metaraminol or norepinephrine can be considered to treat hypotensive effects. A 1/6 molar intravenous infusion of sodium lactate may be used in an attempt to reduce the cardiotoxic effects of quinidine. Forced diuresis using fluids and diuretics along with reduction of urinary pH, may enhance the renal excretion of the drug. Temporary cardiac pacing may be necessary should severe AV block occur. Hemodialysis will effectively remove quinidine, but peritoneal dialysis will not.

To Drug Monograph Index  To Ophthalmic Product Index

**Drug Interactions** - **Digoxin** levels may increase considerably in patients stabilized on digoxin who receive quinidine. Some cardiologists recommend decreasing the digoxin dosage by 1/2 when adding quinidine. Therapeutic drug monitoring of both quinidine and digoxin may be warranted in these cases. **Coumarin anticoagulants** with quinidine may increase the likelihood of bleeding problems developing. Quinidine may increase the neuromuscular blocking effects of drugs like **succinylcholine, tubocurarine or atracurium**. **Phenobarbital, phenytoin or rifampin** may induce hepatic enzymes that metabolize quinidine thus reducing quinidine serum half-life by 50%. **Cimetidine** may increase the effects of quinidine by inhibiting hepatic microsomal enzymes. Use with caution with **other antidysrhythmic agents**, as additive cardiotoxic or other toxic effects may result. Quinidine may antagonize the effects of **pyridostigmine, neostigmine,** or other anticholinesterases in patients with myasthenia gravis.
Quinidine may potentiate the effects of other **drugs having hypotensive effects**.
Additive cardiac depressant effects may be seen if used with other agents that depress cardiac contractility (*e.g.,* other **antiarrhythmic drugs (procainamide, disopyramide, etc.), phenothiazines**). Drugs that alkalinize the urine **(carbonic anhydrase inhibitors, thiazide diuretics, sodium bicarbonate, antacids**, etc.) may decrease the excretion of quinidine, prolonging its half-life. Drugs that acidify the urine **(***e.g.,* **methionine, ammonium chloride)** may increase the excretion of quinidine and decrease serum levels.

**Doses -**
**Horses**:
a) Oral Dosing:
Method 1:Give quinidine sulfate powder by stomach tube or in large gelatin capsules.
Day 1: Give 5 gram test dose; if no adverse reactions (see Adverse Effects) may continue therapy
Days 2, 3: 10 gram *bid*
Days 4, 5: 10 gram *tid*
Days 6, 7: 10 gram *qid*
Days 8,9: 10 gram every 5 hours
Day 10 and thereafter: 15 gram *qid*

Method 2:
Day 1: 5 gram test dose
Day 2: 10 gram every 2 hours until a total dose of 80 grams or less has been given.
Once the arrhythmia is halted, reduce dose total dose by 1/2 every other day until a maintenance dose is reached that prevents recurrence of arrhythmia. If treating atrial fibrillation, quinidine can usually be discontinued 1-2 days after conversion to sinus rhythm. Doses greater than 40 grams per day tend to cause undesirable effects. (Hilwig 1987)

**Monitoring Parameters** - 1) ECG; 2) Blood pressure if possible, during IV administration; 3) Symptoms of toxicity (see Adverse Reactions/Overdosage); 4) Serum levels. Therapeutic serum levels are believed to range from 2.5 - 5.0 micrograms/ml. Levels greater than 10 micrograms/ml are considered to be toxic.

**Client Information** - Oral products should be administered at evenly spaced intervals throughout the day/night. GI upset may be decreased if administered with food. Do not allow animal to chew or crush sustained-release oral dosage forms. Notify veterinarian if animal's condition deteriorates or symptoms of toxicity (*e.g.,* vomiting, diarrhea, weakness, etc.) occur.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:
Quinidine Sulfate (contains 83% anhydrous quinidine alkaloid) Tablets 200 mg, 300 mg; *Quinora*® (Key), Generic; (Rx)

To Drug Monograph Index To Ophthalmic Product Index

Quinidine Sulfate (contains 83% anhydrous quinidine alkaloid) Sustained-Release Tablets 300 mg; *Quinidex*® *Extentabs* (Robins); (Rx)

Quinidine Gluconate (contains 62% anhydrous quinidine alkaloid); Sustained-release Tablets 324 mg; *Quinaglute*® *Dura-Tabs* (Berlex); *Quinalan*® (Lannett); Generic; (Rx)

Quinidine Gluconate Injection 80 mg/ml (50 mg/ml of quinidine), 10 ml vials; Generic (Lilly); (Rx)

Quinidine Polygalacturonate (contains 80% anhydrous quinidine alkaloid); Tablets 275 mg; *Cardioquin*® (Purdue-Frederick); (Rx)

## RANITIDINE HCL

**Chemistry** - An $H_2$ receptor antagonist, ranitidine HCl occurs as a white to pale-yellow granular substance with a bitter taste and a sulfur-like odor. The drug has $pK_a$s of 8.2 and 2.7. One gram is approximately soluble in 1.5 ml of water or 6 ml of alcohol. The commercially available injection has a pH of 6.7-7.3.

**Storage/Stability/Compatibility** - Ranitidine tablets should be stored in tight, light-resistant containers at room temperature. The injectable product should be stored protected from light and at a temperature less than 30°C. A slight darkening of the injectable solution does not affect the potency of the drug. Ranitidine injection is reportedly stable for up to 48 hours when mixed with the commonly used IV solutions (including 5% sodium bicarbonate).

**Pharmacology** - At the $H_2$ receptors of the parietal cells, ranitidine competitively inhibits histamine, thereby reducing gastric acid output both during basal conditions and when stimulated by food, amino acids, pentagastrin, histamine or insulin. Ranitidine is between 3-13 times more potent (on a molar basis) as cimetidine.

Ranitidine can cause gastric emptying times to be delayed, but the clinical significance of this effect is not known. Lower esophageal sphincter pressures may be increased by ranitidine. By decreasing the amount of gastric juice produced, ranitidine also decreases the amount of pepsin secreted.

Ranitidine, unlike cimetidine, does not appear to have any appreciable effect on serum prolactin levels, although it may inhibit the release of vasopressin.

**Uses/Indications -** In veterinary medicine, ranitidine has been used for the treatment and/or prophylaxis of gastric, abomasal and duodenal ulcers, uremic gastritis, stress-related or drug-induced erosive gastritis, esophagitis, duodenal gastric reflux and esophageal reflux. It has also been employed to treat hypersecretory conditions associated with gastrinomas and systemic mastocytosis.

**Pharmacokinetics** - Pharmacokinetic data for veterinary species is limited for this product. In dogs, the oral bioavailability is approximately 81%, serum half-life is 2.2 hours and volume of distribution 2.6 L/kg.

In humans, ranitidine is absorbed rapidly after oral administration, but undergoes extensive first-pass metabolism with a net systemic bioavailability of approximately 50%. Peak levels occur at about 2-3 hours after oral dosing. Food does not appreciably alter the extent of absorption or the peak serum levels attained.

Ranitidine is distributed widely throughout the body and is only 10-19% bound to plasma proteins. Ranitidine is distributed into human milk at levels of 25-100% of those found in the plasma.

Ranitidine is both excreted in the urine by the kidneys (via glomerular filtration and tubular secretion) and metabolized in the liver to inactive metabolites; accumulation of the drug can occur in patients with renal

insufficiency. The serum half-life of ranitidine in humans averages from 2-3 hours. The duration of action at usual doses is from 8-12 hours.

**Contraindications/Precautions** - Ranitidine is contraindicated in patients who are hypersensitive to it. It should be used cautiously and possibly at reduced dosage in patients with diminished renal function. Ranitidine has caused increased serum ALT levels in humans receiving high, IV doses for longer than 5 days. The manufacturer recommends that in high dose, chronic therapy that serum ALT values be considered for monitoring.

**Adverse Effects/Warnings** - Adverse effects appear to be very rare in animals at the dosages generally used. Potential adverse effects (documented in humans) that might be seen include mental confusion and headache. Rarely, agranulocytosis may develop and if given rapidly IV, transient cardiac arrhythmias may be seen. Pain at the injection site may be noted after IM administration.

**Overdosage** - Clinical experience with ranitidine overdosage is limited. In laboratory animals, very high dosages (225 mg/kg/day) have been associated with muscular tremors, vomiting and rapid respirations. Single doses of 1 gram/kg in rodents did not cause death.

Treatment of overdoses in animals should be handled using standard protocols for oral ingestions of drugs; symptoms may be treated symptomatically and supportively if necessary. Hemodialysis and peritoneal dialysis have been noted to remove ranitidine from the body.

**Drug Interactions** - Unlike cimetidine, ranitidine appears to only have minimal effects on the hepatic metabolism of drugs and is unlikely to cause clinically relevant drug interactions via this mechanism. **Propantheline Bromide** delays the absorption, but increases the peak serum level of ranitidine. The relative bioavailability of ranitidine may be increased by 23% when propantheline is administered concomitantly with ranitidine. **Antacids** may decrease the absorption of ranitidine; give at separate times (2 hours apart) if used concurrently. Ranitidine may decrease the renal clearance of **procainamide**, but the clinical relevance of this interaction is unclear at this time. The manufacturer states that ranitidine may alter the bioavailability of certain drugs through pH-dependent effects, changes in volume of distribution or an unknown effect. Further information is pending.

**Drug/Laboratory Interactions -** Ranitidine may cause a false-positive **urine protein** reading when using *Multistix*®. The sulfosalicylic acid reagent is recommended for determining urine protein when the patient is concomitantly receiving ranitidine.

**Doses -**
**Horses**:

a) 0.5 mg/kg *bid* PO (Robinson 1987)
b) Foals: 150 mg PO *bid* (Clark and Becht 1987)
c) 1 mg/kg q8h IV (Duran 1992)

**Monitoring Parameters** -

1) Clinical efficacy (dependent on reason for use); monitored by decrease in symptomatology, endoscopic examination, blood in feces, etc.

**Client Information** - To maximize the benefit of this medication, it must be administered as prescribed by the veterinarian; symptoms may reoccur if dosages are missed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

To Drug Monograph Index To Ophthalmic Product Index

**Human-Approved Products**:

Ranitidine HCl Tablets 75 mg, 150 mg, 300 mg (as base); *Zantac*® (Glaxo Wellcome); (Rx); Zantac 75® (Glaxo Wellcome) (OTC)

Rantidine HCl Effervescent Tablets & Granules: 150 mg; *Zantac EFFERdose*® (Glaxo Wellcome) (Rx)

Rantidine Capsules: 150 mg, 300 mg; *Zantac GELdose*® (Glaxo Wellcome) (Rx)

Ranitidine HCl Oral Syrup 15 mg/ml in UD 10 ml and 480 ml; *Zantac*® (Glaxo Wellcome); (Rx); Rantidine HCl (UDL) (Rx)

Ranitidine HCl Injection: 0.5 mg/ml, 25 mg/ml in 100 ml single dose containers and 2, 10, & 40 ml vials and 2 ml syringes; *Zantac*® (Glaxo Wellcome) (Rx)

Ranitidine HCl 0.5 mg/ml (preservative free in 100ml single dose containers & 25 mg/ml (as HCl) in 2 ml, 10 ml, & 40 ml vials; *Zantac*® (Glaxo); (Rx)

Ranitidine HCl 0.5 mg/ml (preservative free in 100ml single dose containers & 25 mg/ml (as HCl) in 2 ml, 10 ml, & 40 ml vials; *Zantac*® (Glaxo); (Rx)

## RIFAMPIN * PK ADVERSE EFFECT REPORTED

**Chemistry** - A semi-synthetic zwitterion derivative of rifamycin B, rifampin occurs as a red-brown, crystalline powder with a $pK_a$ of 7.9. It is very slightly soluble in water and slightly soluble in alcohol.

**Storage/Stability/Compatibility** - Rifampin capsules should be stored in tight, light-resistant containers, preferably at room temperature (15-30°C).

**Pharmacology** - Rifampin may act as either a bactericidal or bacteriostatic antimicrobial dependent upon the susceptibility of the organism and the concentration of the drug. Rifampin acts by inhibiting DNA-dependent RNA polymerase in susceptible organisms, thereby suppressing the initiation of chain formation for RNA synthesis. It does not inhibit the mammalian enzyme.

Rifampin is active against a variety of mycobacterium species and *Staphylococcus aureus*, *Neisseria*, *Haemophilus*, and *Rhodococcus equi (C. equi)*. At very high levels, rifampin also has activity against poxviruses, adenoviruses, and *Chlamydia trachomatis*. Rifampin also has antifungal activity when combined with other antifungal agents.

**Uses/Indications** - At the present time, the principle use of rifampin in veterinary medicine is in the treatment of *Rhodococcus equi* (*Corynebacterium equi*) infections (usually with erythromycin estolate) in young horses.

In small animals, the drug is sometimes used in combination with other antifungal agents (amphotericin B and 5-FC) in the treatment of histoplasmosis or aspergillosis with CNS involvement.

**Pharmacokinetics** - After oral administration, rifampin is relatively well absorbed from the GI tract. Oral bioavailability is reportedly about 40-70% in horses and 37% in adult sheep. If food is given concurrently, peak plasma levels may be delayed and slightly reduced.
Rifampin is very lipophilic and penetrates most body tissues (including bone and prostate), cells and fluids (including CSF) well. It also penetrates abscesses and caseous material. Rifampin is 70-90% bound to

To Drug Monograph Index To Ophthalmic Product Index

serum proteins and is distributed into milk and crosses the placenta. Mean volume of distribution is approximately 0.9 L/kg in horses, and 1.3 L/kg in sheep.

Rifampin is metabolized in the liver to a deacetylated form which also has antibacterial activity. Both this metabolite and unchanged drug are excreted primarily in the bile, but up to 30% may be excreted in the urine. The parent drug is substantially reabsorbed in the gut, but the metabolite is not. Reported elimination half-lives for various species are: 6-8 hours (horses), 8 hours (dogs), 3-5 hours (sheep). Because rifampin can induce hepatic microsomal enzymes, elimination rates may increase with time.

**Contraindications/Precautions/Reproductive Safety** - Rifampin is contraindicated in patients hypersensitive to it or other rifamycins. It should be used with caution in patients with preexisting hepatic dysfunction.

Rodents given high doses of rifampin 150 - 250 mg/kg/day resulted in some congenital malformations in offspring, but the drug has been used in pregnant women with no reported increases in teratogenicity.

**Adverse Effects/Warnings** - Rifampin can cause red-orange colored urine, tears, sweat and saliva. There are no harmful consequences from this effect. In some species (*e.g.,* humans), rashes, GI distress, and increases in liver enzymes may occur, particularly with long-term use.
Adverse effects in horses are apparently rare when rifampin is given orally. Although not commercially available, intravenous rifampin has caused CNS depression, sweating, hemolysis and anorexia in horses.

**Overdosage/Acute Toxicity** - Symptoms associated with overdosage of oral rifampin generally are extensions of the adverse effects outlined above (GI, orange-red coloring of fluids, and skin), but massive overdoses may cause hepatotoxicity. Should a massive oral overdosage occur, the gut should be emptied following standard protocols. Liver enzymes should be monitored and supportive treatment initiated if necessary.

**Drug Interactions** - Because rifampin has been documented to induce hepatic microsomal enzymes, drugs that are metabolized by these enzymes may have their elimination half-lives shortened and serum levels decreased Drugs that may be affected by this process include **propranolol, quinidine, dapsone, chloramphenicol, corticosteroids, oral anticoagulants (***e.g.,* **warfarin), benzodiazepines (***e.g.,* **diazepam),** and **barbiturates (***e.g.,* **phenobarbital**).
Rifampin may cause decreased serum concentrations of **ketoconazole** if administered concurrently.

**Drug/Laboratory Interactions** - Microbiologic methods of assaying **serum folate** and **vitamin $B_{12}$** are interfered with by rifampin. Rifampin can cause false-positive **BSP** (bromosulfophthalein, sulfobromophthalein) test results, by inhibiting the hepatic uptake of the drug.

**Doses** -
**Horses**:

For treatment of *C. equi* infections in foals:

a) Rifampin 5 mg/kg PO *tid* with erythromycin estolate or ethylsuccinate 25 mg/kg PO *tid*. May cause urine to become red. Use a continuous course of rifampin as intermittent use may be associated with allergic reactions. Treat until chest radiographs and plasma fibrinogen levels return to normal. (Hillidge and Zertuche 1987)

For susceptible infections in foals:

a) 5 mg/kg PO q12h (dose extrapolated from adult horses). Used in combination with erythromycin for *C. equi* infections (see above), but could be used with other agents (*e.g.,* penicillins) to treat other gram positive infections. Should be used with other antimicrobial agents to minimize the potential for bacterial resistance development. (Caprile and Short 1987)

To Drug Monograph Index To Ophthalmic Product Index

**Elephants:**

a) Adverse effects: In one elephant under treatment for tuberculosis, isoniazid (INH) administered orally together with rifampin (8 mg/kg), pyrazinamide (35mg/kg) and vitamin B6 caused partial anorexia. Rifampin was discontinued after the first 6 months of treatment due to failure to achieve therapeutic levels. Rectally administered INH at a dose of 11.5 mg/kg resulted in anorexia, lethargy, and pica. Yellow brown urine was observed and serum AST, total bilirubin, GGT, and bile acids were elevated. Signs resolved within 2-3 days after treatment was stopped. Daily treatment with INH (3.75 mg/kg per rectum) had no adverse effects but symptoms resumed if the dose was increased to 5 mg/kg or greater. When INH and pyrazinamide were administered rectally 4 times weekly, a low grade anemia was observed. The anemia resolved when the INH dose was decreased from 3.75 to 2.5 mg/kg and the PZA dose was decreased from 35 to 25 mg/kg.

- Four elephants receiving daily direct oral administration of isoniazid (7.5 mg/kg) and rifampin (9.9 mg/kg) developed inappetance, lethargy, and pica. Symptoms resolved when the INH dose was reduced to 5.6 mg/kg and the rifampin dose was reduced to 7.5 mg/kg.

- One elephant showed a decreased white blood cell count (from 13,000 / µl to 1,900 / µl) which resolved when INH was discontinued.

- One elephant given INH (10 mg/kg) rectally as the only drug developed lethargy, inappetance and an elevated LDH within 3 weeks. Treatment was discontinued for one month then reinstated at 5 mg/kg. Pyrazinamide (25 mg/kg/day) was added and both drugs were given rectally. Periodic episodes of lethargy on this regimen responded to 1-2 weeks rest (no drugs) then reinstating INH at a half-dose and increasing to a full dose over a period of several weeks. (Mikota, et.al. 2001).

Mikota,S.K., Peddie,L., Peddie,J., Isaza,R., Dunker,F., West,G., Lindsay,W., Larsen,R.S., Salman,M.D., Chatterjee,D., Payeur,J., Whipple,D., Thoen,C., Davis,D.S., Sedgwick,C., Montali,R.J., Ziccardi,M., and Maslow,J. 2001. **Epidemiology and diagnosis of Mycobacterium tuberculosis in captive Asian elephants (Elephas maximus)**. Journal of Zoo and Wildlife Medicine 32:(1):1-16.

b) **Dose selection and pharmacokinetics of rifampin in elephants for the treatment of tuberculosis.**
C. A. Peloquin, J. N. Maslow, S. K. Mikota, A. Forrest, F. Dunker, R. Isaza, et al. Journal of Veterinary Pharmacology and Therapeutics Vol. 29 Issue 6 Pages 581-585.
DOI: JVP789 [pii];10.1111/j.1365-2885.2006.00789.x [doi]

Link to full article:
https://d1wqtxts1xzle7.cloudfront.net/32372288/Peloquin_Pk_of_Rif_2006-libre.pdf?1391599952=&response-content-disposition=inline%3B+filename%3DDose_selection_and_pharmacokinetics_of_r.pdf&Expires=1693243612&Signature=cN6WJjJUbMOefaQ9D36cDho4iJDdWvLCuBqCpWsmpov7mIipmUTPKTQL53BHWW6tme44iFECmXUOMLx6d9gmzqJZfD4Q42x5AuDJKwk5Ujjib-YMOFTZEUhCkjD1-1PVtCEcN~1P3qhPnDUjRGktyZKNRiRQN6yKsXRRXXp7Bq-QaGq1MYHvNoFbHhUYExUniJiieTtXEpu0nnkZzsUwTk-3pM1IZN-SDdG1ajBXvWBmlItvxxZ-~xOD3laajP9ZcoAGA0545VZEJr2gbteKUW4gLTyz9LNQ06n6KMBCLExfQ8uQC~oHrAree6nhAAkYnh-7tsmkEN6dsovUo6qTvQ__&Key-Pair-Id=APKAJLOHF5GGSLRBV4ZA

**The pharmacokinetics of a single oral or rectal dose of concurrently administered isoniazid, rifampin, pyrazinamide, and ethambutol in Asian elephants (Elephas maximus).**
A. P. Brock, R. Isaza, E. F. Egelund, R. P. Hunter and C. A. Peloquin. Journal of Veterinary Pharmacology and Therapeutics 2014 Vol. 37 Issue 5 Pages 472-479.
Accession Number: WOS:000342801400007 DOI: 10.1111/jvp.12119

To Drug Monograph Index To Ophthalmic Product Index

Tuberculosis, caused by Mycobacterium tuberculosis, is a disease of concern in captive Asian elephants (Elephas maximus). Treatment for tuberculosis in elephants utilizes multidrug protocols combining isoniazid, rifampin, pyrazinamide, and/or ethambutol. In this study, a single, coformulated dose of isoniazid 5mg/kg, rifampin 10mg/kg, pyrazinamide 30mg/kg, and ethambutol 30mg/kg was administered orally to six Asian elephants, and rectally to five elephants using a cross-over design. Blood samples were collected serially over 24h. Pyrazinamide and ethambutol concentrations were determined using validated gas chromatography assays. Isoniazid and rifampin concentrations were determined using validated high-performance liquid chromatography assays. Rectal isoniazid produced an earlier T-max compared with oral administration. Oral isoniazid resulted in a comparatively lower C-max, but higher AUC values compared with rectal isoniazid. Oral rifampin and oral ethambutol were well absorbed while rectal rifampin was not. Oral pyrazinamide produced comparatively higher C-max and AUC values compared with rectal pyrazinamide. Results of this study indicate that currently recommended therapeutic monitoring sample collection times for rectal isoniazid and oral rifampin do not provide an accurate assessment of exposure for these drugs. This study demonstrates notable individual variability, indicating that dosing of these medications requires individual monitoring and provides additional information to guide the clinician when treating elephants.

**Population pharmacokinetics of rifampin in the treatment of Mycobacterium tuberculosis in Asian elephants.** E. F. Egelund, R. Isaza, A. P. Brock, A. Alsultan, G. An and C. A. Peloquin. Journal of Veterinary Pharmacology and Therapeutics 2015 Vol. 38 Issue 2 Pages 137-143. DOI: 10.1111/jvp.12156. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84924331732&doi=10.1111%2fjvp.12156&partnerID=40&md5=99c73200d875a041fac5bb14cfda3e0a

The objective of this study was to develop a population pharmacokinetic model for rifampin in elephants. Rifampin concentration data from three sources were pooled to provide a total of 233 oral concentrations from 37 Asian elephants. The population pharmacokinetic models were created using Monolix (version 4.2). Simulations were conducted using ModelRisk. We examined the influence of age, food, sex, and weight as model covariates. We further optimized the dosing of rifampin based upon simulations using the population pharmacokinetic model. Rifampin pharmacokinetics were best described by a one-compartment open model including first-order absorption with a lag time and first-order elimination. Body weight was a significant covariate for volume of distribution, and food intake was a significant covariate for lag time. The median Cmax of 6.07 μg/mL was below the target range of 8-24 μg/mL. Monte Carlo simulations predicted the highest treatable MIC of 0.25 μg/mL with the current initial dosing recommendation of 10 mg/kg, based upon a previously published target AUC0-24/MIC > 271 (fAUC > 41). Simulations from the population model indicate that the current dose of 10 mg/kg may be adequate for MICs up to 0.25 μg/mL. While the targeted AUC/MIC may be adequate for most MICs, the median Cmax for all elephants is below the human and elephant targeted ranges. © 2014 John Wiley & Sons Ltd.

**ISONIAZID AND RIFAMPIN PHARMACOKINETICS IN TWO ASIAN ELEPHANTS (ELEPHAS MAXIMUS) INFECTED WITH MYCOBACTERIUM TUBERCULOSIS.** E. F. Egelund, R. Isaza, A. Alsultan and C. A. Peloquin. Journal of Zoo and Wildlife Medicine 2016 Vol. 47 Issue 3 Pages 868-871. Accession Number: WOS:000385639100021

This report describes the pharmacokinetic profiles of chronically administered oral isoniazid and rifampin in one adult male and one adult female Asian elephant (Elephas maximus) that were asymptomatically infected with Mycobacterium tuberculosis. Rifampin's half-life was reduced when compared to previous single-dose pharmacokinetic profiles of healthy uninfected Asian elephants. Both elephants experienced delayed absorption of isoniazid and rifampin as compared to previous pharmacokinetic studies in this species. The altered pharmacokinetics of both drugs in repeated-dosing clinical situations underscores the need for individual therapeutic drug monitoring for tuberculosis treatment.

To Drug Monograph Index  To Ophthalmic Product Index

**Serum concentrations of antimycobacterial drugs in Asian Elephants (Elephas maximus).** 2016. L. Young, S. Scott, M. Salfinger and E. Ramsay. Proc. AAZV / EAZWV / IZW Joint Conference 2016

Mycobacterium tuberculosis is an important disease of captive Asian elephants (Elephas maximus.) In this study six adult Asian elephants which had Mycobacterium tuberculosis cultured from trunk wash samples or had reactive DPP/MAPIA serologic responses were treated, concurrently, with one to three antimycobacterial drugs. Enrofloxacin hydrochloride, 2.5 mg/kg p.o., s.i.d., was administered to all animals in various foodstuffs for 9-15 mo. Serum enrofloxacin concentrations ranged from 230-2380 µg/ml (targeted concentrations = 125-1000 µg/ml).1 Pyrazinamide (PZA), 30 mg/kg p.o., s.i.d., was administered to five elephants in various foodstuffs for 9-12 mo. Serum PZA concentrations ranged from 26-57 µg/ml (targeted concentrations = 20- 60 µg/ml).2 Ethambutol (EMB), 30 mg/kg p.o., s.i.d., was administered to one elephant for 12 mo. A serum EMB concentration of 4.07 µg/ml was achieved (targeted concentration = 2-6 µg/ml).2 Rifampin (RIF), 10 mg/kg p.o., s.i.d., was administered to one elephant for 9 mo. A serum RIF concentration of 16 µg/ml was achieved (targeted concentration = 8-24 µg/ml). All elephants were monitored for adverse clinical effects throughout treatments. Notable side effects were limited to excess, foamy lacrimation, believed to have occurred secondary to PZA administration. Clinical chemistries and complete blood counts were monitored in all animals and values remained within reference intervals throughout treatments. This study shows antimycobacterial drug dosages may require individuation, but concurrent, long-term, multidrug regimens for the treatment of Mycobacterium tuberculosis in Asian elephants can achieve appropriate therapeutic levels with minimal detrimental side effects.

Also see:
Using therapeutic drug monitoring to dose the antimycobacterial drugs. C. Peloquin. Clinics in Chest Medicine 1997 Vol. 18 Pages 79-97

Clinical pharmacology of the anti-tuberculoisis drugs. C. A. Peloquin.In: Clinical Tuberculosis, edited by P. D. O. Davies. Arnold Publishers 2003

Tuberculosis treatment protocols and complications for elephants. G. Dumonceaux and S. Mikota. Proceedings International Elephant Conservation and Research Symposium 2006 Pages 84-85. Request full paper from smikota@elephantcare.org.

**Monitoring Parameters** -

1) Clinical efficacy
   a) For monitoring *C. equi* infections in foals and response to rifampin/erythromycin: Chest radiographs and plasma fibrinogen levels have been suggested as prognostic indicators when done after 1 week of therapy. (Hillidge and Zertuche 1987)
2) Adverse effects; may consider liver function monitoring with long-term therapy

**Client Information** - Rifampin may cause urine and other secretions (tears, saliva, etc.) to turn red-orange in color. This is not abnormal.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Rifampin Capsules 150 mg, 300 mg; *Rifadin*® (Hoechst Marion Roussel); *Rimactane*® (Ciba); (Rx)

Rifampin Powder for Injection: 600 mg; *Rifadin*® (Hoechst Marion Roussel) (Rx)

To Drug Monograph Index To Ophthalmic Product Index

## SALINE/HYPEROSMOTIC LAXATIVES

### MAGNESIUM SALTS
### SODIUM PHOSPHATE SALTS
### PEG 3350 PRODUCTS

**Chemistry** - Magnesium cation containing solutions of magnesium citrate, magnesium hydroxide, or magnesium sulfate act as saline laxatives. Magnesium citrate solutions contain 4.71 mEq of magnesium per 5 ml. Magnesium hydroxide contains 34.3 mEq of magnesium per gram and milk of magnesia contains 13.66 mEq per 5 ml. One gram of magnesium sulfate (epsom salt) contains approximately 8.1 mEq of magnesium. Solutions containing phosphate anions also act as saline laxatives. These solutions generally contain monobasic and/or dibasic sodium phosphate. Polyethylene glycol 3350 is a non-absorbable compound that acts as an osmotic agent.

**Storage/Stability/Compatibility** - Magnesium citrate solutions should be stored at 2-30°C. Store Milk of Magnesia at temperatures less than 35°C, but do not freeze. PEG 3350 reconstituted (from powder by the pharmacy, client, clinic, etc.) solutions should be kept refrigerated and used within 24 hours.

**Pharmacology** - Although unproven, it is commonly believed that the hyperosmotic effect of the poorly absorbed magnesium cation or phosphate anion causes water retention, stimulates stretch receptors and enhances peristalsis in the small intestine and colon. Recent data, however, suggests that magnesium ions may directly decrease transit times and increase cholecystokinin release.

Polyethylene glycol 3350 is a non-absorbable compound that acts as an osmotic agent. By adding sodium sulfate as the primary sodium source, sodium absorption is minimized. Other electrolytes (bicarbonate, potassium and chloride) are also added so that no net change occurs with either absorption or secretion of electrolytes or water in the gut.

**Uses/Indications -** The saline laxatives are used for their cathartic action to relieve constipation. They are also used to reduce intestinal transit time thereby reducing the absorption of orally ingested toxicants. Polyethylene glycol 3350 balanced electrolyte solutions are used to evacuate the colon prior to intestinal examination or surgery.

**Pharmacokinetics** - While it is unknown how much sodium or phosphate is absorbed after administration of sodium phosphate solutions, it is estimated that up to 20% of the phosphate dose can be absorbed. When magnesium salts are administered, up to 30% of the magnesium dose of magnesium can be absorbed.
Generally, the onset of action of saline cathartics (characterized by a loose, watery stool) occurs in 3-12 hours after dosing in monogastric animals and within 18 hours in ruminants.

**Contraindications/Precautions** - Saline cathartics are contraindicated for long-term or chronic use. Sodium containing laxatives are contraindicated in patients with congestive heart failure or congenital megacolon. PEG 3350 solutions are contraindicated in patients with GI obstruction, gastric retention, bowel perforation, toxic colitis or megacolon. Saline cathartics should be used with extreme caution in patients with renal insufficiency, pre-existing water-balance or electrolyte abnormalities, or cardiac disease.

**Adverse Effects/Warnings** - Except for possible cramping and nausea, adverse effects in otherwise healthy patients generally occur only with the saline cathartics with chronic use or overdoses. Hypermagnesemia manifested by muscle weakness, ECG changes and CNS effects can occur. Hyperphosphatemia with resultant hypocalcemia can occur with chronic overuse or overdoses of phosphate containing products. Hypernatremia can also occur when administering sodium phosphate solutions.

To Drug Monograph Index  To Ophthalmic Product Index

Cats may be particularly sensitive to the electrolyte imbalance effects of sodium phosphate enema solutions and these products are not recommended for use in this species until more data are available.

**Overdosage** - Symptoms of overdosage of magnesium or phosphate containing laxatives are described above. Treatment should consist of monitoring and correcting any fluid imbalances that occur with parenteral fluids.

If hypermagnesemia occurs, furosemide may be used to enhance the renal excretion of the excess magnesium. Calcium has been suggested to help antagonize the CNS effects of magnesium. Hyperphosphatemia may cause hypocalcemia and parenteral calcium therapy may be necessary.

**Drug Interactions** - All orally administered saline laxatives may alter the rate and extent of absorption of other drugs by decreasing intestinal transit times. The extent of these effects have not been well characterized for individual drugs, however. Magnesium laxatives should not be administered with **tetracycline** products

**Doses -**
**Horses**:

Magnesium sulfate (epsom salt):

a) 0.2 gm/kg diluted in 4 L of warm water administered via nasogastric tube. Administer only to well hydrated animals (ideally in conjunction with IV fluid therapy). Do not treat longer than 3 days or there is an increased risk of enteritis or magnesium toxicity occurring. (Clark and Becht 1987)
b) To reduce absorption of toxicants and GI transit time: 500 gm (as a 20% solution) PO. If mineral oil has been used initially, give saline cathartic 30-45 minutes after mineral oil. (Oehme 1987)

**Monitoring Parameters** -

1) Fluid and electrolyte status in susceptible patients or if using high doses or chronically.
2) Clinical efficacy

**Client Information** - Do not give dosages greater than, or for periods of time longer than recommended by veterinarian. Contact veterinarian if patient begins vomiting.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** - Saline cathartic products have apparently not been formally approved for use in domestic animals. They are available without prescription (OTC). PEG 3350 products are available only by prescription and are approved for use in humans.

**Veterinary-Approved Products**: None located

**Human-Approved Products**:
Saline Laxatives (not an inclusive list):

Magnesium Citrate (Citrate of Magnesia): powder and oral solution

Magnesium Hydroxide: powder, suspension (Milk of Magnesia)

Magnesium Sulfate (Epsom Salt): crystals, powder

Sodium Phosphate, Dibasic or Monobasic: powder

Sodium Phosphate, Dibasic 900 mg/5ml with Sodium Phosphate, Monobasic 2.4 gm/5ml oral solution
*Fleet® Phospho®-Soda* (Fleet)

Sodium Phosphate, Dibasic 60 mg/ml with Sodium Phosphate, Monobasic 160 mg/ml rectal solution
*Fleet® Enema* (Fleet), *Fleet® Pediatric Enema* (Fleet)

Hyperosmotic Laxatives (not an inclusive list):

Polyethylene Glycol-Electrolyte Solution

To Drug Monograph Index To Ophthalmic Product Index

*OCL*® Solution (Abbott) per 100 ml: 146 mg Sodium Chloride, 168 mg Sodium Bicarbonate, 1.29 grams Sodium Sulfate Decahydrate, 75 mg potassium chloride, 6 grams PEG-3350 and 30 ml Polysorbate-80

CoLyte® (R&C) Packets to make 2 liters of solution: 2.92 gm Sodium Chloride, 3.36 gm Sodium Bicarbonate, 11.36 gm Sodium Sulfate, 1.49 gm potassium chloride, 120 gm PEG-3350 (Also available in 1 gallon and 6 liter sizes)

*GoLYTELY*® (Braintree Labs) contains per 4800 ml container: 5.86 gm Sodium Chloride, 6.74 gm Sodium Bicarbonate, 22.74 gm Sodium Sulfate, 2.97 gm potassium chloride, 236 gm PEG-3350

## SODIUM BICARBONATE

**Chemistry** - An alkalinizing agent, sodium bicarbonate occurs as a white, crystalline powder having a slightly saline or alkaline taste. It is soluble in water and insoluble in alcohol. One gram of sodium bicarbonate contains about 12 mEq each of sodium and bicarbonate; 84 mg of sodium bicarbonate contains 1 mEq each of sodium and bicarbonate. A 1.5% solution of sodium bicarbonate is approximately isotonic. An 8.4% solution of sodium bicarbonate can be made isotonic by diluting each ml with 4.6 ml of sterile water for injection.

Sodium bicarbonate may also be known as: Baking Soda, Sodium Hydrogen Carbonate, Sodium Acid Carbonate, or by its chemical abbreviation, $NaHCO_3$.

**Storage/Stability/Compatibility** - Sodium bicarbonate tablets should be stored in tight containers, preferably at room temperature (15-30°C). Sodium bicarbonate injection should be stored at temperatures less than 40°C and preferably at room temperature; avoid freezing.
Sodium bicarbonate powder is stable in dry air, but will slowly decompose upon exposure to moist air.

Sodium bicarbonate is reportedly **compatible** with the following intravenous solutions and drugs: Dextrose in water, dextrose/saline combinations, dextrose-Ringer's combinations, sodium chloride injections, amikacin sulfate, aminophylline, amobarbital sodium, amphotericin B, atropine sulfate, bretylium tosylate, carbenicillin disodium, cefoxitin sodium, cephalothin sodium, cephapirin sodium, chloramphenicol sodium succinate, chlorothiazide sodium, cimetidine HCl, clindamycin phosphate, ergonavine maleate, erythromycin gluceptate/lactobionate, Innovar®, heparin sodium, hyaluronidase, hydrocortisone sodium succinate, kanamycin sulfate, lidocaine HCl, metaraminol bitartrate, methotrexate sodium, methyldopate HCl, nafcillin sodium, netilmicin sulfate, oxacillin sodium, oxytocin, phenobarbital sodium, phenylephrine HCl, phenytoin sodium, phytonadione, potassium chloride, prochlorperazine edisylate, and sodium iodide.

Sodium bicarbonate **compatibility information conflicts** or is dependent on diluent or concentration factors with the following drugs or solutions: lactated Ringer's injection, Ringer's injection, sodium lactate 1/6 M, ampicillin sodium, calcium chloride/gluconate, methicillin sodium, penicillin G potassium, pentobarbital sodium, promazine HCl, thiopental sodium, vancomycin HCl, verapamil HCl, and vitamin B-complex w/C. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

Sodium bicarbonate is reportedly **incompatible** with the following solutions or drugs: alcohol 5%/dextrose 5%, $D_5$ lactated Ringer's, amrinone lactate, ascorbic acid injection, carmustine, cisplatin, codeine phosphate, corticotropin, dobutamine HCl, epinephrine HCl, glycopyrrolate, hydromorphone HCl, imipenem-cilastatin, regular insulin, isoproterenol HCl, labetolol HCl, levorphanol bitartrate, magnesium sulfate, meperidine HCl, methadone HCl, metoclopramide HCl, norepinephrine bitartrate, oxytetracycline HCl,

To Drug Monograph Index To Ophthalmic Product Index

pentazocine lactate, procaine HCl, secobarbital sodium, streptomycin sulfate, succinylcholine chloride, tetracycline HCl,

**Pharmacology** - Bicarbonate ion is the conjugate base component of bicarbonate:carbonic acid buffer, the principal extracellular buffer in the body.

**Uses/Indications** - Sodium bicarbonate is indicated to treat metabolic acidosis and to alkalinize the urine. It is also used as adjunctive therapy in treating hypercalcemic or hyperkalemia crises.

**Contraindications/Precautions/Reproductive Safety** - Parenterally administered sodium bicarbonate is considered generally contraindicated in patients with metabolic or respiratory alkalosis, excessive chloride loss secondary to vomiting or GI suction, at risk for development of diuretic-induced hypochloremic alkolosis, or with hypocalcemia where alkalosis may induce tetany.

Use with extreme caution and give very slowly in patients with hypocalcemia. Because of the potential sodium load, use with caution in patients with CHF, nephrotic syndrome, hypertension, oliguria, or volume overload. Reproductive safety studies have not been performed. Assess risk versus benefit before using.

**Adverse Effects/Warnings** - Sodium bicarbonate therapy (particularly high-dose parenteral use) can lead to metabolic alkalosis, hypokalemia, hypocalcemia, “overshoot” alkalosis, hypernatremia, volume overload, congestive heart failure, shifts in the oxygen dissociation curve causing decreased tissue oxygenation, and paradoxical CNS acidosis leading to respiratory arrest.

When sodium bicarbonate is used during cardiopulmonary resuscitation, hypercapnia may result if the patient is not well ventilated; patients may be predisposed to ventricular fibrillation.
Oral & parenteral bicarbonate (especially at higher doses) may contribute significant amounts of sodium and result in hypernatremia and volume overload; use with caution in patients with CHF, or acute renal failure.

**Overdosage/Acute Toxicity** - Sodium bicarbonate can cause severe alkalosis, with irritability or tetany if overdosed or given too rapidly. Dosages should be thoroughly checked and frequent monitoring of electrolyte and acid/base status performed.

Treatment may consist of simply discontinuing bicarbonate if alkalosis is mild, or by using a rebreathing mask. Severe alkalosis may require intravenous calcium therapy. Sodium chloride or potassium chloride may be necessary if hypokalemia is present.

**Drug Interactions** - Because oral sodium bicarbonate can either increase or reduce the rate and/or extent of absorption of many orally administered drugs, it is recommended to avoid giving other drugs within 1-2 hours of sodium bicarbonate. Oral sodium bicarbonate may increase the amount of **naproxen** absorbed. Oral sodium bicarbonate may reduce the amount and/or extent absorbed of the following drugs: anticholinergic agents, **Histamine$_2$ blocking agents (***e.g.,* **cimetidine, ranitidine)**, **iron products, ketoconazole**, and **tetracyclines**. Sodium bicarbonate may reduce the efficacy of **sucralfate** if administered concurrently.
When urine is alkalinized by sodium bicarbonate, excretion of certain drugs (*e.g.,* **quinidine, amphetamines, ephedrine**) is decreased, and excretion of weakly acidic drugs (*e.g.,* **salicylates**) is increased. The solubility of **ciprofloxacin & enrofloxacin** is decreased in an alkaline environment. Patients with alkaline urine should be monitored for signs of crystalluria.
Concurrent use of sodium bicarbonate in patients receiving potassium-wasting diuretics (*e.g.,* **thiazides, furosemide**) may cause hypochloremic alkalosis. Patients receiving high dosages of sodium bicarbonate and **ACTH** or **glucocorticoids** may develop hypernatremia.

To Drug Monograph Index  To Ophthalmic Product Index

**Doses** –
**Horses:**

For metabolic acidosis:

a) Associated with colic; if pH is <7.3 and base deficit is >10 mEq/L estimate bicarbonate requirement using the formula: bicarbonate deficit ($HCO^{-3}$ mEq) = base deficit (mEq/L) x 0.4 x body weight (kg). May administer as a 5% sodium bicarbonate solution. Each L of solution contains 600 mEq of bicarbonate (hypertonic) and should not be administered any faster than 1 - 2 L/hr. Because acidotic horses with colic tend also to be dehydrated, may be preferable to give as isotonic sodium bicarbonate (150 mEq/L). (Stover 1987)

**Monitoring Parameters** -

1) Acid/base status
2) Serum electrolytes
3) Urine pH (if being used to alkalinize urine)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Sodium bicarbonate 5% (0.6 mEq/ml) in 500 ml vials (297.5 mEq/500 ml)
Sodium bicarbonate 8.4% (1 mEq/ml) in 50 ml (50 mEq/vial), 100 ml (100 mEq/vial) and 500 ml (500 mEq/vial) vials
Available generically labeled; (Rx). Approval status unknown.

**Human-Approved Products**:

Injectable Products:
Sodium bicarbonate 4% (0.48 mEq/ml) in 5 & 10 ml vials
Sodium bicarbonate 4.2% (0.5 mEq/ml) in 5 & 10 ml syringes
Sodium bicarbonate 5% (0.6 mEq/ml) in 500 ml vials (297.5 mEq/500 ml)
Sodium bicarbonate 7.5% (0.9 mEq/ml) in 50 ml amps, syringes and vials (44.6 mEq/50 ml)
Sodium bicarbonate 8.4% (1 mEq/ml) in 10 ml syringes (10 mEq) & 50 ml vials (50 mEq/vial)
Available generically labeled; (Rx).

Oral Products:
Oral Tablets 325 mg (5 grain), 650 mg (10 grain)
May be labeled generically or as Soda Mint; (OTC)

**Sodium Chloride Injections - see the Intravenous Fluids section in the appendix**

**Sodium Hyaluronate - see Hyaluronate Sodium**

## SODIUM IODIDE

**Chemistry** - Sodium iodide occurs as colorless, odorless crystals or white crystalline powder. It will develop a brown tint upon degradation. Approximately 1 gram is soluble in 0.6 ml of water and 2 ml of alcohol.

**Storage/Stability/Compatibility** - Commercially available veterinary injectable products should generally be stored at room temperature (15- 30° C). Sodium iodide injection is reportedly incompatible with vitamins B & C injection.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - While the exact mode of action for its efficacy in treating actinobacillosis is unknown, iodides probably have some effect on the granulomatous inflammatory process. Iodides have little, if any *in vitro* antibiotic activity.

**Uses/Indications** - The primary use for sodium iodide is in the treatment of actinobacillosis and actinomycosis in cattle. It has been used as an expectorant with little success in a variety of species and occasionally as a supplement for iodine deficiency disorders. In horses, oral sodium iodide has been the classical treatment for sporotrichosis.

**Pharmacokinetics** - Little published information appears to be available. Therapeutic efficacy of intravenous sodium iodide for actinobacillosis is rapid, with beneficial effects usually seen within 48 hours of therapy.

**Contraindications/Precautions/Reproductive Safety -** Sodium iodide injection labels state that it should not be given to lactating animals or to animals with hyperthyroidism. Do not inject intramuscularly (IM).

Iodides should be given slowly intravenously and with caution to horses as severe generalized reactions have been reported.

Anecdotal reports that iodides can cause abortion in cattle persist and label information of some veterinary products state not to use in pregnant animals. Clearly, potential risks versus benefits of therapy must be weighed.

**Adverse Effects/Warnings** - In ruminants, the adverse effect profile is related to excessive iodine (see Overdosage below). Young animals may be more susceptible to iodism than adults. Foals have developed goiter when mares have been excessively supplemented.

**Overdosage** - Excessive iodine in animals can cause excessive tearing, nasal discharge, scaly haircoats/dandruff, hyperthermia, decreased milk production and weight gain, coughing, inappetence and diarrhea.

**Drug Interactions** - Iodides may enhance the efficacy of **thyroid medications** and may decrease the efficacy of **antithyroid** medications.

**Doses -**
**Horses**:
For treatment of sporotrichosis:
a) Sodium iodide 20 - 40 mg/kg orally daily for several weeks (Fadok 1992)

**Monitoring Parameters/Client Information** - Ruminants: 1) Clinical efficacy 2) Signs of iodism (excessive tearing, nasal discharge, scaly haircoats/dandruff, hyperthermia, decreased milk production and weight gain, coughing, inappetence, and diarrhea). Although formal withholding times were not located, there is concern about using this product in animals about to be slaughtered. In the interest of public health, author recommends not using within 30 days of slaughter.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products**:
Sodium Iodide Injection 20 g/100 ml (20%; 200 mg/ml) in 250 ml vials—available as multi- or single use vials; Generic; (Rx)

**Human-Approved Products**: NOTE: The following are listed for information purposes.

To Drug Monograph Index To Ophthalmic Product Index

The above monograph pertains to the veterinary injectable product only.

Sodium Iodide$^{123}$ Oral Capsules 3.7 mBq and 7.4 mBq (Note: Radioactive isotope used for thyroid diagnostic procedures) (Mallinckrodt); (Rx)

Sodium Iodide$^{131}$ Capsules and Oral solution (Note: Radioactive isotope used for treatment of hyperthyroidism and thyroid carcinoma; requires NRC approval for use); (Bracco, Mallinckrodt); (Rx)

## SODIUM SULFATE
## GLAUBER'S SALT

**Chemistry** - Sodium sulfate (hexahydrate form) occurs as large, colorless, odorless, crystals or white crystalline powder. It will effloresce in dry air and partially dissolve in its own water of crystallization at about 33°C. 1 gram is soluble in about 2.5 ml of water.

**Storage/Stability/Compatibility** - Store in tight containers at temperatures not exceeding 30°C.

**Pharmacology** - When given orally, sodium sulfate acts as a saline cathartic (draws water into small intestine). Sodium sulfate is considered to be the most effective saline cathartic on a molar basis. Sulfates also react with a variety of cations to form non-absorbable compounds, which may explain its efficacy in reducing copper loads and to reduce gut calcium.

**Uses/Indications** - Sodium sulfate is used as a saline cathartic, primarily in food animals.

**Pharmacokinetics** - Sodium sulfate is not appreciably absorbed from the GI tract and thereby acts a saline cathartic. Sodium may be absorbed however, after exchanging with other cations.

**Contraindications/Precautions** - Saline cathartics should not be used in dehydrated animals. Because of the drug's high sodium content, it should be used with caution in patients with severe CHF or in patients otherwise susceptible to sodium retention.

**Adverse Effects/Warnings** - Diarrhea, cramping and flatulence may result. Electrolyte abnormalities may occur with chronic use.

**Doses** -
**Cattle:**

As a cathartic:

a) 500 - 750 g PO as a 6% solution via stomach tube (Davis 1993)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**: None

Sodium sulfate (hexahydrate) is available from chemical supply houses.

## SODIUM THIOSULFATE

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - Used systemically for cyanide or arsenic poisoning and topically as an antifungal, sodium thiosulfate occurs as large, colorless crystals or coarse, crystalline powder. It is very soluble in water, deliquescent in moist air and effloresces in dry air at temperatures >33°C.

**Storage/Stability/Compatibility** - Unless otherwise stated by the manufacturer, store at room temperature. Crystals should be stored in tight containers.

**Pharmacology** - By administering thiosulfate, an exogenous source of sulfur is available to the body, thereby allowing it hasten the detoxification of cyanide using the enzyme rhodanese. Rhodanese (thiosulfate cyanide sulfurtransferase) converts cyanide to the relatively nontoxic thiocyanate ion. Thiocyanate is then excreted in the urine.

Sodium thiosulfate's topical antifungal activity is probably due to its slow release of colloidal sulfur.

While sodium thiosulfate has been recommended for treating arsenic (and some other heavy metal) poisoning, it's proposed mechanism of action is not known. Presumably the sulfate moiety may react with and chelate the metal, allowing its removal.

**Uses/Indications** - Sodium thiosulfate (alone or in combination with sodium nitrite) is useful in the treatment of cyanide toxicity. It has been touted for use in treating arsenic or other heavy metal poisonings, but its efficacy is in question for these purposes. However, because sodium thiosulfate is relatively non-toxic and inexpensive, it may be tried to treat arsenic poisoning. When used in combination with sodium molybdate sodium thiosulfate may be useful for the treatment of copper poisoning.

Sodium thiosulfate may also be useful for the topical treatment for some fungal infections (Tinea). In humans, sodium thiosulfate has been used to reduce the nephrotoxicity of cisplatin therapy.

**Pharmacokinetics** - Sodium thiosulfate is relatively poorly absorbed from the GI tract. When substantial doses are given PO, it acts a saline cathartic. When administered intravenously, it is distributed in the extracellular fluid and then rapidly excreted via the urine.

**Contraindications/Precautions/Reproductive Safety** - There are no absolute contraindications to the use of the drug. Safe use during pregnancy has not been established; use when benefits outweigh the potential risks.

**Adverse Effects/Warnings** - The drug is relatively non-toxic. Large doses by mouth may cause profuse diarrhea. Injectable forms should be given slowly IV.

**Doses** -
**Horses:**

For cyanide toxicity: First give sodium nitrite at a dose of 16 mg/kg IV followed with a 20% solution of sodium thiosulfate given at a dose of 30 - 40 mg/kg IV. If repeating treatment, use sodium thiosulfate only. (Bailey and Garland 1992a)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Sodium Thiosulfate for Injection 500 mg multidose vials, 300 mg/mL.*Cya-dote Injection*® (Anthony) (Rx). Approved for use in animal not to be used for food or lactating dairy animals.

**Human-Approved Products**:

Sodium Thiosulfate for Injection 25% (250 mg/ml) in 50 ml vials; Generic; (Rx)

To Drug Monograph Index To Ophthalmic Product Index

## SPECTINOMYCIN HCL

**Chemistry** - An aminocyclitol antibiotic obtained from *Streptomyces spectabilis*, spectinomycin is available as the dihydrochloride pentahydrate. It occurs as a white to pale buff, crystalline powder with $pK_a$s of 7 and 8.7. It is freely soluble in water and practically insoluble in alcohol.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, spectinomycin products should be stored at room temperature (15-30°C).

**Pharmacology** - Spectinomycin is primarily a bacteriostatic antibiotic that inhibits protein synthesis in susceptible bacteria by binding to the 30S ribosomal subunit.

Spectinomycin has activity against a wide variety of gram positive and gram negative bacteria, including *E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Salmonella*, *Streptococci*, *Staphylococcus* and *Mycoplasma*. It has minimal activity against anaerobes, most strains of *Pseudomonas*, *Chlamydia*, or *Treponema*. In human medicine, spectinomycin is used principally for its activity against *Neissiera gonorrhoeae*.

**Uses/Indications** - Although occasionally used in dogs, cats, horses and cattle for susceptible infections, spectinomycin is only approved for use in chickens, turkeys and swine. Refer to the Dosage section below for more information on approved uses.

**Pharmacokinetics** - After oral administration only about 7% of the dose is absorbed, but the drug that remains in the GI tract is active. When injected SQ or IM, the drug is reportedly well absorbed with peak levels occurring in about 1 hour.

Tissue levels of absorbed drug are lower than those found in the serum. Spectinomycin does not appreciably enter the CSF or the eye and is not bound significantly to plasma proteins. It is unknown whether spectinomycin crosses the placenta or enters milk.

Absorbed drug is excreted via glomerular filtration into the urine mostly unchanged. No specific pharmacokinetic parameters were located for veterinary species.

**Contraindications/Precautions/Reproductive Safety** - Spectinomycin is contraindicated in patients hypersensitive to it. The reproductive safety of the drug is not known.

**Adverse Effects/Warnings** - When used as labeled, adverse effects are unlikely with this drug. It is reported that parenteral use of this drug is much safer than with other aminocyclitol antibiotics, but little is known regarding prolonged use of the drug. It is probably safe to say that spectinomycin is significantly less ototoxic and nephrotoxic than other commonly used aminocyclitol antibiotics, but can cause neuromuscular blockade. Parenteral calcium administration will generally reverse the blockade.

Adverse effects that have been reported in human patients receiving the drug in single or multidose studies include soreness at injection site, increases in BUN, alkaline phosphatase and SGPT, and decreases in hemoglobin, hematocrit and creatinine clearance. Although increases in BUN and decreases in creatinine clearance and urine output have been noted, overt renal toxicity has not been demonstrated with this drug.

**Overdosage/Acute Toxicity** - No specific information was located on oral overdoses, but because the drug is negligibly absorbed after oral administration, significant toxicity is unlikely via this route. Injected doses of 90 mg produced transient ataxia in turkey poults.

To Drug Monograph Index To Ophthalmic Product Index

**Drug Interactions** - Antagonism has been reported when spectinomycin is used with **chloramphenicol** or **tetracycline**.

**Doses -**
**Horses**:

For susceptible infections:

a) 20 mg/kg IM *tid* (Robinson 1987)
b) For pneumonia: 20 mg/kg IM q8h; may cause local myositis. Insufficient data to comment on use. (Beech 1987b)

**Monitoring Parameters** -

1) Clinical efficacy

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Spectinomycin Injection 100 mg/ml 500 ml vials; *Spectam® Injectable* (Rhone Merieux); (OTC) Approved for use in turkey poults and newly hatched chicks.

Spectinomycin Water Soluble Concentrate 50% Powder in 128 g (64 g spectinomycin), 200 g (100 g spectinomycin), 1000 g (500 g spectinomycin) packets; *Spectam® Water Soluble Concentrate* (Rhone Merieux); (OTC) Approved for use in chickens (not layers). Slaughter withdrawal = 5 days.

Spectinomycin Oral Solution 50 mg/ml in 240 ml pump bottle and 500 and 1000 ml refill bottles; *Spectam Scour-Halt®* (Rhone Merieux); (OTC) Approved for use in swine (Not older than 4 weeks of age or greater than 15 lbs of b.w.). Slaughter w'drawal = 21 days.

Spectinomycin Oral Solution 50 mg/ml in 240 ml pump bottle and 500 and 1000 ml refill bottles; *Spectinomycin Oral Liquid* (Syntex); (OTC) Approved for use in swine (Not older than 4 weeks of age or greater than 15 lbs of b.w.). Slaughter w'drawal = 21 days.

Spectinomycin combination products:

Spectinomycin/Lincomycin in a 2:1 ratio Soluble Powder

*LS 50 Water Soluble Powder* (Upjohn); (OTC) Approved for use in chickens. No withdrawal time required.

**Human-Approved Products**:

Spectinomycin Powder for Injection 400 mg (as the HCl) per ml after reconstitution. 2 g vial with 3.2 ml diluent and 4 g vial with 6.2 ml diluent.; *Trobicin®* (Upjohn); (Rx)

## STANOZOLOL

**Chemistry** - An anabolic steroid, stanozolol occurs as an odorless, nearly colorless, crystalline powder that can exist in two forms: prisms, melting at approximately 235°C, and needles that melt at about 155°C. It is sparingly soluble in alcohol and insoluble in water.

**Storage/Stability/Compatibility** - Stanozolol tablets should be stored in tight, light-resistant packaging, preferably at room temperature.

**Pharmacology** - Stanozolol possess the actions of other anabolic agents. It may be less androgenic than other anabolics that are routinely used in veterinary medicine, however. Refer to the discussion in the Boldenone monograph for more information.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - Labeled indications for the stanozolol product *Winstrol®-V* (Winthrop/Upjohn) include "... to improve appetite, promote weight gain, and increase strength and vitality..." in dogs, cats and horses. The manufacturer also states that "Anabolic therapy is intended primarily as an adjunct to other specific and supportive therapy, including nutritional therapy."

Like nandrolone, stanozolol has been used to treat anemia of chronic disease. Because stanozolol has been demonstrated to enhance fibrinolysis after parenteral injection, it may be efficacious in the treatment of feline aortic thromboembolism or in the treatment of thrombosis in nephrotic syndrome. However, at present, clinical studies and/or experience are apparently lacking for this indication.

**Pharmacokinetics** - No specific information was located for this agent. It is generally recommended that the injectable suspension be dosed on a weekly basis in both small animals and horses.

**Contraindications/Precautions** - Stanozolol is contraindicated in pregnant animals and in breeding stallions and should not be administered to horses intended for food purposes.
The manufacturer recommends using stanozolol cautiously in patients with cardiac and renal function and with enhanced fluid and electrolyte monitoring.

In humans, anabolic agents are also contraindicated in patients with hepatic dysfunction, hypercalcemia, patients with a history of myocardial infarction (can cause hypercholesterolemia), pituitary insufficiency, prostate carcinoma, in selected patients with breast carcinoma, benign prostatic hypertrophy and during the nephrotic stage of nephritis.
The anabolic agents are category X (risk of use outweighs any possible benefit) agents for use in pregnancy and are contraindicated because of possible fetal masculinization.

**Adverse Effects/Warnings** - The manufacturer (Winthrop/Upjohn) lists as adverse effects in dogs, cats and horses only "mild androgenic effects" and then only when used with excessively high doses for a prolonged period of time.

Potentially (from human data), adverse reactions of the anabolic agents in dogs and cats could include: sodium, calcium, potassium, water, chloride, and phosphate retention; hepatotoxicity, behavioral (androgenic) changes and reproductive abnormalities (oligospermia, estrus suppression).

**Overdosage** - No information was located for this specific agent. In humans, sodium and water retention can occur after overdosage of anabolic steroids. It is suggested to treat supportively and monitor liver function should an inadvertent overdose be administered.

**Drug Interactions** - Anabolic agents as a class may potentiate the effects of **anticoagulants**. Monitoring of PT's and dosage adjustment, if necessary of the anticoagulant are recommended.
Diabetic patients receiving **insulin** may need dosage adjustments if anabolic therapy is added or discontinued. Anabolics may decrease blood glucose and decrease insulin requirements.
Anabolics may enhance the edema that can be associated with **ACTH** or **adrenal steroid** therapy.

**Drug/Laboratory Interactions -** Concentrations of **protein bound iodine (PBI)** can be decreased in patients receiving androgen/anabolic therapy, but the clinical significance of this is probably not important.
Androgen/anabolic agents can decrease amounts of **thyroxine-binding globulin** and decrease **total $T_4$** concentrations and increase **resin uptake of $T_3$ and $T_4$**. Free thyroid hormones are unaltered and, clinically, there is no evidence of dysfunction.
Both **creatinine** and **creatine excretion** can be decreased by anabolic steroids. Anabolic steroids can increase the urinary excretion of **17-ketosteroids**. Androgenic/anabolic steroids may alter **blood glucose**

To Drug Monograph Index To Ophthalmic Product Index

levels. Androgenic/anabolic steroids may suppress **clotting factors II, V, VII, and X**. Anabolic agents can affect **liver function tests** (BSP retention, SGOT, SGPT, bilirubin, and alkaline phosphatase).

**Doses -**
**Horses**:

As an anabolic agent per labeled indications:

a) 0.55 mg/kg (25 mg per 100 pounds of body weight) IM deeply. May repeat weekly for up to and including 4 weeks. (Package Insert; *Winstrol®-V* —Winthrop/Upjohn)

**Monitoring Parameters** - 1) Androgenic side effects; 2) Fluid and electrolyte status, if indicated; 3) Liver function tests if indicated; 4) RBC count, indices, if indicated; 5) Weight, appetite

**Client Information** - Tablets may be crushed and administered with food. Because of the potential for abuse of anabolic steroids by humans, many states have included, or are considering including this agent as a controlled drug. It should be kept in a secure area and out of the reach of children.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Stanozolol Suspension for Injection 50 mg/ml in 10 ml and 30 ml vials; *Winstrol®-V* (Upjohn); (Rx) Approved for cats, dogs and horses.

Stanozolol Oral Tablets 2 mg; Oral Chewable Tablets 2 mg (dogs only); *Winstrol®-V* (Upjohn); (Rx) Approved for cats, dogs and horses. In horses, the manufacturer recommends using the injectable product only.

**Human-Approved Products**:

Stanozolol Oral Tablets 2 mg; *Winstrol®* (Winthrop); (Rx)

Note: All stanozolol products are now controlled drugs (C-IV) in the USA.

## SUCCINYLCHOLINE CHLORIDE

**Chemistry** - A depolarizing neuromuscular blocking agent, succinylcholine chloride occurs as an odorless, white, crystalline powder. The dihydrate form melts at 190°C and the anhydrous form at 160°C. Aqueous solutions are acidic with a pH of approximately 4. One gram is soluble in about 1 ml of water and about 350 ml of alcohol. Commercially available injections have a pH from 3-4.5. Succinylcholine may also be known as suxemethonium chloride.

**Storage/Stability/Compatibility** - Commercial injectable solutions should be stored refrigerated (2°-8°C). One manufacturer (Glaxo Wellcome - *Anectine®*) states that multiple dose vials are stable for up to 2 weeks at room temperature with no significant loss of potency.

The powder forms of the drug are stable indefinitely when stored unopened at room temperature. After reconstitution with either $D_5W$ or normal saline, they are stable for 4 weeks at 5°C or 1 week at room temperature, but because they contain no preservative, it is recommended they be used within 24 hours.

Succinylcholine chloride is **compatible** with all commonly used IV solutions, amikacin sulfate, cephapirin sodium, isoproterenol HCl, meperidine HCl, norepinephrine bitartrate, scopolamine HBr. It may not be compatible with pentobarbital sodium and is **incompatible** with sodium bicarbonate and thiopental sodium.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - An ultrashort-acting depolarizing skeletal muscle relaxant, succinylcholine bonds with motor endplate cholinergic receptors to produce depolarization (perceived as fasiculations). The neuromuscular block remains as long as sufficient quantities of succinylcholine remain, and is characterized by a flaccid paralysis. Other pharmacologic effects are discussed in the precautions and adverse effects sections.

**Uses/Indications** - Succinylcholine chloride is indicated for short-term muscle relaxation needed for surgical or diagnostic procedures, to facilitate endotracheal intubation in some species, and to reduce the intensity of muscle contractions associated with electro- or pharmacological- induced convulsions. Dogs, cats, and horses are the primary veterinary species where succinylcholine chloride has been used.

**Pharmacokinetics** - The onset of action, with complete muscle relaxation, after IV administration is usually within 30 seconds to 1 minute. In humans this effect lasts for 2-3 minutes and then gradually diminishes within 10 minutes. The very short duration of action after a single IV dose is thought to occur because the drug diffuses away from the motor end-plate. If multiple injections or a continuous infusion is performed, the brief activity is a result of rapid hydrolysis by pseudocholinesterases at the site of action. After IM injection, the onset of action is generally within 2-3 minutes and may persist for 10-30 minutes. Dogs exhibit a prolonged duration of action (≈ 20 minutes); this species appears unique in this idiosyncratic response.

Succinylcholine is metabolized by plasma pseudocholinesterases to succinylmonocholine and choline and 10% of it is excreted unchanged in the urine. Succinylmonocholine is partially excreted in the urine and may accumulate in patients with impaired renal function. Succinylmonocholine has approximately 1/20th the neuromuscular blocking activity of succinylcholine, but if it accumulates, prolonged periods of apnea may result.

**Contraindications/Precautions** - Succinylcholine is contraindicated in patients with severe liver disease, chronic anemias, malnourishment (chronic), glaucoma or penetrating eye injuries, predisposition to malignant hyperthermia, and increased CPK values with resultant myopathies. As succinylcholine can exacerbate the effects of hyperkalemia, it should be used with extreme caution in patients who have suffered traumatic wounds or burns, are receiving quinidine or digitalis therapy, have preexisting hyperkalemia or electrolyte imbalances, as arrhythmias or cardiac arrest may occur. It should also be used with caution in patients with pulmonary, renal, cardiovascular, metabolic or hepatic dysfunction.

It is unknown if succinylcholine can cause fetal harm. The drug does cross the placenta in low concentrations and a newly delivered neonate may show signs of neuromuscular blockade if the mother received high doses or prolonged administration of the drug prior to delivery.
Succinylcholine should not be used if organophosphate agents have been given or applied recently.

Succinylcholine chloride does not have analgesic effects; and should be used with appropriate analgesic/sedative/anesthetic agents.
In horses, the following additional recommendations have been made by the American Association of Equine Practitioners:

1) Inform the owner that succinylcholine chloride is to be used as a restraining agent, not as an anesthetic.
2) Obtain history before use; do not use in horses if within 30 days they have received, an antibiotic ending in “mycin”, organophosphate insecticides or anthelmintics, any other cholinesterase inhibitor, or procaine.
3) Do not use in debilitated, excited, or exhausted horses.
4) If possible, withhold food for 4-6 hours before use.
5) Dosage of 0.088mg/kg IV may be used to paralyze skeletal muscles without causing respiratory depression. Higher doses may cause apnea and death without respiratory support. Lower doses may be possible if animal is used with a preanesthetic agent.

To Drug Monograph Index  To Ophthalmic Product Index

6) After administration, have someone hold the horse that is familiar with the actions of succinylcholine chloride so that the animal does not fall forward on its nose. Be prepared to administer oxygen and artificial respiration.
7) If death occurs, a necropsy should be performed.

**Adverse Effects/Warnings** - Succinylcholine chloride can cause muscle soreness, histamine release, malignant hyperthermia, excessive salivation, hyperkalemia, rash, and myoglobinemia/myoglobinuria. Cardiovascular effects can include bradycardia, tachycardia, hypertension, hypotension, or arrhythmias.

**Overdosage** - Inadvertent overdoses, or patients deficient in pseudocholinesterase may result in prolonged apnea. Mechanical ventilation with $O_2$ should be used until recovery. Repeated or prolonged high dosages may cause patients to convert from a phase I to a phase II block.

**Drug Interactions** - **Furosemide, phenothiazines, oxytocin, quinidine, procainamide,** beta**-adrenergic blockers (propranolol), lidocaine, magnesium salts, and isoflurane** may enhance the actions of succinylcholine. **Diazepam** may reduce the duration of action of succinylcholine.
Succinylcholine may cause a sudden outflux of potassium from muscle cells, thus causing arrhythmias in **digitilized** patients. Drugs such as **neostigmine or organophosphates,** which can inhibit pseudo-cholinesterases, should not be used with succinylcholine.
Intravenous **procaine** (competes for the pseudocholinesterase enzyme) and **cyclophosphamide** (decreases plasma pseudocholinesterase) may prolong succinylcholine's effects.
**Thiazide diuretics** and **Amphotericin B** may increase succinylcholine's effects by causing electrolyte imbalances. Increased incidences of bradycardia and sinus arrest may occur if used concurrently with **narcotic analgesics**. Concomitant administration with **inhalation anesthetics (halothane, cyclopropane, nitrous oxide, diethyl ether)** may induce increased incidences of cardiac effects (bradycardia, arrhythmias, sinus arrest and apnea) and in susceptible patients, malignant hyperthermia.

**Doses -**
**Horses**: See Precautions above.
a) 0.088 mg/kg (Muir )
b) 0.088 - 0.11 mg/kg IV, IM (Mandsager 1988)

**Elephants:** Succinylcholine is used as a euthanasia agent during culling operations. Elephant references are listed below. The reader is referred to the specific articles for further information.

a) Pitts,N.I. and Mitchell,G. 2003**. In vitro succinylcholine hydrolysis in plasma of the African elephant (Loxodonta africana) and impala (Aepyceros melampus).** Comp Biochem Physiol C Toxicol Pharmacol 134:(1):123-129 **Abstract:** In elephants the time lapsed from i.m. injection of an overdose of the muscle relaxant succinylcholine (SuCh) until death, is significantly longer than in impala. To determine a difference in the rate of SuCh hydrolysis, once the drug enters the circulation, contributes to this phenomenon we have measured the rate of hydrolysis of SuCh in elephant and impala plasma, and by elephant erythrocytes. Rate of hydrolysis was determined by incubating SuCh in plasma or erythrocyte lysate at 37 degrees C and quantifying the choline produced. Plasma SuCh hydrolytic activity in elephant plasma (12.1+/-1.7 Ul(-1) mean+/-S.D.; n=9) was significantly higher than it was in impala plasma (6.6+/-0.6 Ul(-1); n=5), but were approximately 12 and 21 times lower, respectively, than in human plasma. Elephant erythrocyte lysate had no SuCh hydrolytic activity. Applying this data to previous studies, we can show that the ratio of SuCh absorption to SuCh hydrolysis is expected to be 1.25:1 and 1.41:1 for elephants and impala respectively. It will thus take at least 1.7 times longer for elephant to achieve a plasma SuCh concentration similar to that in impala. We conclude that a more rapid hydrolysis of SuCh in elephant plasma is one factor that contributes to the longer time to death compared to impala.

To Drug Monograph Index To Ophthalmic Product Index

b) Pitts,N.I. and Mitchell,G. 2002. **Pharmacokinetics and effects of succinylcholine in African elephant (Loxodonta africana) and impala (Aepyceros melampus).** Eur J Pharm Sci 15:(3):251-260 **Abstract:** The phenomenon of slow onset of succinylcholine (Sch) effect in elephants was investigated by analyzing blood concentrations of Sch and its metabolite choline in elephant and impala. To assess whether the slow onset phenomenon is related to the pharmacokinetics of Sch following i.m. administration, we analyzed the time course of plasma concentrations of intact drug and its metabolite and determined its pharmacological effects. Blood samples were obtained from anaesthetized elephant (n=6) and impala (n=7) following i.m. administration of a lethal dose of Sch. Time from Sch injection to onset of apnoea and to death was significantly longer for elephant than impala (mean+/-S.D. apnoea 4.4+/-1.5 and 2.3+/-0.9 min, respectively; death 32.6+/-7.3 and 6.2+/-3.4 min, respectively). The C(max) was not different between elephants and impala (20.3+/-7.9 vs. 14.4+/-6.8 nmol ml(-1), respectively) but the t(max) was significantly longer for elephants (23.0+/-7.6 vs. 3.7+/-2.2 min). Analysis of the plasma Sch and choline concentrations over time revealed that the relative amount of Sch entering the circulation within the first 30 s after i.m. injection is greater for impala than elephant. No greater rate in the plasma hydrolysis of Sch in elephant compared to impala was apparent.

c) Kramer,B. and Hattingh,J. 1995. **The neuromuscular junction in the African elephant *Loxodonta africana* and African buffalo *Syncerus caffer*.** South African Journal of Wildlife Research 25:(1):p14, 3p, 2bw **Abstract:** Differences in the physiological response to the drug succinyldicholine occur between the African elephant *Loxodonta africana* and African buffalo *Syncerus caffer*, irrespective of the route of administration of the drug. The response in elephants has suggested the presence of unique acetylcholine receptors in their respiratory muscles. In this paper the first observations of the neuromuscular junction in the African elephant and African buffalo are reported. While the basic structure of the junction was found to be typically mammalian in both species, differences were found in the morphology of the postjunctional area where these receptors reside. Elucidation of the structure and function of this junction in these animals is important in the selection of drugs that act as neuromuscular blockers.

d) Hattingh,J., Pitts,N.I., De-Vos,N.I., Moyes,D.G., and Ganhao,M.F. 1991. **The response of animals to suxamethonium (succinyldicholine) and succinylmonocholine.** Journal of the South African Veterinary Association 62:(3):126-129 **Abstract:** The time which elapses before cessation of breathing, and blood pressure and blood gas changes after the i.m. administration of suxamethonium, or a mixture of suxamethonium and hexamethonium, was compared in immobilized African elephants (Loxodonta africana) and buffaloes (Synceros caffer). In addition, the respiratory responses of elephants and other animals to i.v. administration of suxamethonium and succinylmonocholine are reported, as are the effects of darting animals with succinylmonocholine. Respiration was affected in a similar fashion in all species investigated. However, the characteristic gradual decrease in respiratory rate seen in elephants during culling, using suxamethonium, resembles the effects observed when succinylmonocholine is administered. It is suggested that elephants are killed by this first breakdown product of suxamethonium during culling and/or that unique acetylcholine receptors may be involved.

e) Hattingh,J., Pitts,N.I., Ganhao,M.F., Moyes,D.G., and de Vos,V. 1990. **Blood constituent responses of animals culled with succinyldicholine and hexamethonium.** J.S.Afr.Vet.Assoc. 61:117-118 **Abstract:** Blood constituent responses of elephants and buffaloes culled in the Kruger National Park, using a mixture of succinyldicholine and hexamethonium, were compared to those of animals culled with succinyldicholine only. The results show a decreased physiological response in the animals culled with the mixture, characterized by lower total catecholamine, cortisol and glucose concentrations. Neither a delay of up to 30 min in obtaining blood samples from culled animals, nor a delay of up to 30 min in processing samples obtained immediately after cessation of respiration, gave any significant difference in the blood constituents which were measured.

f) Hattingh,J. 1984**. Effects of etorphine and succinyldicholine on blood composition in elephant and buffalo.** South African Journal of Zoology 19:286-290

To Drug Monograph Index To Ophthalmic Product Index

h) Hattingh,J., Wright,P.G., de Vos,V., McNairn,I.S., Ganhao,M.F., Silove,M., Wolverson,G., and Cornelius,S.T. 1984. **Blood composition in culled elephants and buffaloes.** J.S.Afr.Vet.Assoc. 55:(4):157-164 **Abstract:** Blood composition of succinyldicholine culled elephants and buffaloes was compared with that of undisturbed animals shot in the brain. The results show statistically significant differences in a number of variables including plasma ACTH and cortisol concentrations. The observed changes are attributed to stress induced by a combination of herding and darting with succinyldicholine and asphyxia. Extrapolation from blood oxygen tensions suggests that this stress may be perceived for an undetermined period which is probably longer in elephants than buffaloes.

**Monitoring Parameters** -

1) Level of muscle relaxation
2) Cardiac rate/rhythm
3) Respiratory depressant effect

**Client Information** - This drug should only be used by professionals familiar with its use.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Succinylcholine Chloride for Injection 20 mg/ml, 50 mg/ml, 100 mg/ml in 10 ml vials and amps and 5 ml syringes; *Anectine*® (Glaxo Wellcome); *Quelicin*® (Abbott): Succinylcholine Chloride (Organon) (Rx)

Succinylcholine Chloride Powder for Infusion 500 mg or 1 gram vials; *Anectine Flo-Pak*® (Glaxo Wellcome); (Rx)

## SUCRALFATE

**Chemistry** - A basic, aluminum complex of sucrose sulfate, sucralfate occurs as a white, amorphous powder. It is practically insoluble in alcohol or water.

Sucralfate is structurally related to heparin, but does not posses any appreciable anticoagulant activity. It is also structurally related to sucrose, but is not utilized as a sugar by the body. Sucralfate is also known as aluminum sucrose sulfate, basic.

**Storage/Stability/Compatibility** - Store sucralfate tablets in tight containers at room temperature.

**Pharmacology** - While the exact mechanism of action of sucralfate as an antiulcer agent is not known, the drug has a local effect rather than a systemic one. After oral administration, sucralfate reacts with hydrochloric acid in the stomach to form a paste-like complex that will bind to the proteinaceous exudates that generally are found at ulcer sites. This insoluble complex forms a barrier at the site and protects the ulcer from further damage caused by pepsin, acid or bile. Sucralfate may have some cytoprotective effects, possibly by stimulation of prostaglandin $E_2$ and $I_2$. Sucralfate also has some antacid activity, but it is believed that this is not of clinical importance. Sucralfate does not significantly affect gastric acid output, or trypsin or pancreatic amylase activity. It may decrease the rate of gastric emptying.

**Uses/Indications -** Sucralfate has been used in the treatment of oral, esophageal, gastric and duodenal ulcers. It has also been employed to prevent drug-induced (*e.g.,* aspirin) gastric erosions.

**Pharmacokinetics** - Animal studies have indicated that only 3-5% of an oral dose is absorbed which is excreted in the urine unchanged within 48 hours. The remainder of the drug is converted to sucrose sulfate

To Drug Monograph Index To Ophthalmic Product Index

in the gut by reacting with hydrochloric acid and is excreted in the feces within 48 hours. The duration of action (binding to ulcer site) may persist up to 6 hours after oral dosing.

**Contraindications/Precautions** - There are no known contraindications to the use of sucralfate. Because it may cause constipation, it should be used with caution in animals where decreased intestinal transit times may be deleterious.

It is unknown if sucralfate crosses the placenta and whether it may be used safely during pregnancy. In rats, dosages up to 38 times those used in humans caused no impaired fertility and doses up to 5O times normal caused no symptoms of teratogenicity.

**Adverse Effects/Warnings** - Adverse effects are uncommon with sucralfate therapy. Constipation is the most prominent adverse effect reported in humans (2%) and dogs taking the drug.

**Overdosage** - Overdosage is unlikely to cause any significant problems. Laboratory animals receiving up to 12 grams/kg orally demonstrated no incidence of mortality.

**Drug Interactions** - **Cimetidine, tetracycline, phenytoin and digoxin** bioavailability may be reduced if administered with sucralfate. To avoid this problem, give sucralfate at least 2 hours apart from these other drugs. Because sucralfate requires an acidic environment to be effective, give sucralfate doses before (at least 1/2 hour) **cimetidine (or other $H_2$ antagonist) or antacids**.

**Doses -**
**Horses**:

a) Foals: 1 - 2 grams PO *qid* (Clark and Becht 1987)
b) 2 mg/kg PO *tid* (Robinson 1987)

**Monitoring Parameters** -

1) Clinical efficacy (dependent on reason for use); monitored by decrease in symptomatology, endoscopic examination, blood in feces, etc.

**Client Information** - To maximize the benefit of this medication, it must be administered as prescribed by the veterinarian; symptoms may reoccur if dosages are missed. Unless otherwise instructed, give this medication on an empty stomach (1 hour before feeding or 2 hours after) and at bedtime.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Sucralfate 1 gram tablets (scored); *Carafate*® (Hoechst Marion Roussel); Generic. (Rx)
Sucralfate Suspension: 1 g/10 ml in 420 ml; *Carafate*® (Hoechst Marion Roussel) (Rx)

## SULFADIAZINE/TRIMETHOPRIM PK
## SULFAMETHOXAZOLE/TRIMETHOPRIM

Note: In the practice of veterinary medicine in the United States, two separate combinations with trimethoprim are used clinically. There are trimethoprim/sulfadiazine products approved for use in dogs, cats and horses in both parenteral and oral dosage forms. Many veterinarians also will use the human

approved, trimethoprim/sulfamethoxazole oral products because of economic considerations. In Canada, sulfadoxine is available in combination with trimethoprim for veterinary use.

**Chemistry** - Trimethoprim occurs as odorless, bitter-tasting, white to cream-colored crystals or crystalline powder. It is very slightly soluble in water and slightly soluble in alcohol.
Sulfadiazine occurs as an odorless or nearly odorless, white to slightly yellow powder. It is practically insoluble in water and sparingly soluble in alcohol.

Sulfamethoxazole occurs as a practically odorless, white to off-white, crystalline powder. Approximately 0.29 mg is soluble in 1 ml of water and 20 mg are soluble in 1 ml of alcohol.
In combination, these products may be known as: Co-trimoxazole, SMX-TMP, TMP-SMX, trimethoprim-sulfamethoxazole, sulfamethoxazole-trimethoprim, sulfadiazine-trimethoprim, trimethoprim-sulfadiazine, TMP-SDZ, SDZ-TMP, Co-trimazine or by their various trade names.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, trimethoprim/sulfadiazine and co-trimoxazole products should be stored at room temperature (15-30°C) in tight containers.

**Pharmacology** - Alone, sulfonamides are bacteriostatic agents and trimethoprim is bactericidal, but in combination, the potentiated sulfas are bactericidal. Potentiated sulfas sequentially inhibit enzymes in the folic acid pathway, thereby inhibiting bacterial thymidine synthesis. The sulfonamide blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid (DFA), and trimethoprim blocks the conversion of DFA to tetrahydrofolic acid by inhibiting dihydrofolate reductase.

The *in vitro* optimal ratio for most susceptible bacteria is approximately 1:20 (trimethoprim:sulfa), but synergistic activity can reportedly occur with ratios of 1:1 - 1:40. The serum concentration of the trimethoprim component is considered to be more important than the sulfa concentration. For most susceptible bacteria, the MIC's for TMP are generally above 0.5 micrograms/ml.

The potentiated sulfas have a fairly broad spectrum of activity. Gram positive bacteria that are generally susceptible include most streptococci, many strains of staphylococcus and *Nocardia*. Many gram negative organisms of the family Enterobacteriaceae are susceptible to the potentiated sulfas, but not *Pseudomonas aeruginosa*. Some protozoa (*Pneumocystis carinii*, Coccidia and Toxoplasma) are also inhibited by the combination. Potentiated sulfas reportedly have little activity against most anaerobes, but opinions on this vary.

Resistance will develop slower to the combination of drugs than to either one alone. In gram negative organisms, resistance is usually plasmid-mediated.

**Uses/Indications** - Although only approved for use in dogs and horses, trimethoprim/sulfadiazine *et al* is used in many species to treat infections caused by susceptible organisms. See Dosage section for more information.

**Pharmacokinetics** - Trimethoprim/sulfa is well absorbed after oral administration, with peak levels occurring about 1-4 hours after dosing. The drug is more slowly absorbed after subcutaneous absorption, however. In ruminants, the trimethoprim is apparently trapped in the ruminoreticulum after oral administration and undergoes some degradation.
Trimethoprim/sulfa is well distributed in the body. When meninges are inflamed, the drugs enter the CSF in levels of about 50% of those found in the serum. Both drugs cross the placenta and are distributed into milk. The volume of distribution for trimethoprim in various species are: 1.49 L/kg (dogs), and 0.59-1.51 L/kg (horses). The volume of distribution for sulfadiazine in dogs is 1.02 L/kg.

To Drug Monograph Index To Ophthalmic Product Index

Trimethoprim/sulfa is both renally excreted unchanged via glomerular filtration and tubular secretion and metabolized by the liver. The sulfas are primarily acetylated and conjugated with glucuronic acid and trimethoprim is metabolized to oxide and hydroxylated metabolites. Trimethoprim may be more extensively metabolized by the liver in adult ruminants than in other species. The serum elimination half-lives for trimethoprim in various species are: 2.5 hours (dogs), 1.91-3 hours (horses), 1.5 hours (cattle). The serum elimination half-lives for sulfadiazine in various species are: 9.84 hours (dogs), 2.71 hours (horses), 2.5 hours (cattle). While trimethoprim is quite rapidly eliminated from the serum, the drug may persist for a longer period of time in tissues.

Because of the number of variables involved it is extremely difficult to apply pharmacokinetic values in making dosage recommendations with these combinations. Each drug (trimethoprim and the sulfa) has different pharmacokinetic parameters (absorption, distribution, elimination) in each species. Since different organisms have different MIC values and the optimal ratio of trimethoprim to sulfa also differs from organism to organism, this problem is exacerbated.

There is considerable controversy regarding the frequency of administration of these combinations. The veterinary product, trimethoprim/sulfadiazine is labeled for once daily administration in dogs and horses, but many clinicians believe that the drug is more efficacious if given twice daily, regardless of which sulfa is used.

**Contraindications/Precautions/Reproductive Safety** - The manufacturer states that trimethoprim/sulfadiazine should not be used in dogs or horses showing marked liver parenchymal damage, blood dyscrasias, or in those with a history of sulfonamide sensitivity. It is not for use in horses (or approved for other animals) intended for food.

This combination should be used with caution in patients with pre-existing hepatic disease.
Safety of trimethoprim/sulfa has not been clearly established in pregnant animals. Reports of teratogenicity (cleft palate) have been reported in some rat studies. Fetal mortality was also increased in rabbits receiving high doses of trimethoprim. Dog studies have not demonstrated any teratogenic effects. However, this combination should be used in pregnant females only when the benefits clearly outweigh the risks of use. Studies thus far in male animals have not demonstrated any decreases in reproductive performance.

**Adverse Effects/Warnings** - Adverse effects noted in dogs: keratoconjunctivitis sicca (which may be irreversible), acute neutrophilic hepatitis with icterus, vomiting, anorexia, diarrhea, fever, hemolytic anemia, urticaria, polyarthritis, facial swelling, polydipsia, polyuria and cholestasis. Potentiated sulfonamides may cause hypothyroidism in the dog, particularly with extended therapy. Acute hypersensitivity reactions manifesting as Type I (anaphylaxis) or Type III reaction (serum sickness) can also be seen. Hypersensitivity reactions appear to be more common in large breed dogs; Doberman Pinschers may possibly be more susceptible to this effect than other breeds. Other hematologic effects (anemias, agranulocytosis) are possible, but are fairly rare in dogs.

Adverse effects noted in cats may include anorexia, leukopenias and anemias.
In horses, transient pruritis has been noted after intravenous injection. Oral therapy has resulted in diarrhea development in some horses. If the 48% injectable product is injected IM, SQ, or extravasates after IV administration, swelling, pain and minor tissue damage may result. Hypersensitivity reactions and hematologic effects (anemias, thrombocytopenia, or leukopenias) may also be seen; long term therapy should include periodic hematologic monitoring.

**Overdosage/Acute Toxicity** - Manifestations of an acute overdosage can include symptoms of GI distress (nausea, vomiting, diarrhea), CNS toxicity (depression, headache, and confusion), facial swelling, bone marrow depression and increases in serum aminotransferases. Oral overdoses can be treated by emptying the stomach (following usual protocols) and initiating symptomatic and supportive therapy. Acidification of the urine may increase the renal elimination of trimethoprim, but could also cause sulfonamide crystalluria,

particularly with sulfadiazine containing products. Complete blood counts (and other laboratory parameters) should be monitored as necessary. Bone marrow suppression associated with chronic overdoses may be treated with folinic acid (leucovorin) if severe. Peritoneal dialysis is not effective in removing TMP or sulfas from the circulation.

**Drug Interactions** - Trimethoprim/sulfa may prolong the clotting times in patients receiving **coumarin (warfarin)** anticoagulants. Sulfonamides may displace other highly bound drugs, such as **methotrexate, phenylbutazone, thiazide diuretics, salicylates, probenicid and phenytoin.** Although the clinical significance of these interactions is not entirely clear, patients should be monitored for enhanced effects of the displaced agents. **Antacids** may decrease the bioavailability of sulfonamides if administered concurrently. Trimethoprim may decrease the therapeutic effect of **cyclosporine (systemic)** and increase the risk of nephrotoxicity developing.

**Drug/Laboratory Interactions** - When using the Jaffe alkaline picrate reaction assay for **creatinine** determination, trimethoprim/sulfa may cause an overestimation of approximately 10%. Sulfonamides may give false-positive results for **urine glucose** determinations when using the Benedict's method.

**Doses** -

Note: There is significant controversy regarding the frequency of dosing these drugs. See the pharmacokinetic section above for more information. Unless otherwise noted, doses are for combined amounts of trimethoprim/sulfa.

**Horses**:

For susceptible infections:

a) 15 mg/kg IV q8-12h (Brumbaugh 1987)
b) Foals: 15 mg/kg IV q12h (dose extrapolated from adult horses) (Caprile and Short 1987)
c) 22 mg/kg IV q24h or 30 mg/kg PO q24h (Upson 1988)
d) 30 mg/kg PO once daily or 21.3 mg/kg IV once daily (Package inserts; *Tribrissen*®—Coopers)
e) 24 mg/kg PO, IV or IM q12h (Baggot and Prescott 1987)

**Elephants:**

a) 22 mg/kg PO 4-6 times/day to maintain trough concentrations above the MIC in African elephants, however, the authors suggest favorable clinical response which is the basis for BID dosing in horses may also be effective in elephants. Page,C.D., Mautino,M., Derendorf,H.D., and Anhalt,J.P. 1991. **Comparative pharmacokinetics of trimethoprim-sulfamethoxazole administered intravenously and orally to captive elephants.** Journal of Zoo and Wildlife Medicine 22:(4):409-416 **Abstract:** Three healthy captive female African elephants (*Loxodonta africana*) were used to determine the pharmacokinetics of trimethoprim-sulfamethoxazole (TMP-SMZ) after a single i.v. and a single oral dose of 3.7mg/kg TMP and 18.3mg/kg SMZ. A 2-mo wash-out period was allowed between the i.v. and oral trials. An adult female Asian elephant (*Elephas maximus*) was also used in this investigation; however, pharmacokinetic parameters calculated from data from this animal were not used to calculate mean pharmacokinetic parameters for TMP-SMZ in African elephants. Serum concentrations of TMP-SMZ were measured by high-performance liquid chromatography on blood samples collected via venous catheterization predose, over 12 hr after i.v. drug administration, and over 24 hr after oral drug administration. For African elephants, the mean terminal half-life ($t_{1/2,z}$), clearance (CL), and volume distribution at steady state ($Vd_{ss}$) of TMP following i.v. administration were 1.4 + 0.7 hr, 856.0 + 114.0 ml/hr/kg, and 1.1 + 0.4 L/kg, respectively. For SMZ, these parameters were 1.83 + 0.06 hr, 93.6 + 10.8 ml/hr/kg, and 0.2 + 0.02 L/kg, respectively. Following oral administration, the mean $t_{1/2,z}$ was 3.0 + 1.1 hr, the maximum concentration ($C_{max}$) was 0.43 + 0.07 micrograms/ml at time ($t_{max}$) 1.7 + 0.6 hr, and the bioavailability (F) was 61.2 + 21.3% for TMP. For SMZ, the mean $t_{1/2,z}$ was 2.0 + 0.3 hr, the $C_{max}$ was 30.7 + 2.5 micrograms/ml at $t_{max}$ 3.0 + 1.0 hr, and F was 81.7 + 17.5%. Calculated pharmacokinetic parameters

To Drug Monograph Index To Ophthalmic Product Index

from this investigation were similar to values reported in horses. Based on these findings, metabolic scaling should not be employed to calculate the dose of TMP-SMZ in elephants.

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects; with chronic therapy, periodic complete blood counts should be considered.
3) Thyroid function tests should be considered (baseline and ongoing) particularly in dogs recieving long term treatment

**Client Information** - If using suspension, shake well before using. Does not need to be refrigerated. Animals must be allowed free access to water and must not become dehydrated while on therapy.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Trimethoprim (TMP)/Sulfadiazine (SDZ) Oral Tablets:

30's: 5 mg TMP/25 mg SDZ (coated tablets)
120's: 20 mg TMP/100 mg SDZ (coated tablets)
480's: 80 mg TMP/400 mg SDZ (uncoated, scored tablets)
960's: 160 mg TMP/800 mg SDZ (uncoated, unscored tablets)

*Tribrissen*® (Schering), (Rx) Approved for use in dogs.

Trimethoprim (TMP)/Sulfadiazine (SDZ) Oral Paste. Each gram contains 67 mg trimethoprim and 333 mg sulfadiazine. Available in 37.5 gram (total weight) syringes.; *Tribrissen*® *400 Oral Paste* (Schering) (Rx) Approved for use in horses.

In Canada, trimethoprim and sulfadoxine are available for use in cattle and swine (*Trivetrin*®—Wellcome; *Borgal*®—Hoechst). They have a slaughter withdrawal of 10 days and milk withdrawal of 96 hours.

**Human-Approved Products**:

Trimethoprim (alone) Tablets: 100 mg and 200 mg; *Proloprim*® (Glaxo Wellcome); *Trimpex*® (Roche); generic, (Rx)

Trimethoprim 80 mg and Sulfamethoxazole 400 mg Tablets; Trimethoprim 160 mg and Sulfamethoxazole 800 mg Tablets; *Bactrim*®*, Bactrim-DS*® (Roche); *Septra*®, *Septra*® *DS*, (Glaxo Wellcome); *Cotrim*®*, Cotrim-DS*® (Lemmon), generic; (Rx)

Trimethoprim 8 mg/ml and Sulfamethoxazole 40 mg/ml oral suspension in pint bottles; *Bactrim Pediatric*® (Roche); *Septra*® (Glaxo Wellcome); *Cotrim Pediatric*® (Lemmon) (Rx), Sulfatrim, generic (Rx); generic; (Rx)

Trimethoprim 16 mg/ml and Sulfamethoxazole 80 mg/ml for IV infusion in 5, 10, 20 and 30 ml vials ; *Bactrim*® *IV*(Roche); *Septra*® *IV*(Glaxo Wellcome); generic (Rx)

Because of the unavailability of veterinary trimethoprim/sulfadiazine injection in the USA, the human injectable product has been used. Before giving IV, the product must be diluted, generally at a rate of 1 ml of TMP/SMZ injection per 25 mls of dextrose 5% injection. Once diluted the injection should be used within 6 hours. Some reports of administering the drug SubQ to ruminants have also been received. To minimize potential local reactions, the injection should be diluted at a rate of about 1 ml TMP/SMZ injection to 5 ml dextrose 5%.

## SULFADIMETHOXINE

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - A long-acting sulfonamide, sulfadimethoxine occurs as an odorless or almost odorless, creamy white powder. It is very slightly soluble in water and slightly soluble in alcohol.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, store sulfadimethoxine products at room temperature and protect from light. Sulfadimethoxine injection should be stored at room temperature (15-30°C). If crystals form due to exposure to cold temperatures, either warm the vial or store at room temperature for several days to resolubolize the drug. Efficacy is not impaired by this process.

**Information on the Pharmacology, Contraindications, Precautions, Reproductive Safety, Adverse Effects, Warnings**, **Overdosage, Acute Toxicity**, **Drug Interactions**, **Drug/Laboratory Interactions, Monitoring Parameters & Client Information** for the sulfonamide agents can be found in the TMP/Sulfa monographs.

**Uses/Indications** - Sulfadimethoxine injection and tablets are approved for use in dogs and cats for respiratory, genitourinary, enteric and soft tissue infections caused by susceptible organisms. Sulfadimethoxine is also used in the treatment of coccidiosis in dogs although not approved for this indication.

In horses, sulfadimethoxine injection is approved for the treatment of respiratory infections caused by *Streptococcus equi*.

In cattle, the drug is approved for treating shipping fever complex, calf diphtheria, bacterial pneumonia and foot rot caused by susceptible organisms.

In poultry, sulfadimethoxine is added to drinking water to treat coccidiosis, fowl cholera and infectious coryza.

**Pharmacokinetics** - In dogs, cats, swine and sheep, sulfadimethoxine is reportedly readily absorbed and well distributed. Relative volumes of distribution range from 0.17 L/kg in sheep to 0.35 L/kg in cattle and horses. The drug is also highly protein bound.

In most species, sulfadimethoxine is acetylated in the liver to acetylsulfadimethoxine and excreted unchanged in the liver. In dogs, the drug is not appreciably hepatically metabolized and renal excretion is the basis for the majority of elimination of the drug. Sulfadimethoxine's long elimination half-lives are a result of its appreciable reabsorption in the renal tubules. Serum half-lives reported in various species are: swine (14 hours), sheep (15 hours) and horses (11.3 hours).

**Doses -**
**Horses**:

For susceptible infections:

a) 55 mg/kg PO or IV q12h (Upson 1988)
b) 55 mg/kg IV or PO initially, then 27.5 mg/kg q24h IV (Package insert; *Albon*®—Roche)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products:**

Sulfadimethoxine Injection 400 mg/ml (40%) in 100 ml and 250 ml vials

*Albon*® (Pfizer); (Rx) Approved for use in dogs, cats, horses and cattle. Not to be used in horses intended for food or calves to be processed for veal. Slaughter withdrawal = 5 days (cattle); milk withdrawal = 60 hours.

Sulfadimethoxine Oral Tablets 125 mg, 250 mg, 500 mg

To Drug Monograph Index To Ophthalmic Product Index

*Albon*® (Pfizer), (Rx) Approved for use in dogs and cats.

Sulfadimethoxine Oral Suspension 50 mg/ml in 1 oz. and 16 oz. bottles

*Albon*® (Pfizer); (Rx) Approved for use in dogs and cats.

Sulfadimethoxine Oral Suspension 125 mg/ml 5% in 2 and 16 oz. bottles

*Albon*® (Pfizer) (Rx) Approved for use in dogs and cats.

Sulfadimethoxine Oral Boluses 5 g, & 15 g

*Albon*® (Pfizer); (OTC) Approved for use in cattle. Slaughter withdrawal = 7 days (cattle); milk withdrawal = 60 hours.

Sulfadimethoxine Oral Boluses Sustained-Release 12.5 g

*Albon*® (Pfizer); (Rx) Approved for use in non-lactating cattle. Slaughter withdrawal = 21 days (cattle)

Sulfadimethoxine Soluble Powder 94.6 g/packet (for addition to drinking water)

*Albon*® (Pfizer); (OTC) Approved for use in dairy calves, dairy heifers, beef cattle, broiler and replacement chickens only, and meat-producing turkeys. Slaughter withdrawal = 7 days (cattle); 5 days (poultry—do not use in chickens over 16 weeks old or in turkeys over 24 weeks old).

Sulfadimethoxine 12.5% Concentrated Solution (for addition to drinking water); *Albon*® (Pfizer); Generic (OTC) Approved for use in chickens, turkeys and cattle. Slaughter withdrawal = 7 days (cattle); 5 days (poultry—do not use in chickens over 16 weeks old or in turkeys over 24 weeks old).

**Human-Approved Products:** None

## SULFADIMETHOXINE/ORMETOPRIM

**Chemistry** - A diaminopyrimidine structurally related to trimethoprim, ormetoprim occurs as a white, almost tasteless powder. The chemistry of sulfadimethoxine is described in the previous monograph.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, store tablets in tight, light resistant containers at room temperature.

**Pharmacology** - Sulfadimethoxine/ormetoprim shares mechanisms of action and probably the bacterial spectrum of activity with trimethoprim/sulfa. Alone, sulfonamides are bacteriostatic agents, but in combination with either ormetoprim or trimethoprim, the potentiated sulfas are bactericidal. Potentiated sulfas sequentially inhibit enzymes in the folic acid pathway, thereby inhibiting bacterial thymidine synthesis. The sulfonamide blocks the conversion of para-aminobenzoic acid (PABA) to dihydrofolic acid (DFA) and ormetoprim blocks the conversion of DFA to tetrahydrofolic acid by inhibiting dihydrofolate reductase.

The potentiated sulfas have a fairly broad spectrum of activity. Gram positive bacteria that are generally susceptible include, most streptococci, many strains of staphylococcus, and *Nocardia*. Many gram negative organisms of the family Enterobacteriaceae are susceptible to the potentiated sulfas, but not *Pseudomonas aeruginosa*. Some protozoa (*Pneumocystis carinii*, Coccidia and Toxoplasma) are also inhibited by the combination. Potentiated sulfas reportedly have little activity against most anaerobes, but opinions on this vary.

Resistance will develop slower to the combination of drugs, than to either one alone. In gram negative organisms, resistance is usually plasmid-mediated.

**Uses/Indications** - The present approved indications for this combination are for the treatment of skin and soft tissue infections in dogs caused by susceptible strains of *Staphylococcus aureus* and *E. coli*. Because

clinical experience with this drug is extremely limited at the time of this writing, further uses and indications may be forthcoming.

**Pharmacokinetics** - The pharmacokinetics of sulfadimethoxine are outlined in the previous monograph. Pharmacokinetic data for ormetoprim is not available at the time of this writing, but the manufacturer claims that therapeutic levels are maintained over 24 hours at recommended doses.

**Contraindications/Precautions/Reproductive Safety** - The manufacturer states that ormetoprim/sulfadimethoxine should not be used in dogs or horses showing marked liver parenchymal damage, blood dyscrasias, or in those with a history of sulfonamide sensitivity.

This combination should be used with caution in patients with pre-existing hepatic or thyroid disease.

Safety of ormetoprim/sulfadimethoxine has not been established in pregnant animals. Reports of teratogenicity (cleft palate) have been reported in some lab animals with trimethoprim/sulfa.

**Adverse Effects/Warnings** - Adverse effects with this combination have not been reported at recommended doses, but the number of evaluated patients is very small at the time of this writing. This combination would be expected to exhibit an adverse reaction profile in dogs similar to that seen with trimethoprim/sulfa, including: keratoconjunctivitis sicca (which may be irreversible), acute neutrophilic hepatitis with icterus, vomiting, anorexia, diarrhea, fever, hemolytic anemia, urticaria, polyarthritis, facial swelling, polydipsia, polyuria and cholestasis. Acute hypersensitivity reactions manifesting as Type I (anaphylaxis) or Type III reaction (serum sickness) can also be seen. Hypersensitivity reactions appear to be more common in large breed dogs; Doberman Pinschers may possibly be more susceptible to this effect than other breeds. Other hematologic effects (anemias, agranulocytosis) are possible, but fairly rare in dogs.

Long-term (8 weeks) therapy at recommended doses with ormetoprim/sulfadimethoxine (27.5 mg/kg once daily) resulted in elevated serum cholesterol, thyroid and liver weights, mild follicular thyroid hyperplasia and enlarged basophilic cells in the pituitary. The manufacturer states that the principal treatment-related effect of extended or excessive usage is hypothyroidism.

**Overdosage/Acute Toxicity** - In experimental studies in dogs, doses greater than 80 mg/kg resulted in slight tremors and increased motor activity in some dogs. Higher doses may result in depression, anorexia or seizures.

It is suggested that very high oral overdoses be handled by emptying the gut using standard precautions and protocols and by treating symptoms supportively and symptomatically.

**Drug Interactions**; **Drug/Laboratory Interactions** - None have been noted for this combination, but it would be expected that the potential interactions outlined for the trimethoprim/sulfa monograph would also apply to this combination; refer to that monograph for more information.

**Doses** -

**Dogs**:

For susceptible infections:

a) Initially 55 mg/kg (combined drug) PO on the first day of therapy, then 27.5 mg/kg PO once daily for at least 2 days after remission of clinical signs. Not approved for treatment longer than 21 days. (Package insert; *Primor*®—SKB)

**Elephants:**

a) Sulfadimethoxine/ormetoprim (Primor; 1200:100mg of sulfadimethoxine/200 mg

To Drug Monograph Index To Ophthalmic Product Index

ormetoprim): 16.2 – 18.5 mg/kg po BID on day 1 then 9.25 mg/kg thereafter. This regimen has been used for 30 days with positive therapeutic results and no adverse effects. For more severe infections: 23.2 – 26.4 mg/kg po BID on day 1 then 13.2 mg/kg thereafter. Diarrhea may result at the higher dose but will resolve with the discontinuation of treatmentSchmidt, M.J: Senior Research Veterinarian, Washington Park Zoo, Portland, Oregon, personal communication, 1986. In: Olsen,J.H., 1999. **Antibiotic therapy in elephants**. In: Fowler,M.E. and Miller R.E. (Editors), Zoo and Wild Animal Medicine: Current Therapy 4. W.B. Saunders, Philadelphia, PA,USA p. 537.

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects

**Client Information** - Animals must be allowed free access to water and must not become dehydrated while on therapy.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Sulfadimethoxine/Ormetoprim Tablets (scored)

120's: 100 mg Sulfadimethoxine, 20 mg Ormetoprim
240's: 200 mg Sulfadimethoxine, 40 mg Ormetoprim
600's: 500 mg Sulfadimethoxine, 100 mg Ormetoprim
1200's: 1000 mg Sulfadimethoxine, 200 mg Ormetoprim

*Primor*® (Pfizer); (Rx) Approved for use in dogs.

**Human-Approved Products**: None

## TERBUTALINE SULFATE

**Chemistry** - A synthetic sympathomimetic amine, terbutaline sulfate occurs as a slightly bitter-tasting, white to gray-white, crystalline powder that may have a faint odor of acetic acid. One gram is soluble in 1.5 ml of water or 250 ml of alcohol. The commercially available injection has its pH adjusted to 3-5 with hydrochloric acid.

**Storage/Stability/Compatibility** - Terbutaline tablets should be stored in tight containers at room temperature (15-30°C). Tablets have an expiration date of 3 years beyond the date of manufacture. Terbutaline injection should be stored at room temperature (15-30°C), and protected from light. The injection has an expiration date of 2 years after the date of manufacture. Terbutaline injection is stable over a pH range of 1-7. Discolored solutions should not be used. It is compatible with $D_5W$ and aminophylline.

**Pharmacology** - Terbutaline stimulates beta-adrenergic receptors found principally in bronchial, vascular, and uterine smooth muscles ($beta_2$) and bronchial and vascular smooth muscle relaxation occurs with resultant reduced airway resistance. At usual doses it has little effect on cardiac ($beta_1$) receptors and usually does not cause direct cardiostimulatory effects. Occasionally, a tachycardia develops which may be a result of either direct beta stimulation or a reflex response secondary to peripheral vasodilation. Terbutaline has virtually no alpha-adrenergic activity.

To Drug Monograph Index To Ophthalmic Product Index

**Uses/Indications** - Terbutaline is used as a bronchodilating agent in the adjunctive treatment of cardiopulmonary diseases (including tracheobronchitis, collapsing trachea, pulmonary edema, and allergic bronchitis) in small animals.
It has been used occasionally in horses for its bronchodilating effects, but adverse effects have limited its use in this species. A related compound, clenbuterol, has been used to a much greater extent for treating bronchoconstriction in the horse, but it is not available commercially in the United States.

Oral and intravenous terbutaline has been used successfully (in humans) in the inhibition of premature labor symptoms.

**Pharmacokinetics** - The pharmacokinetics of this agent have apparently not been thoroughly studied in domestic animals. In humans, only about 33-50% of an oral dose is absorbed; peak bronchial effects occur within 2-3 hours and activity persists for up to 8 hours. Terbutaline is well absorbed following SQ administration with an onset of action occurring within 15 minutes, peak effects at 30-60 minutes, and a duration of activity for up to 4 hours.

Terbutaline is distributed into milk, but at levels of approximately 1% of the oral dose given to the mother. Terbutaline is principally excreted unchanged in the urine (60%), but is also metabolized in the liver to an inactive sulfate conjugate.

**Contraindications/Precautions** - Terbutaline is contraindicated in patients hypersensitive to it. One veterinary school formulary (Schultz 1986) states that terbutaline is contraindicated in dogs and cats with heart disease, especially with CHF or cardiomyopathy. It should be used with caution in patients with diabetes, hyperthyroidism, hypertension, seizure disorders, or cardiac disease (especially with concurrent arrhythmias).

**Adverse Effects/Warnings** - Most adverse effects are dose-related and are those that would be expected with sympathomimetic agents, including increased heart rate, tremors, CNS excitement (nervousness) and dizziness. These effects are generally transient and mild and do not require discontinuation of therapy. After parenteral injection in horses, sweating and CNS excitation have been reported.

Transient hypokalemia has been reported in humans receiving beta-adrenergic agents. If an animal is susceptible to developing hypokalemia, it is suggested that additional serum potassium monitoring be done early in therapy.

**Overdosage** - Symptoms of significant overdose after systemic administration may include arrhythmias (bradycardia, tachycardia, heart block, extrasystoles), hypertension, fever, vomiting, mydriasis, and CNS stimulation. If a recent oral ingestion, it should be handled like other overdoses (empty gut, give activated charcoal and a cathartic) if the animal does not have significant cardiac or CNS effects. If cardiac arrhythmias require treatment, a beta blocking agent (*e.g.,* propranolol) can be used, but may precipitate bronchoconstriction.

**Drug Interactions** - Use of terbutaline with **other sympathomimetic amines** may increase the risk of developing adverse cardiovascular effects. **Beta-adrenergic blocking agents** (*e.g.,* propranolol) may antagonize the actions of terbutaline. **Tricyclic antidepressants or monoamine oxidase inhibitors** may potentiate the vascular effects of terbutaline. Use with inhalation anesthetics (*e.g.*, **halothane, isoflurane, methoxyflurane**), may predispose the patient to ventricular arrhythmias, particularly in patients with preexisting cardiac disease—use cautiously. Use with **digitalis** glycosides may increase the risk of cardiac arrhythmias.

**Doses** -
**Horses**:

To Drug Monograph Index To Ophthalmic Product Index

a) 0.0033 mg/kg IV (Robinson 1987)
b) 0.025 mg/kg once daily PO; 0.0033 mg/kg IV (Schultz 1986)
c) 0.13 mg/kg PO q8h (McConnell and Hughey 1987)
d) 30 mg PO *tid* (in a 450 kg horse); usually used in combination with aminphylline and prednisone. (Duran 1992)

**Monitoring Parameters** -
1) Clinical symptom improvement; auscultation
2) Cardiac rate, rhythm (if indicated)
3) Serum potassium, early in therapy if animal susceptible to hypokalemia

**Client Information** - Contact veterinarian if animal's condition deteriorates or becomes acutely ill.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Terbutaline Sulfate Oral Tablets 2.5 mg, 5 mg; *Brethine*® (Geigy); *Bricanyl*® (Hoechst Marion Roussel); (Rx)

Terbutaline Injection 1 mg/ml in 2 ml amps with 1 ml fill; *Brethine*® (Geigy), *Bricanyl*®*S* (Hoechst Marion Roussel); (Rx)

Also available in a metered-dose inhaler.

## TETRACYCLINE HCL

**Chemistry** - An antibiotic obtained from *Streptomyces aureofaciens*, or derived semisynthetically from oxytetracycline, tetracycline HCl occurs as a moderately hygroscopic, yellow, crystalline powder. About 100 mg/ml is soluble in water and 10 mg/ml soluble in alcohol. Tetracycline base has a solubility of about 0.4 mg per ml of water and 20 mg per ml of alcohol. Commercially available tetracycline HCl for IM injection also contains magnesium chloride, procaine HCl and ascorbic acid.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, tetracycline oral tablets and capsules should be stored in tight, light resistant containers at room temperature (15-30°C). The oral suspension and powder for injection should be stored at room temperature. Avoid freezing the oral suspension.

After reconstituting the IM product, it may be stored at room temperature but should be used within 24 hours of reconstitution. After reconstituting the intravenous product with sterile water to a concentration of 50 mg/ml, the preparation is stable for 12 hours at room temperature. If further diluted in an appropriate IV fluid, use immediately.

Tetracycline HCl for intravenous injection is reportedly **compatible** with the following IV fluids and drugs: 0.9% sodium chloride, $D_5W$, $D_5W$ in normal saline, Ringer's injection, lactated Ringer's injection, 10% invert sugar, dextrose-Ringer's and lactated Ringer's combinations, ascorbic acid, cimetidine HCl, colistimethate sodium, corticotropin, ephedrine sulfate, isoproterenol HCl, kanamycin sulfate, lidocaine HCl, metaraminol bitartrate, norepinephrine bitartrate, oxytetracycline HCl, oxytocin, potassium chloride, prednisolone sodium phosphate, procaine HCl, promazine HCl, and vitamin B complex with C.

To Drug Monograph Index To Ophthalmic Product Index

Drugs that are reportedly **incompatible** with tetracycline, data conflicts, or compatibility is concentration/time dependent, include: amikacin sulfate, aminophylline, ampicillin sodium, amobarbital sodium, amphotericin B, calcium chloride/gluconate, carbenicillin disodium, cephalothin sodium, cephapirin sodium, chloramphenicol sodium succinate, dimenhydrinate, erythromycin gluceptate/lactobionate, heparin sodium, hydrocortisone sodium succinate, meperidine HCl, morphine sulfate, methicillin sodium, methohexital sodium, methyldopate HCl, oxacillin sodium, penicillin G potassium/sodium, phenobarbital sodium, sodium bicarbonate, thiopental sodium, and warfarin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology/Uses/Indications** - Refer to the oxytetracycline monograph just preceding this one for information for tetracycline.

**Pharmacokinetics** - Both oxytetracycline and tetracycline are readily absorbed after oral administration to fasting animals. Bioavailabilities are approximately 60-80%. The presence of food or dairy products can significantly reduce the amount of tetracycline absorbed, with reductions of 50% or more possible. After IM administration, tetracycline is erratically and poorly absorbed with serum levels usually lower than those attainable with oral therapy.

Tetracyclines as a class, are widely distributed to heart, kidney, lungs, muscle, pleural fluid, bronchial secretions, sputum, bile, saliva, urine, synovial fluid, ascitic fluid, and aqueous and vitreous humor. Only small quantities of tetracycline and oxytetracycline are distributed to the CSF, and therapeutic levels may not be achievable. While all tetracyclines distribute to the prostate and eye, doxycycline or minocycline penetrate better into these and most other tissues. Tetracyclines cross the placenta, enter fetal circulation and are distributed into milk. The volume of distribution of tetracycline is approximately 1.2 - 1.3 L/kg in small animals. The amount of plasma protein binding is about 20 - 67% for tetracycline.

Both oxytetracycline and tetracycline are eliminated unchanged primarily via glomerular filtration. Patients with impaired renal function can have prolonged elimination half-lives and may accumulate the drug with repeated dosing. These drugs apparently are not metabolized, but are excreted into the GI tract via both biliary and nonbiliary routes and may become inactive after chelation with fecal materials. The elimination half-life of tetracycline is approximately 5-6 hours in dogs and cats.

**Contraindications/Precautions/Reproductive Safety/**

**Adverse Effects/Warnings/ Overdosage/Acute Toxicity/Drug Interactions/-Drug-Laboratory Interactions** - Refer to the oxytetracycline monograph for information for tetracycline.

**Doses -**
**Horses**:

For susceptible infections:

a) 5 - 7.5 mg/kg IV q12h (Brumbaugh 1987)

**Monitoring Parameters** -

1) Adverse effects
2) Clinical efficacy
3) Long-term use or in susceptible patients: periodic renal, hepatic, hematologic evaluations

**Client Information** - Avoid giving this drug orally within 1-2 hours of feeding, giving milk or dairy products. If gastrointestinal upset occurs, giving with a small amount of food may help, but this will also reduce the amount drug absorbed.

To Drug Monograph Index To Ophthalmic Product Index

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary -Approved Products:**

Tetracycline Oral Suspension 100 mg/ml (approximately 5 mg/drop) in 15 ml and 30 ml bottles

*Panmycin Aquadrops*® (Upjohn); (Rx) Approved for use in dogs and cats.

Tetracycline HCl Oral Boluses 500 mg

*Polyotic*® *Oblets*® (American Cyanimid) (Rx) Approved for use in calves and sheep. Slaughter withdrawal = 12 days calves; = 5 days sheep.

*Panmycin*® *Oral Boluses* (Upjohn); (OTC) Approved for use in calves. Slaughter withdrawal = 12 days.

Tetracycline HCl Soluble Powder as a water additive

*Polyotic Soluble Powder*® (10 g or 25 g tetracycline HCl/lb); (OTC)

*Polyotic Soluble Powder Concentrate*® (102.4 g tetracycline HCl/lb); (OTC) Both are approved for use in calves, and swine. Slaughter withdrawal = 4 days calves; = 7 days swine

*Tetracycline HCl Soluble Powder-324*® (324 g tetracycline HCl/lb); (OTC) Approved for use in calves, swine, chickens, and turkeys. Slaughter withdrawal = 4 days swine, chickens, and turkeys; = 5 days calves

**Human-Approved Products**:

Tetracycline HCl Oral Capsules: 100 mg (capsules only from Richlyn Labs), 250 mg, 500 mg; Many trade names, including: *Achromycin-V*® (Lederle), *Sumycin '250'*® & 500 (Apothecon); *Panmycin*® (Upjohn), generic; (Rx)

Tetracycline HCl Tablets: 500 mg; *Tetracycline*® (Dr's Pharm); *Sumycin 500*® (Apothecon) (Rx)

Tetracycline HCl Oral Suspension 25 mg/ml in 60, 473, & 480 ml; *Achromycin-V*® (Lederle) (Rx), *Sumycin Syrup*® (Apothecon);*Tetralan Syrup*® (Lannett); generic; (Rx)

Tetracycline HCl Fiber: 12.7 mg/23 cm *Actisite*® (Alza) (Rx)

Tetracycline HCl Topical solution: 2.2 mg/ml *Topicycline*® (Roberts) (Rx)

**Theophylline - see Aminophylline**

## THIABENDAZOLE

**Chemistry** - The prototypic benzimidazole, thiabendazole occurs as an odorless or nearly odorless, tasteless, white to practically white powder. It has a melting range of 296°-303°C and a $pK_a$ of 4.7. Thiabendazole is practically insoluble in water and slightly soluble in alcohol.

**Storage/Stability/Compatibility** - Thiabendazole tablets, boluses and oral suspension should be stored in tight containers.

**Uses/Indications** - Thiabendazole has been used for the removal of the following parasites in **dogs**: ascarids (*Toxocara canis, T. leonina*), *Strongyloides stercoralis*, and *Filaroides.* It has also been used systemically as an anti-fungal agent in the treatment of nasal aspergillosis and penicillinosis. Topical and otic use of thiabendazole for the treatment of various fungi is also commonly employed.

Thiabendazole is indicated (labeled) for the removal of the following parasites in **cattle**: *Haemonchus spp., Ostertagia spp., Trichostrongylus spp., Nematodirus spp., Cooperia spp. and Oesophagostomum radiatum*.

To Drug Monograph Index To Ophthalmic Product Index

Thiabendazole is indicated (labeled) for the removal of the following parasites in **sheep** and **goats**: *Haemonchus spp., Ostertagia spp., Trichostrongylus spp., Nematodirus spp., Cooperia spp., Chabertia spp., Bunostomum spp. and Oesophagostomum spp.*.
Thiabendazole is indicated (labeled) for the removal of the following parasites in **horses**: *Strongylus spp., craterstomum spp., Oesphagodontus spp., Posteriostomum spp., Cyathostomum spp., Cylicocylus spp., Cylicostephanus spp., Oxyuris spp.*, and *Parasacaris spp*..

Thiabendazole is indicated (labeled) for the removal or prevention of the following parasites in **swine**: large roundworms (*Ascaris suum*) (prevention), and in baby pigs infested with *Strongyloides ransomi*.

Although not approved, thiabendazole has been used in pet birds and llamas. See the Dosage section for more information.

In many geographic areas, significant thiabendazole resistance problems have developed and for many parasites other anthelmintics would be a better choice for treatment.

**Pharmacokinetics** - Thiabendazole is relatively well absorbed (for a benzimidazole) and is distributed throughout body tissues. Peak levels occur in approximately 2-7 hours after dosing. Absorbed drug is rapidly metabolized in the liver by hydroxylation, glucuronidation and sulfate formation. Within 48 hours of dosing, 90% of the drug is excreted in the urine (as metabolites) and 5% in the feces. Less than 1% of the drug is excreted in the urine unchanged. Five days after a dose, the drug is virtually eliminated from the body.

**Contraindications/Precautions** - Thiabendazole has not been demonstrated to be a teratogen and is considered to be generally safe to use during pregnancy. However, in high doses it has been implicated in causing toxemia in ewes.

**Adverse Effects/Warnings** - At recommended doses, thiabendazole is usually well tolerated by approved species. In dogs, vomiting, diarrhea, hair loss and lethargy are possible side effects, notably with high dose or long-term therapy. Dachshunds have been reported to be particularly sensitive to thiabendazole. Toxic epidermal necrolysis (TEN) has been reported in dogs receiving thiabendazole, but the incidence appears to be very rare.

**Overdosage/Toxicity** - Thiabendazole has a safety margin of at least 20 times the recommended dose in horses. Doses of 800 - 1000 mg/kg are necessary to cause anorexia and depression in sheep. The minimum lethal dose is 700 mg/kg in cattle and 1200 mg/kg in sheep.
It is unlikely that a modest overdose would cause significant problems. If a massive overdose occurs, treat supportively and symptomatically. See the Adverse effects section for more information.

**Drug Interactions** - Thiabendazole may compete with **xanthines** (*e.g.,* **theophylline, aminophylline**) for metabolizing sites in the liver, thereby increasing xanthine blood levels.

**Doses -**
**Horses**:

For susceptible parasites:

a) 44 mg/kg PO. (Robinson 1987)
b) 44 mg/kg; 88 mg/kg for ascarids. (Roberson 1988b)
c) 50 - 100 mg/kg PO (Brander, Pugh, and Bywater 1982)

**Elephants:**

a) 20 mg/kg orally as a single dose for helminthiasis.

To Drug Monograph Index  To Ophthalmic Product Index

a) Chandrasekharan,K. 2002. **Specific diseases of Asian elephants.** Journal of Indian Veterinary Association Kerala 7:(3):31-34

a) Chandrasekharan,K., Radhakrishnan,K., Cheeran,J.V., Nair,K.N.M., and Prabhakaran,T. 1995. **Review of the Incidence, Etiology and Control of Common Diseases of Asian Elephants with Special Reference to Kerala.** In: Daniel,J.C. (Editor), A Week with Elephants; Proceedings of the International Seminar on Asian Elephants. Bombay Natural History Society; Oxford University Press, Bombay, India pp. 439-449

a) Chandrasekharan,K., 1992. **Prevalence of infectious diseases in elephants in Kerala and their treatment.** In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 148-155

b) 32 mg/kg orally for strongylosis resulted in a 84.6 – 95.3 % reduction in eggs per gram (EPG). Chandrasekharan,K., Cheeran,J.V., Nair,K.N.M., Ramanujam,K.N., and Radhakrishnan,K. 1982. **Comparative efficacy of 6 anti-helminthics against strongylosis in elephants.** Kerala Journal of Veterinary Science 13:15-20 Summary: Anthelmintic efficacy of six drugs was compared under field conditions against strongylosis in elephants. Mebendazole at 3 and 4 mg/kg, Levamisole 3 mg/kg and Morantel tartrate 5 mg/kg were proved to be 100% effective. Mebendazole at 2 mg/kg and 2.5 mg/kg, Thiabendazole at 32 mg/kg. Bephenium hydroxynaphthoate at 25 mg/kg and Disophenol at 3 mg/kg were found to be effective only in 79.1 to 92.2 %, 88.1 to 100%, 84.6 to 95.3 %, 85.9 to 100% and 68.3 to 84 % cases respectively.

**Client Information** - Shake suspension well before using. Follow veterinarian's or label directions carefully.

**Dosage Forms/Preparations/FDA Approval Status/Withdrawal Times-** Food residue tolerances: 0.1 ppm in uncooked meat of cattle, pheasants, swine, sheep and goats. 0.05 ppm in milk.

**Veterinary-Approved Products**:

Thiabendazole Oral Suspension 4 g/fl. oz. (135 mg/ml)

*Equizole® Suspension* (MSD); (OTC) Approved for use in dairy and beef cattle, sheep, goats, and horses. Milk withdrawal = 96 hours. Slaughter withdrawal = 3 days (cattle); 30 days (sheep & goats)

Thiabendazole Oral Suspension 6 g/fl. oz. (203 mg/ml)

*Omnizole®-Six Wormer Suspension* (MSD); (OTC) Approved for use in dairy and beef cattle, sheep, goats, and horses. Milk withdrawal = 96 hours. Slaughter withdrawal = 3 days (cattle); 30 days (sheep & goats)

Thiabendazole Oral Suspension (Drench) 25 g/fl. oz. (845 mg/ml)

*TBZ® Cattle Wormer* (Drench) (MSD); (OTC) Approved for use in dairy and beef cattle. Milk withdrawal = 96 hours. Slaughter withdrawal = 3 days

Thiabendazole Oral Suspension 17.5 g/fl. oz. (592 mg/ml)

*Thibenzole® Sheep and Goat Wormer* (MSD); (OTC) Approved for use in sheep and goats. Milk withdrawal = 96 hours. Slaughter withdrawal = 30 days

Thiabendazole Oral Paste 50% (500 mg/g), 43% (430 mg/g), 20% (200 mg/g)

*TBZ® Cattle Wormer Paste 50%, TBZ® Wormer Paste 43%* (MSD); (OTC) Approved for use in dairy and beef cattle. Milk withdrawal=96 hours. Slaughter withdrawal = 3 days

Thiabendazole Oral Boluses (Tablets) 15 g (cattle), 2 g (calf, sheep, goat)

To Drug Monograph Index To Ophthalmic Product Index

*TBZ® Calf, Sheep, and Goat Wormer* (MSD); (OTC) Approved for use in non-lactating dairy and beef cattle, goats, and sheep. Slaughter withdrawal = 3 days (calves); 30 days (goats, sheep)

Thiabendazole Medicated Premixes are available in: 22%, 44.1%, 66.1%, 88.2% concentrations. A thiabendazole medicated block (15 g/lb) is also available. An oral suspension of thiabendazole (2 g/oz) in combination with piperazine (2.5 g/oz) is available for use in horses. It is a prescription only medication (Rx) with the proprietary name: *Equizole® A* (MSD).

**Human-Approved Products**:

Thiabendazole Oral Chewable Scored Tablets 500 mg; *Mintezol®* (Merck); (Rx)

Thiabendazole Oral Suspension 100 500 mg/5 ml, 120 ml bottle; *Mintezol®* (Merck); (Rx)

## THIAMINE HCL
## VITAMIN B1

**Chemistry** - A water-soluble B-complex vitamin, thiamine HCl occurs as bitter-tasting, white, small hygroscopic crystals, or crystalline powder that has a characteristic yeast-like odor. Thiamine HCl is freely soluble in water and slightly soluble in alcohol and has $pK_a$s of 4.8 & 9.0. The commercially available injection has a pH of 2.5-4.5. Thiamine HCl may also be known as Aneurine HCl, Thiamin HCl, Thiamine Chloride, Thiaminium Chloride Hydrochloride, or Vitamin $B_1$.

**Storage/Stability/Compatibility** - Thiamine HCl for injection should be protected from light and stored at temperatures less than 40°C and preferably between 15-30°C; avoid freezing.

Thiamine HCl is unstable in alkaline or neutral solutions or with oxidizing or reducing agents. It is most stable at a pH of 2.

Thiamine HCl is reportedly **compatible** with all commonly used intravenous replacement fluids. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Thiamine combines with adenosine triphosphate (ATP) to form a compound (thiamine diphosphate/thiamine pyrophosphate) that is employed for carbohydrate metabolism, but does not effect blood glucose concentrations.

Absence of thiamine results in decreased transketolase activity in red blood cells and increased pyruvic acid blood concentrations. Without thiamine triphosphate, pyruvic acid is not converted into acetyl-CoA, diminished NADH results with anaerobic glycolysis producing lactic acid. Lactic acid production is further increased secondary to pyruvic acid conversion. Lactic acidosis may occur.

**Uses/Indications** - Thiamine is indicated in the treatment or prevention of thiamine deficiency states. Symptoms of thiamine deficiency may be manifested as gastrointestinal (anorexia, salivation), neuromuscular/CNS signs (ataxia, seizures, loss of reflexes), or cardiac effects (brady- or tachyarrhythmias). Deficiency states may be secondary to either a lack of thiamine in the diet or the presence of thiamine destroying compounds in the diet (*e.g.,* bracken fern, raw fish, amprolium, thiaminase-producing bacteria in ruminants).

Thiamine has also been used in the adjunctive treatment of lead poisoning and ethylene glycol toxicity (to facilitate the conversion of glyoxylate to nontoxic metabolites).

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacokinetics** - Thiamine is absorbed from the GI tract and is metabolized by the liver. Elimination is renal, the majority being metabolites.

**Contraindications/Precautions/Reproductive Safety** - Thiamine injection is contraindicated in animals hypersensitive to it or any component of it.

**Adverse Effects/Warnings** - Hypersensitivity reactions have occurred after injecting this agent. Some tenderness or muscle soreness may result after IM injection.

**Overdosage/Acute Toxicity** - Very large doses of thiamine in laboratory animals have been associated with neuromuscular or ganglionic blockade, but the clinical significance is unknown. Hypotension and respiratory depression may also occur with massive doses. A lethal dose of 350 mg/kg has been reported. Generally, no treatment should be required with most overdoses.

**Drug Interactions** - Thiamine may enhance the activity of **neuromuscular blocking agents**; clinical significance is unknown.

**Drug/Laboratory Interactions** - Thiamine may cause false-positive serum **uric acid** results when using the phosphotungstate method of determination or **urobilinogen** urine spot tests using Ehrlich's reagent. The Schack and Wexler method of determining **theophylline** concentrations may be interfered with by large doses of thiamine.

**Doses -**
**Horses**:
For thiamine deficiency:
a) 0.5 - 5 mg/kg IV, IM or PO (Robinson 1987)
b) 100 - 1000 mg IM, SQ, or IV (depending on formulation). (Phillips 1988b)

**Monitoring Parameters** -
1) Efficacy

**Client Information** - Epidemiologic investigation as to the cause of thiamine deficiency (diet, plants, raw fish, etc.) should be performed with necessary changes made to prevent recurrence.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:
Thiamine HCl for Injection 200 mg/ml and 500 mg/ml in 30 and 100 ml vials
Available generically labeled; (Rx) Labeled for use in small and large animals. Approval status is uncertain.
There are several B-complex vitamin preparations available that may also have thiamine included.

**Human-Approved Products**:
Thiamine Oral Tablets 50 mg, 100 mg, 250 mg, & 500 mg; Available generically labeled; (OTC)
Thiamine Enteric Coated Tablets 20 mg; *Thiamilate*® (Tyson) (OTC)
Thiamine HCl for Injection 100 mg/ml in 1, 2, 10 and 30 ml vials & 1 ml amps; Available generically labeled; (Rx)

## THIAMYLAL SODIUM

To Drug Monograph Index To Ophthalmic Product Index

**Note**: Thiamylal is not available commercially at the time of this update but is still listed in the FDA's "Green Book". Most veterinary anestheisologists are recommending using thiopental as an alternative. The monograph remains in the VDH with the hope that the product may find its way back to the market in the near future.

**Chemistry** - A thiobarbiturate, thiamylal sodium occurs as a pale yellow, hygroscopic powder with an unpleasant odor. It is soluble in water and a 5% solution in water has a pH of 10.5-11.5.

**Storage/Stability/Compatibility** - Thiamylal is stable in the dry form when stored in airtight vials. Thiamylal should be diluted with only sterile water for injection, sodium chloride injection, or $D_5W$ (Note: A veterinary manufacturer (Bio-Ceutic) recommends using only sterile water or sodium chloride for injection). After reconstitution, solutions are stable for 2 days when refrigerated (6 days according to some sources), but should generally be used within 24 hours. Do not administer any solution that has a visible precipitate. Little specific compatibility information is available other than not mixing with atropine, succinylcholine or tubocararine. Because of their chemical similarities, the compatibility listings in the thiopental monograph may be used as general guidelines with regard to thiamylal.

**Pharmacology** - The thiobarbiturates, because of their high lipid solubility, rapidly enter the CNS and produce profound hypnosis and anesthesia. See the monograph: Barbiturates, Pharmacology of, for more information.

**Uses/Indications** - Because of their rapid action and short duration, the thiobarbiturates are excellent induction agents for general anesthesia when used with other anesthetics or as the sole anesthetic agent for very short procedures.

**Pharmacokinetics** - Following IV injection of therapeutic doses, hypnosis and anesthesia occur within one minute. The drug rapidly enters the CNS and then redistributes to muscle and adipose tissue in the body. The short duration of action of these agents is due less to rapid metabolism than to this redistribution out of the CNS and into muscle and fat stores. Greyhounds and other sight hounds may exhibit longer recovery times than other breeds, which may be due to these breed's low body fat levels or differences in the metabolic handling of these agents.

Thiamylal is metabolized by the hepatic microsomal system. There was no information found regarding specific pharmacokinetic parameters in humans, dogs or horses. A paper on the pharmacokinetics of thiamylal in cats (Wertz et al. 1988) found a rapid first distribution phase ($t_{1/2}$ = 1.91 minutes) followed by a second slower distributory phase ($t_{1/2}$ = 26.5 minutes). The elimination half-life in cats was found to average 14.3 hours with a short period of anesthesia induced (dosage of 13.2 mg/kg IV) followed by a prolonged state of sedation. The authors concluded that based on the pharmacokinetic profile in cats, thiamylal should be used as an induction agent only followed by other anesthetic agents (*e.g.,* halothane).

**Contraindications/Precautions** - The following are considered to be absolute contraindications to the use of thiobarbiturates: abscence of suitable veins for IV administration, history of hypersensitivity reactions to the barbiturates, and status asthmaticus. Relative contraindications include: metabolic acidosis, severe cardiovascular disease or preexisting ventricular arrhythmias, shock, increased intracranial pressure, myasthenia gravis, asthma, and conditions where hypnotic effects may be prolonged (*e.g.,* severe hepatic disease, myxedema, severe anemia, excessive premedication, etc). These relative contraindications do not preclude the use of thiamylal, but dosage adjustments must be considered and the drug must be given slowly and cautiously.

Because greyhounds (and other sight hounds) metabolize thiobarbiturates much more slowly than methohexital, many clinicians recommend using methohexital instead. Siamese cats may develop more CNS depression than other feline breeds.

To Drug Monograph Index To Ophthalmic Product Index

Thiobarbiturates readily crosses the placental barrier and should be used with caution during pregnancy.

Extravasation and intra-arterial injections should be avoided because of the high alkalinity of the solution. Severe CNS toxicity and tissue damage has resulted in horses receiving intra-carotid injections of thiobarbiturates. Do not administer intrapleurally or intraperitoneally.

**Adverse Effects/Warnings** - The manufacturer (Bio-Ceutic) lists the following possible adverse reactions: circulatory depression, thrombophlebitis, pain at injection site, respiratory depression including apnea, laryngospasm, bronchospasm, salivation, emergence delirium, injury to nerves adjacent to injection site, skin rashes, urticaria, nausea, and emesis.

In dogs, thiamylal has an approximate arrhythmogenic incidence of 60-85%. Ventricular bigeminy is the most common arrhythmia seen, is usually transient (over within 2 minutes) and generally responds to additional oxygen. Incidence may be reduced to approximately 25% by using a phenothiazine tranquilizer pre-operatively. Although the incidence of arrhythmias is higher with thiamylal than thiopental, thiamylal is considered to be less cardiotoxic.

Administration of catecholamines may augment the arrhythmogenic effects of the thiobarbiturates, while lidocaine may inhibit it. Systemic arterial pressure may be increased, but this is probably only clinically significant in patients with preexisting small vessel disease.

Repeated administration of thiamylal is not advised as recovery times can be become significantly prolonged. Should parasympathetic side effects (*e.g.,* salivation, bradycardia) occur, they may be managed with the use of anticholinergic agents (atropine, glycopyrrolate).

**Overdosage** - Treatment of thiobarbiturate overdosage consists of supporting respirations ($O_2$, mechanical ventilation) and giving cardiovascular support (do not use catecholamines, *e.g.,* epinephrine, etc).

**Drug Interactions** - A fatal interaction has been reported in a dog receiving the proprietary product, ***Diathal***® (procaine penicillin G, dihydrostreptomycin sulfate, diphemanil methylsulfate, and chlorpheniramine maleate) and thiamylal. Avoid using thiamylal with this combination.
The ventricular fibrillatory effects of **epinephrine** and **norepinephrine** are potentiated when used with thiobarbiturates and halothane. CNS and respiratory depressant effects of **CNS depressants (narcotics, phenothiazines, antihistamines, etc.)** may be enhanced by thiobarbiturate administration. Thiamylal with **furosemide** may cause or increase postural hypotension. **Sulfisoxasole** IV has been shown to compete with thiopental at plasma protein binding sites. This may also occur with thiamylal and other sulfonamides.

**Doses** -
Note: Atropine sulfate or glycopyrrolate are often administered prior to thiobarbiturate anesthesia to prevent parasympathetic side effects. Some clinicians question, however, whether routine administration of the anticholinergic agents are necessary. Thiobarbiturates are administered strictly to effect; doses are guidelines only.

The manufacturer (Bio-Ceutic) recommends rapid injection 1/3 - 1/2 of the calculated dosage to carry the patient through the excitatory phase, then, if no apnea or severe respiratory depressant effects are seen, administer to the level of anesthesia desired.

**Horses**:

a) For light anesthesia: One gram IV (jugular) for an animal weighing from 500 - 1100 lbs.;Deeper anesthesia: 7.3 mg/kg IV (Package Insert; *Bio-Tal*® — Bio-Ceutic)
b) 4.4 - 6.6 mg/kg IV after sedation and guaifenesin; or 6.6 - 8.8 mg/kg IV after tranquilization. (Mandsager 1988)

To Drug Monograph Index To Ophthalmic Product Index

**Monitoring Parameters** -

1) Level of hypnosis/anesthesia
2) Respiratory status; cardiac status (rate/rhythm/blood pressure)

**Client Information** - This drug should only be used by professionals familiar with its effects in a setting where adequate respiratory support can be performed.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

Note: Thiamylal is not currently available, it was (and perhaps again?) available as:

Thiamylal Sodium for Injection; available in 1 gram, 5 gram, & 10 gram vials for reconstitution and 5 gram ampules (Note: Veterinary products are available in 1 & 5 gram vials only)

*Bio-Tal*® (Bio-Ceutic), *Surital*® (Parke-Davis); (Rx) Approved for use in dogs, cats, cattle, horses, and swine. No milk or meat withdrawal times are required.

**Preparation of Solution for Administration-**

The following table may be used to determine amount of diluent necessary to obtain desired concentrations:

| % Solution | mg/ml (calc.) | 1 GRAM VIAL mls to add | 5 GRAM VIAL mls to add |
|---|---|---|---|
| 0.5% | 5 | 200 ml | 1000 ml |
| 2.0% | 20 | 50 ml | 250 ml |
| 2.5% | 25 | 40 ml | 200 ml |
| 4.0% | 40 | 25 ml | 125 ml |

Sterile water for injection is the preferred diluent. If preparing solutions for a maintenance continuous drip, use $D_5W$ or sterile isotonic saline to avoid hypotonic solutions. Some dextrose solutions may be acidic enough to cause precipitation. Do not use cloudy or precipitated solutions.

## THIOPENTAL SODIUM

**Chemistry** - A thiobarbiturate, thiopental occurs as a bitter-tasting, white to off-white, crystalline powder or a yellow-white hygroscopic powder. It is soluble in water (1 gram in 1.5 ml) and alcohol. Thiopental has a $pK_a$ of 7.6 and is a weak organic acid.

**Storage/Stability/Compatibility** - When stored in the dry form, thiopental sodium is stable indefinitely. Thiopental should be diluted with only sterile water for injection, sodium chloride injection, or $D_5W$. Concentrations of less than 2% in sterile water should not be used as they may cause hemolysis. After reconstitution, solutions are stable for 3 days at room temperature and for 7 days if refrigerated. However, as no preservative is present, it is recommended it be used within 24 hours after reconstitution. After 48 hours, the solution has been reported to attack the glass bottles it is stored in. Thiopental may also adsorb to plastic IV tubing and bags. Do not administer any solution that has a visible precipitate.

The following agents have been reported to be **compatible** when mixed with thiopental: aminophylline, chloramphenicol sodium succinate, hyaluronidase, hydrocortisone sodium succinate, neostigmine methylsulfate, oxytocin, pentobarbital sodium, phenobarbital sodium, potassium chloride, scopolamine HBr, sodium iodide, and tubocurarine chloride (recommendations conflict with regard to tubocurarine; some clinicians recommend not mixing with thiopental).

The following agents have been reported to be **incompatible** when mixed with thiopental: Ringer's injection, Ringer's injection lactate, amikacin sulfate, atropine sulfate, benzquinamide, cephapirin sodium,

chlorpromazine, codeine phosphate, dimenhydrinate, diphenhydramine, ephedrine sulfate, glycopyrrolate, hydromorphone, insulin (regular), levorphanol bitartrate, meperidine, metaraminol, morphine sulfate, norepinephrine bitartrate, penicillin G potassium, prochlorperazine edisylate, promazine HCl, promethazine HCl, succinylcholine chloride, and tetracycline HCl. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology** - Because of their high lipid solubility, thiobarbiturates rapidly enter the CNS and produce profound hypnosis and anesthesia. They are also known as ultrashort-acting barbiturates. See the monograph: Barbiturates, Pharmacology of, for additional information.

**Uses/Indications** - Because of their rapid action and short duration, the thiobarbiturates are excellent induction agents for general anesthesia with other anesthetics or as the sole anesthetic agent for very short procedures.

**Pharmacokinetics** - Following IV injection of therapeutic doses, hypnosis and anesthesia occur within one minute. The drug rapidly enters the CNS and then redistributes to muscle and adipose tissue in the body. The short duration of action of these agents is due less to rapid metabolism than to this redistribution out of the CNS and into muscle and fat stores. Greyhounds and other sight hounds may exhibit longer recovery times than other breeds. This may be due to these breeds low body fat levels or differences in the metabolic handling of the thiobarbiturates.

Thiopental is metabolized by the hepatic microsomal system and several metabolites have been isolated. The elimination half-life in dogs has been reported as being approximately 7 hours and in sheep, 3-4 hours. Very little of the drug is excreted unchanged in the urine (0.3% in humans), so dosage adjustments are not necessary in patients with chronic renal failure.

**Contraindications/Precautions** - The following are considered to be absolute contraindications to the use of thiopental: absence of suitable veins for IV administration, history of hypersensitivity reactions to the barbiturates, and status asthmaticus. Relative contraindications include: severe cardiovascular disease or preexisting ventricular arrhythmias, shock, increased intracranial pressure, myasthenia gravis, asthma, and conditions where hypnotic effects may be prolonged (*e.g.,* severe hepatic disease, myxedema, severe anemia, excessive premedication, etc). These relative contraindications do not preclude the use of thiopental, but dosage adjustments must be considered and the drug must be given slowly and cautiously.

Because greyhounds (and other sight hounds) metabolize thiobarbiturates much more slowly than methohexital, many clinicians recommend using methohexital instead.

Thiopental readily crosses the placental barrier and should be used with caution during pregnancy.

In horses, thiopental should not be used if the patient has preexisting leukopenia. Some clinicians feel that thiopental should not be used alone in the horse as it may cause excessive ataxia and excitement.

Concentrations of less than 2% in sterile water should not be used as they may cause hemolysis. Extravasation and intra-arterial injections should be avoided because of the high alkalinity of the solution. Severe CNS toxicity and tissue damage has resulted in horses receiving intra-carotid injections of thiobarbiturates.

**Adverse Effects/Warnings** - In dogs, thiopental has an approximate arrhythmogenic incidence of 40%. Ventricular bigeminy is the most common arrhythmia seen and is usually transient and generally responds to additional oxygen. Administration of catecholamines may augment the arrhythmogenic effects of the thiobarbiturates, while lidocaine may inhibit it. Cardiac output may also be reduced, but is probably only clinically significant in patients experiencing heart failure.

To Drug Monograph Index  To Ophthalmic Product Index

Cats are susceptible to developing apnea after injection and may also develop a mild arterial hypotension.

Horses can exhibit symptoms of excitement and severe ataxia during the recovery period if the drug is used alone. Horses also can develop transient leukopenias and hyperglycemia after administration. A period of apnea and moderate tachycardia and a mild respiratory acidosis may also develop after dosing.

Too rapid IV administration can cause significant vascular dilatation and hypoglycemia. Repeated administration of thiopental is not advised as recovery times can become significantly prolonged. Parasympathetic side effects (*e.g.,* salivation, bradycardia) may be managed with the use of anticholinergic agents (atropine, glycopyrrolate).

**Overdosage** - Treatment of thiobarbiturate overdosage consists of supporting respirations ($O_2$, mechanical ventilation) and giving cardiovascular support (do not use catecholamines, *e.g.,* epinephrine, etc).

**Drug Interactions** - A fatal interaction has been reported in a dog receiving the proprietary product, ***Diathal***® (procaine penicillin G, dihydrostreptomycin sulfate, diphemanil methylsulfate, and chlorpheniramine maleate) and the related compound thiamylal. Avoid using thiopental with this product. The ventricular fibrillatory effects of **epinephrine** and **norepinephrine** are potentiated when used with thiobarbiturates and halothane. CNS and respiratory depressant effects of **CNS depressants (narcotics, phenothiazines, antihistamines, etc.)** may be enhanced by thiobarbiturate administration. Thiopental with **furosemide** may cause or increase postural hypotension. **Sulfisoxasole** IV has been shown to compete with thiopental at plasma protein binding sites. This may also occur with other sulfonamides.

**Doses** - Note: Atropine sulfate or glycopyrrolate are often administered prior to thiobarbiturate anesthesia to prevent parasympathetic side effects. Some clinicians question, however, whether routine administration of the anticholinergic agents are necessary.
Thiobarbiturates are administered strictly to effect; doses are guidelines only.

**Horses**:

a) With preanesthetic tranquilization: 6 - 12 mg/kg IV (an average of 8.25 mg/kg is recommended); Without preanesthetic tranquilization: 8.8-15.4 mg/kg IV (an average horse: 9.9 - 11 mg/kg IV) (*Pentothal*® package insert; Ceva Laboratories)
b) One gram of thiopental per 90 kg body weight as a 10% solution given evenly over 20 seconds 15 minutes after premedication with either 0.22 mg/kg IV xylazine or 0.05 mg/kg IV acepromazine. (Booth 1988a)
c) 5.5 mg/kg IV after sedation and administration with guaifenesin; or 8.8 - 11 mg/kg IV after tranquilization. (Mandsager 1988)

**Elephants:**

a) One tusker (approx.3000kg) was immobilized with 100 g chloral hydrate orally and 4 grams thiopentone sodium IV. Another tusker (approx 3000 kg) was immobilized with 1600 mg Flaxedil (gallamine triethiodide) IM and 4 grams thiopentone sodium IV. In both cases, induction occurred within 5 minutes of thiopentone administration. Both elephants became recumbent and surgical anesthesia was achieved adequate to permit scarification and suturing. Duration of anesthesia was 60 minutes when chloral hydrate was used and 40 minutes when Flaxedil was used. Nayar,K.N.M., Radhakrishnan,K., Chandrasekharan,K., Cheeran,J.V., Ravindran,S., and George,P.O., 1992. **Anaesthesia for surgical manipulations in the elephant.** In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 156-158 Abstract: Anaesthesia using chloral hydrate, thiopentone sodium, xylazine and

To Drug Monograph Index To Ophthalmic Product Index

ketamine was induced in ten elephants. The effects, duration of induction and anaesthesia were recorded. Post anaesthesia complications were not encountered in any of the animals. Surgical manipulations could be carried out under anaesthesia induced with these drugs.

**Monitoring Parameters** -

1) Level of hypnosis/anesthesia
2) Respiratory status; cardiac status (rate/rhythm/blood pressure)

**Client Information** - This drug should only be used by professionals familiar with its effects in a setting where adequate respiratory support can be performed.

**Dosage Forms/Preparations** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Thiopental Sodium Powder for Injection: 2% (20 mg/ml) in 1, 2.5 & 5 g kits, 400 mg syringes; 2.5% (25 mg/ml) in 250 & 500 mg vials and 500 mg, 1, 2.5, 5 and 10 g kits, 250 & 500 mg syringes; *Pentothal*® (Abbott/Ceva); Generic; (Rx) (C-III)

**Preparation of Solution for Administration:** The veterinary labeled product comes in a 5 gram kit for dilution to 2.5% or 5%. If using other products without diluent, use only sterile water for injection, normal saline, or $D_5W$ to dilute. A 5 gram vial diluted with 100 mls will yield a 5% solution and diluted with 200 ml will yield a 2.5% solution. Discard reconstituted solutions after 24 hours.

Also known as thiopentone sodium, thiopental is a Class-III controlled substance and is a legend (Rx) drug.

## THYROTROPIN THYROID-STIMULATING HORMONE

**Chemistry** - Obtained from bovine anterior pituitary glands, thyrotropin is a highly purified preparation of thyroid-stimulating hormone (TSH). Thyrotropin is a glycoprotein and has a molecular weight of approximately 28,000 - 30,000. Thyrotropin is measured in International Units (IU), with 7.5 micrograms of thyrotropin approximately equivalent to 0.037 units. Commercially available thyrotropin is available as a lyophilized powder for reconstitution and is practically free of any adrenocorticotropic, somatotropic, gonadotropic and posterior pituitary hormones. Thyrotropin may also be known as TSH, thyrotrophin, thyroid-stimulating hormone or thyrotropic hormone.

**Storage/Stability/Compatibility** - Thyrotropin lyophilized powder for injection is reportedly stable in the dry state. However, the veterinary manufacturer recommends storing the powder below 59°F, and after reconstituting, storing in the refrigerator and discarding any unused drug after 48 hours. However, recent information has suggested that reconstituted TSH is stable for at least 3 weeks when refrigerated. The human-approved product may be kept refrigerated (2-8°C) for up to 2 weeks after reconstituting.

**Pharmacology** - Thyrotropin increases iodine uptake by the thyroid gland and increases the production and secretion of thyroid hormones. With prolonged use, hyperplasia of thyroid cells may occur.

**Uses/Indications -** The labeled indications for *Dermathycin*® (Coopers/P/M; Mallinckrodt) is for “the treatment of acanthosis nigricans and for temporary supportive therapy in hypothyroidism in dogs.” In actuality however, TSH is used in veterinary medicine principally as a diagnostic agent in the TSH stimulation test to diagnose primary hypothyroidism.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacokinetics** - No specific information was located; exogenously administered TSH apparently exerts maximal increases in circulating $T_4$ approximately 4-8 hours after IM or IV administration.

**Contraindications/Precautions** - The veterinary manufacturer (Coopers) lists adrenocortical insufficiency and hyperthyroidism as contraindications to TSH use for treatment purposes in dogs. In humans, TSH is contraindicated in patients with coronary thrombosis, hypersensitive to bovine thyrotropin, or with untreated Addison's disease.

**Adverse Effects/Warnings** - Because the product is derived from bovine sources, anaphylaxis may occur in patients sensitive to bovine proteins, particularly with repeated use.

**Overdosage** - Chronic administration at high dosages can produce symptoms of hyperthyroidism. Massive overdoses can cause symptoms resembling thyroid storm. Refer to the levothyroxine monograph for more information on treatment.

**Drug Interactions**; **Drug/Laboratory Interactions -** For reference, refer to the information listed in the Levothyroxine monograph for more information.

**Doses -**
**Horses**:

For TSH stimulation test:

a) Draw pre-dose sample, then 5 - 10 IU of bovine TSH IV. Draw follow-up samples 4-8 hours after dosing. Normal thyroid gland should produce a 2-4 times increase in serum $T_3$ and $T_4$ levels. (Chen and Li 1987)

**Client Information** - Usually TSH will be used by professional staff. If the drug is to be used at home, the owner should follow directions carefully, shake the vial well after reconstituting, and store in the refrigerator.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**:

Thyroid Stimulating Hormone (Veterinary) 5 IU per vial (with 5 ml of Water for Injection as diluent); *Dermathycin*® (Schering Plough); (Rx) Approved for use in dogs. This product may not be currently on the market.

**Human-Approved Products**:

Thyrotropin (Thyroid Stimulating Hormone) Powder for Injection 10 IU per vial (with diluent); *Thyrotropar*® (Armour); (Rx)

**Thyroxine Sodium - See Levothyroxine**

## TICARCILLIN DISODIUM

For general information on the penicillins, including adverse effects, contraindications, overdosage, drug interactions and monitoring parameters, refer to the monograph: Penicillins, General Information.

**Chemistry** - An alpha-carboxypenicillin, ticarcillin disodium occurs as a white to pale yellow, hygroscopic powder or lyophilized cake with $pK_a$s of 2.55 and 3.42. More than 600 mg is soluble in 1 ml of water. Potency of ticarcillin disodium is expressed in terms of ticarcillin and one gram of the disodium contains not

less than 800 mg of ticarcillin anhydrous. One gram of the commercially available injection contains 5.2-6.5 mEq of sodium and after reconstituting the injection has a pH of 6-8.

**Storage/Stability/Compatibility** - Ticarcillin injectable powder for injection should be stored at temperatures of less than 30°C (room temperature or colder).

If stored at room temperature after reconstitution, polymer conjugates can form that may increase the likelihood of hypersensitivity reactions occurring. Therefore, many clinicians recommend either refrigerating the solution or administering within 30 minutes of reconstitution. From a potency standpoint, the drug should be used generally within 24 hours if stored at room temperature and 72 hours if refrigerated, but the manufacturer has specific recommendations depending on the concentration of the drug and the solution. Refer to the package insert for more specific recommendations. Frozen solutions are reportedly stable for at least 30 days when stored at -20°C.

Ticarcillin disodium solutions are reportedly physically **compatible** with the following solutions and drugs: $D_5W$, Ringer's Injection, Lactated Ringer's Injection, Sodium chloride 0.9%, Sterile water for injection, acyclovir sodium, hydromorphone HCl, meperidine HCl, methylprednisolone sodium succinate, morphine Sulfate, ranitidine HCl, perphenazine and verapamil HCl.

Ticarcillin disodium solutions are reportedly physically **incompatible** with the aminoglycoside antibiotics; refer to the drug interaction information in the Penicillins, General Information monograph for more information. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

**Pharmacology/Uses/Indications** - A ticarcillin disodium product is approved for intrauterine use in horses in the treatment of endometritis in horses caused by *beta hemolytic streptococci*.
Ticarcillin disodium injection is used in veterinary species in the treatment of systemic *Pseudomonas aeruginosa* infections, often in combination with an appropriate aminoglycoside agent. When compared with carbenicillin, ticarcillin is about twice as potent (on a weight basis) in the treatment against susceptible *Pseudomonas*. Synergy may occur against some *Pseudomonas* strains when used in combination with aminoglycosides, but *in vitro* inactivation of the aminoglycoside may also occur (see Drug Interactions) if the drugs are physically mixed together or in patients with severe renal failure.

**Pharmacokinetics (specific)** - Ticarcillin is not appreciably absorbed after oral administration and must be given parenterally to achieve therapeutic serum levels. When given IM to humans, the drug is readily absorbed with peak levels occurring about 30-60 minutes after dosing. The reported bioavailability in the horse after IM administration is about 65%.

After parenteral injection, ticarcillin is distributed into pleural fluid, interstitial fluid, bile, sputum and bone. Like other penicillins, CSF levels are low in patients with normal meninges (about 6% of serum levels), but increased (39% of serum levels) if meninges are inflamed. The volume of distribution is reportedly 0.34 L/kg in dogs and 0.22-0.25 L/kg in the horse. The drug is 45-65% bound to serum proteins (human). Ticarcillin is thought to cross the placenta and is found in small quantities in milk. In cattle, mastitic milk levels of ticarcillin are approximately twice those found in normal milk, but are too low to treat most causal organisms.

Ticarcillin is eliminated primarily by the kidneys, via both tubular secretion and glomerular filtration. Concurrent probenecid administration can slow elimination and increase blood levels. In humans, about 10-15% of the drug is metabolized by hydrolysis to inactive compounds. The half-life in dogs and cats is reportedly 45-80 minutes and about 54 minutes in the horse. Clearance is 4.3 ml/kg/min in the dog and 2.8-3.2 ml/kg/min in the horse.

To Drug Monograph Index  To Ophthalmic Product Index

**Doses -**
**Horses**:

For susceptible systemic infections:

a) 44 mg/kg q5h IV or *tid* IM. (Robinson 1987)
b) Foals: 50 mg/kg IV q6-8h (Dose extrapolated from data obtained from adult horses; use lower dose or longer interval in premature foals or those less than 7 days old.) (Caprile and Short 1987)

For treatment of endometritis secondary to susceptible bacteria:

a) 6 grams intrauterine per day for 3 days during estrus. Reconstitute vial with 25 ml of Sterile Water for Injection, USP or Sodium Chloride Injection, USP. After dissolved, further dilute to a total volume of 100-500 ml with sterile water or sterile normal saline and aseptically instill into uterus. (Package insert; *Ticillin*®—Beecham)

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Ticarcillin Disodium Sterile Powder for Intrauterine Infusion 6 g vial; *Ticillin*® (Pfizer); (Rx) Approved for use in horses.

**Human-Approved Products**:

Ticarcillin Disodium Powder for Injection (contains 5.2 mEq sodium./g) 1 g, 3 g, 6 g, 20 g, & 30 g in vials; *Ticar*® (SK-Beecham); (Rx)

Also available with human approval is a ticarcillin/clavulanic acid injectable preparation (*Timentin*®—Beecham) that would be effective against many penicillinase-producing strains of bacteria, such as most *Staphylococcus* species.

## TILETAMINE HCL/ZOLAZEPAM HCL

***Telazol***

**Chemistry** - Tiletamine is an injectable anesthetic agent chemically related to ketamine. Zolazepam is a diazepinone minor tranquilizer. The pH of the injectable product after reconstitution is 2.2 - 2.8.

**Storage/Stability/Compatibility** - After reconstitution, solutions may be stored for 4 days at room temperature and 14 days if refrigerated. Do not use solutions that contain a precipitate or are discolored.

**Pharmacology** - In cats, tiletamine decreases cardiac rate and blood pressure after IM injections. Its effect on respiratory activity is controversial, and until these effects have been clarified respiratory function should be closely monitored. The pharmacology of this drug combination is similar to that of ketamine and diazepam. For more information refer to the monographs for those agents.

**Uses/Indications** - *Telazol*® is indicated for restraint or anesthesia combined with muscle relaxation in cats, and for restraint and minor procedures of short duration (≈30 minutes) which require mild to moderate analgesia in dogs. Although not officially approved, it has been used also in horses and many exotic and wild species.

**Pharmacokinetics** - Little pharmacokinetic information is available for these agents. The onset of action may be variable and be very rapid; animals should be observed carefully after injection.

To Drug Monograph Index To Ophthalmic Product Index

In cats, the onset of action is reported to be within 1-7 minutes after IM injection. Duration of anesthesia is dependent on dosage, but is usually about 0.33-1 hour at peak effect. This is reported to be approximately 3 times the duration of ketamine anesthesia. The duration of effect of the zolazepam component is longer than that of the tiletamine, so there is a greater degree of tranquilization than anesthesia during the recovery period. The recovery times vary in length from approximately 1-5.5 hours.

In dogs, the onset of action following IM injection averages 7.5 minutes. The mean duration of surgical anesthesia is about 27 minutes, with recovery times averaging approximately 4 hours. The duration of the tiletamine effect is longer than that of zolazepam, so there is a shorter duration of tranquilization than there is anesthesia. Less than 4% of the drugs are reported to be excreted unchanged in the urine in the dog.

**Contraindications/Precautions** - *Telazol*® is contraindicated in animals with pancreatic disease, severe cardiac or pulmonary disease. Animals with renal disease may have prolonged durations of anesthetic action or recovery times.

*Telazol*® crosses the placenta and may cause respiratory depression in newborns; the manufacturer lists its use in cesarian section as being contraindicated. The teratogenic potential of the drug is unknown, and it is not recommended to be used during any stage of pregnancy.

Because *Telazol*® may cause hypothermia, susceptible animals (small body surface area, low ambient temperatures) should be monitored carefully and supplemental heat applied if needed. Like ketamine, *Telazol*® does not abolish pinnal, palpebral, pedal, laryngeal, and pharyngeal reflexes and its use (alone) may not be adequate if surgery is to be performed on these areas.
This drug has been reported to be contraindicated in rabbits.

Cat's eyes remain open after receiving *Telazol*® , and they should be protected from injury and an ophthalmic lubricant (*e.g., Lacrilube*®) should be applied to prevent excessive drying of the cornea. Cats reportedly do not tolerate endotracheal tubes well with this agent.

Dosages may need to be reduced in geriatric, debilitated, or animals with renal dysfunction.

**Adverse Effects/Warnings** - Respiratory depression is a definite possibility, especially with higher dosages of this product. Apnea may occur; observe animal carefully. Pain after IM injection (especially in cats) has been noted which may be a result of the low pH of the solution. Athetoid movements (constant succession of slow, writhing, involuntary movements of flexion, extension, pronation, etc) may occur; do not give additional *Telazol*® in the attempt to diminish these actions.

In dogs, tachycardia may be a common effect and may last for 30 minutes. Insufficient anesthesia after recommended doses has been reported in dogs.

Other adverse effects listed by the manufacturer include: emesis during emergence, excessive salivation and bronchial/tracheal secretions (if atropine not administered beforehand), transient apnea, vocalization, erratic and/or prolonged recovery, involuntary muscular twitching, hypertonia, cyanosis, cardiac arrest, pulmonary edema, muscle rigidity, and either hypertension or hypotension.

**Overdosage** - The manufacturer claims a 2X margin of safety in dogs, and a 4.5 times margin of safety in cats. A preliminary study in dogs (Hatch et al. 1988) suggests that doxapram at 5.5 mg/kg will enhance respirations and arousal after *Telazol*®. In massive overdoses, it is suggested that mechanically assisted ventilation be performed if necessary and other symptoms be treated symptomatically and supportively.

To Drug Monograph Index  To Ophthalmic Product Index

**Drug Interactions** - Little specific information is available presently on drug interactions with this product. In dogs, **chloramphenicol** apparently has no effect on recovery times with *Telazol*®, but in cats, anesthesia is prolonged on average of 30 minutes by chloramphenicol. Cats wearing flea collars have not been demonstrated to have prolonged anesthesia times.
**Phenothiazines** can cause increased respiratory and cardiac depression when used with this product. The dosage of **barbiturate** or **volatile anesthetics** may need to be reduced when used concomitantly with *Telazol*®. For general guidelines with regard to drug interactions with this product, please refer to the ketamine and diazepam monographs.

**Doses -**
**Horses**:

a) Xylazine 1.1 mg/kg IV, 5 minutes prior to *Telazol*® at 1.65 - 2.2 mg/kg IV (Hubbell, Bednarski, and Muir 1989)

**Exotic Species**:

a) An extensive list of suggested *Telazol*® dosages may be found in the article by E. Schobert entitled, "*Telazol*® Use in Wild and Exotic Animals" in the October 1987 issue of *Veterinary Medicine*.

**Elephants:**

a) African elephant: 3 mg/kg ; dose based on a single case in which the elephant became recumbent in 2 minutes and recovered in 6 hours. Kreeger,T.J., Arnemo,J.M., and Raath,J.P., 2002. **Handbook of wildlife chemical immobilization**. Wildlife Pharmaceuticals Inc., Fort Collins, Colorado, U.S.A., pp 183.

## TILMICOSIN

**Chemistry** - A semi-synthetic macrolide antibiotic, tilmicosin phosphate is commercially available in a 300 mg/ml (of tilmicosin base) injection with 25% propylene glycol.

**Storage/Stability/Compatibility** - Store the injection at or below room temperature. Avoid exposure to direct sunlight.

**Pharmacology** - Like other macrolides, tilmicosin has activity primarily against gram positive bacteria, although some gram negative bacteria are affected and the drug reportedly has some activity against mycoplasma. Preliminary studies have shown that 95% of studied isolates of *Pasturella haemolytica* are sensitive.

**Uses/Indications** - Tilmicosin is indicated fort the treatment of bovine respiratory diseases (BRD) caused by *Pasturella haemolytica*.

**Pharmacokinetics** - Tilmicosin apparently concentrates in lung tissue. At 3 days post injection, the lung:serum ratio is about 60:1. $MIC_{95}$ concentrations (3.12 micrograms/ml) for *P. Haemolytica* persist for a minimum of 3 days after a single injection.

**Contraindications/Precautions/Reproductive Safety** - Not to be used in automatically powered syringes or to be given intravenously as fatalities may result. Tilmicosin has been shown to be fatal in swine, non-human primates and potentially fatal in horses.
Safe use in pregnant animals or in animals to be used for breeding purposes has not been demonstrated.

To Drug Monograph Index  To Ophthalmic Product Index

**Adverse Effects/Warnings** - If administered IM, a local tissue reaction may occur resulting in trim loss. Edema may be noted at the site of subcutaneous injection.
Avoid contact with eyes.

**Overdosage/Acute Toxicity** - The cardiovascular system is apparently the target of toxicity in animals. In cattle, doses up to 50 mg/kg did not cause death, but SQ doses of 150 mg/kg did cause fatalities. Doses as low as 10 mg/kg in swine caused increased respiration, emesis and seizures; 20 mg/kg caused deaths in most animals tested. In monkeys, 10 mg/kg administered once caused no signs of toxicity, but 20 mg/kg caused vomiting and 30 mg/kg caused death.
In cases of human injection, contact physician immediately. The manufacturer has emergency telephone numbers to assist in dealing with exposure: 1-800-722-0987 or 1-317-276-2000.

**Drug Interactions** - In swine, **epinephrine** increased the mortality associated with tilmicosin. No other specific information noted; refer to the erythromycin monograph for potential interactions.

**Doses** -
**Cattle**:

For susceptible infections (subcutaneous injection behind the shoulders and over the ribs is suggested).

a) For treatment of pneumonic pasteurellosis in cattle: 10 mg/kg SQ every 72 hours. (Shewen and Bateman 1993)
b) Package insert (*Micotil*® 300; Elanco): 10 mg/kg SubQ (not more than 15 ml per injection site)

**Monitoring Parameters** - 1) Efficacy; 2) Withdrawal times

**Client Information** - If clients are administering the drug, they should be warned about the potential toxicity to humans, swine and horses if accidentally injected. They should also be carefully instructed in proper injection techniques. Avoid contact with eyes.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Tilmicosin for Subcutaneous Injection 300 mg/ml in 100 ml and 250 ml multi-dose vials; *Micotil® 300 Injection* (Elanco); (Rx) Approved for use in cattle. Not approved for use in female dairy cattle 20 months or older. Do not use in veal calves. Slaughter withdrawal = 28 days.

**Human-Approved Products**: None

## TOBRAMYCIN SULFATE

**Chemistry** - An aminoglycoside derived from *Streptomyces tenebrarius*, tobramycin occurs as a white to off-white, hygroscopic powder that is freely soluble in water and very slightly soluble in alcohol. The sulfate salt is formed during the manufacturing process. The commercial injection is a clear, colorless solution and the pH is adjusted to 6-8 with sulfuric acid and/or sodium hydroxide.

**Storage/Stability/Compatibility** - Tobramycin sulfate for injection should be stored at room temperature (15-30°C); avoid freezing and temperatures above 40°C. Do not use the product if discolored.

While the manufacturers state that tobramycin should not be mixed with other drugs, it is reportedly **compatible** and stable in most commonly used intravenous solutions (not compatible with dextrose and

alcohol solutions, Polysal, Polysal M, or Isolyte E, M or P) and compatible with the following drugs: aztreonam, bleomycin sulfate, calcium gluconate, cefoxitin sodium, ciprofloxacin lactate, clindamycin phosphate (not in syringes), floxacillin sodium, metronidazole (with or without sodium bicarbonate), ranitidine HCl, and verapamil HCl. Several other drugs have been demonstrated to be compatible at Y-sites (see Trissell for more info).

The following drugs or solutions are reportedly **incompatible** or only compatible in specific situations with tobramycin: cefamandole naftate, furosemide and heparin sodium. Compatibility is dependent upon factors such as pH, concentration, temperature and diluents used. It is suggested to consult specialized references for more specific information (*e.g., Handbook on Injectable Drugs* by Trissel; see bibliography).

*In vitro* inactivation of aminoglycoside antibiotics by beta-lactam antibiotics is well documented. See also the information in the Drug Interaction and Drug/Lab Interaction sections.

**Pharmacology** - Tobramycin, like the other aminoglycoside antibiotics, act on susceptible bacteria presumably by irreversibly binding to the 30S ribosomal subunit thereby inhibiting protein synthesis. It is considered to be a bactericidal antibiotic.

Tobramycin's spectrum of activity include coverage against many aerobic gram negative and some aerobic gram positive bacteria, including most species of *E. coli*, *Klebsiella*, *Proteus*, *Pseudomonas*, *Salmonella*, *Enterobacter*, *Serratia*, *Shigella*, *Mycoplasma*, and *Staphylococcus*.

Antimicrobial activity of the aminoglycosides are enhanced in an alkaline environment.
The aminoglycoside antibiotics are inactive against fungi, viruses and most anaerobic bacteria.

**Uses/Indications** - While there are no approved veterinary tobramycin products in the U.S., tobramycin may be useful clinically to treat serious gram negative infections in most species. It is often used in settings where gentamicin-resistant bacteria are a clinical problem. The inherent toxicity of the aminoglycosides limit their systemic use to serious infections when there is either a documented lack of susceptibility to other less toxic antibiotics or when the clinical situation dictates immediate treatment of a presumed gram negative infection before culture and susceptibility results are reported.

Whether tobramycin is less nephrotoxic than either gentamicin or amikacin when used clinically is controversial. Laboratory studies indicate that in a controlled setting in laboratory animals, it may indeed be so.

**Pharmacokinetics** - Tobramycin, like the other aminoglycosides is not appreciably absorbed after oral or intrauterine administration, but it is absorbed from topical administration (not skin or urinary bladder) when used in irrigations during surgical procedures. Patients receiving oral aminoglycosides with hemorrhagic or necrotic enteritises may absorb appreciable quantities of the drug. Subcutaneous injection results in slightly delayed peak levels and with more variability than after IM injection. Bioavailability from extravascular injection (IM or SQ) is greater than 90%.

After absorption, aminoglycosides are distributed primarily in the extracellular fluid. They are found in ascitic, pleural, pericardial, peritoneal, synovial and abscess fluids, and high levels are found in sputum, bronchial secretions and bile. Aminoglycosides (other than streptomycin) are minimally protein bound (<20%) to plasma proteins. Aminoglycosides do not readily cross the blood-brain barrier nor penetrate ocular tissue. CSF levels are unpredictable and range from 0-50% of those found in the serum. Therapeutic levels are found in bone, heart, gallbladder and lung tissues after parenteral dosing. Aminoglycosides tend to accumulate in certain tissues such as the inner ear and kidneys, that may help explain their toxicity. Aminoglycosides cross the placenta and fetal concentrations range from 15-50% of those found in maternal serum.

To Drug Monograph Index  To Ophthalmic Product Index

Elimination of aminoglycosides after parenteral administration occurs almost entirely by glomerular filtration. Patients with decreased renal function can have significantly prolonged half-lives. In humans with normal renal function, elimination rates can be highly variable with the aminoglycoside antibiotics.

**Contraindications/Precautions/Reproductive Safety** - Aminoglycosides are contraindicated in patients who are hypersensitive to them. Because these drugs are often the only effective agents in severe gram-negative infections, there are no other absolute contraindications to their use. However, they should be used with extreme caution in patients with preexisting renal disease with concomitant monitoring and dosage interval adjustments made. Other risk factors for the development of toxicity include age (both neonatal and geriatric patients), fever, sepsis and dehydration.

Because aminoglycosides can cause irreversible ototoxicity, they should be used with caution in "working" dogs (*e.g.,* "seeing-eye", herding, dogs for the hearing impaired, etc.).

Aminoglycosides should be used with caution in patients with neuromuscular disorders (*e.g.,* myasthenia gravis) due to their neuromuscular blocking activity.

Because aminoglycosides are eliminated primarily through renal mechanisms, they should be used cautiously, preferably with serum monitoring and dosage adjustment in neonatal or geriatric animals.

Aminoglycosides are generally considered contraindicated in rabbits/hares as they adversely affect the GI flora balance in these animals.

Tobramycin can cross the placenta. It has been demonstrated to concentrate in fetal kidneys and while rare, may cause 8th cranial nerve toxicity or nephrotoxicity in fetuses. Total irreversible deafness has been reported in some human babies whose mothers received tobramycin during pregnancy. Because the drug should only be used in serious infections, the benefits of therapy may exceed the potential risks.

**Adverse Effects/Warnings** - The aminoglycosides are infamous for their nephrotoxic and ototoxic effects. The nephrotoxic (tubular necrosis) mechanisms of these drugs are not completely understood, but are probably related to interference with phospholipid metabolism in the lysosomes of proximal renal tubular cells, resulting in leakage of proteolytic enzymes into the cytoplasm. Nephrotoxicity is usually manifested by increases in BUN, creatinine, nonprotein nitrogen in the serum and decreases in urine specific gravity and creatinine clearance. Proteinuria and cells or casts may also be seen in the urine. Nephrotoxicity is usually reversible once the drug is discontinued. While gentamicin may be more nephrotoxic than the other aminoglycosides, the incidences of nephrotoxicity with all of these agents require equal caution and monitoring.

Ototoxicity (8th cranial nerve toxicity) of the aminoglycosides can be manifested by either auditory and/or vestibular symptoms and may be irreversible. Vestibular symptoms are more frequent with streptomycin, gentamicin, or tobramycin. Auditory symptoms are more frequent with amikacin, neomycin, or kanamycin, but either forms can occur with any of the drugs. Cats are apparently very sensitive to the vestibular effects of the aminoglycosides.

The aminoglycosides can also cause neuromuscular blockade, facial edema, pain/inflammation at injection site, peripheral neuropathy and hypersensitivity reactions. Rarely, GI symptoms, hematologic and hepatic effects have been reported.

**Overdosage/Acute Toxicity** - Should an inadvertent overdosage be administered, three treatments have been recommended. Hemodialysis is very effective in reducing serum levels of the drug, but is not a viable option for most veterinary patients. Peritoneal dialysis also will reduce serum levels, but is much less efficacious. Complexation of drug with either carbenicillin or ticarcillin (12-20 g/day in humans) is reportedly nearly as effective as hemodialysis.

To Drug Monograph Index To Ophthalmic Product Index

**Drug Interactions** - Aminoglycosides should be used with caution with other nephrotoxic, ototoxic, and neurotoxic drugs. These include **amphotericin B**, **other aminoglycosides**, **acyclovir**, **bacitracin** (parenteral use), **cisplatin**, **methoxyflurane**, **polymyxin B**, or **vancomycin**. The concurrent use of aminoglycosides with **cephalosporins** is controversial. Potentially, cephalosporins could cause additive nephrotoxicity when used with aminoglycosides, but this interaction has only been well documented with cephaloridine (no longer marketed) and cephalothin. Concurrent use with loop (**furosemide**, **ethacrynic acid**) or osmotic diuretics (**mannitol**, **urea**) may increase the nephrotoxic or ototoxic potential of the aminoglycosides. Concomitant use with **general anesthetics** or **neuromuscular blocking agents** could potentiate neuromuscular blockade. Synergism against *Pseudomonas aeruginosa* and *enterococci* may occur with beta**-lactam antibiotics** and the aminoglycosides. This effect is apparently not predictable and its clinical usefulness is in question.

**Drug/Laboratory Interactions** - Tobramycin **serum concentrations** may be falsely decreased if the patient is also receiving beta-lactam antibiotics and the serum is stored prior analysis. It is recommended that if assay is delayed, samples be frozen and if possible, drawn at times when the beta-lactam antibiotic is at a trough level.

**Doses** - Note: There is significant inter-patient variability with regards to aminoglycoside pharmacokinetic parameters. To insure therapeutic levels and to minimize the risks for toxicity development, it is recommended to consider monitoring serum levels for this drug.
**Horses**:

For susceptible infections: 1 - 1.7 mg/kg q8h IV (slowly) or IM (Note: This is a human dose and should be used as a general guideline only) (Walker 1992)

**Monitoring Parameters** - 1) Efficacy (cultures, clinical signs and symptoms associated with infection); 2) Renal toxicity; baseline urinalysis, serum creatinine/BUN. Casts in the urine are often the initial sign of impending nephrotoxicity. Frequency of monitoring during therapy is controversial. It can be said that monitoring daily urinalyses early in the course of treatment or daily creatinines once casts are seen or increases are noted in serum creatinine levels are not too frequent; 3) Gross monitoring of vestibular or auditory toxicity is recommended; 4) Serum levels if possible; see the reference by Aronson and Aucoin in Ettinger (Aronson and Aucoin 1989) for more information.

**Client Information** - With appropriate training, owners may give subcutaneous injections at home, but routine monitoring of therapy for efficacy and toxicity must still be done. Clients should also understand that the potential exists for severe toxicity (nephrotoxicity, ototoxicity) developing from this medication.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products**: None

**Human-Approved Products**:

Tobramycin Sulfate Injection 10 mg/ml in 6 & 7 ml vials and 40 mg/ml in 1.5 & 2 ml syringes and 2 & 30 ml vials ; *Nebcin*® (Lilly); Generic; (Rx)

Tobramycin Sulfate Powder for Injection: 30 mg/ml in 1.2 g vials *Nebcin*® (Lilly); Generic (Rx)

Also available in ophthalmic preparations.

## TOLAZOLINE HCL

To Drug Monograph Index To Ophthalmic Product Index

**Chemistry** - An alpha adrenergic blocking agent, tolazoline HCl is structurally related to phentolamine. It occurs as a white to off-white, crystalline powder possessing a bitter taste and a slight aromatic odor. Tolazoline is freely soluble in ethanol or water. The commercially available (human) injection has pH between 3 and 4.

**Storage/Stability/Compatibility** - Commercially available injection products should be stored between 15-30°C and protected from light. The drug is reportedly physically compatible with the commonly used IV solutions.

**Pharmacology** - By directly relaxing vascular smooth muscle, tolazoline has peripheral vasodilating effects and decreases total peripheral resistance. Tolazoline also is a competitive alpha$_1$ and alpha$_2$ adrenergic blocking agent, explaining its mechanism for reversing the effects of xylazine. Tolazoline is rapid acting (usually within 5 minutes of IV administration), but has a short duration of action and repeat doses may be required.

**Uses/Indications** - Tolazoline is approved and indicated for the reversal of effects associated with xylazine in horses. It has also been used for this purpose in a variety of other species as well, but less safety and efficacy data is available.

In humans, the primary uses for tolazoline are: treatment of persistent pulmonary hypertension in newborns, adjunctive treatment and diagnosis of peripheral vasospastic disorders and as a provocative test for glaucoma after subconjunctival injection.

**Pharmacokinetics** - After IV injection in horses, tolazoline is widely distributed. Animal studies have demonstrated that tolazoline is concentrated in the liver and kidneys. Half life in horses at recommended doses is approximately 1 hour.

**Contraindications/Precautions/Reproductive Safety -** The manufacturer does not recommend use in horses exhibiting signs of stress, debilitation, cardiac disease, sympathetic blockage, hypovolemia or shock. Safe use for foals has not been established.

Tolazoline should be considered contraindicated in patients known to be hypersensitive to it, or who have coronary artery or cerebrovascular disease. Humans having any of the above contraindicative conditions, should use extra caution when handling the agent.
Safety during pregnancy, in breeding or lactating animals has not been established. It is unknown if the drug enters maternal milk.

**Adverse Effects/Warnings** - In horses adverse effects that may occur include: transient tachycardia; peripheral vasodilatation presenting as sweating and injected mucous membranes of the gingiva and conjunctiva; hyperalgesia of the lips (licking, flipping of lips); piloerection; clear lacrimal and nasal discharge; muscle fasciculations; apprehensiveness. Adverse effects should diminish with time and generally disappear within 2 hours of dosing. Potential for adverse effects increase if tolazoline is given at higher than recommended dosages or if xylazine has not been previously administered.

**Overdosage** - In horses given tolazoline alone (no previous xylazine), doses of 5X recommended resulted in gastrointestinal hypermotility with resultant flatulence and defecation or attempt to defecate. Some horses exhibited mild colic and transient diarrhea. Intraventricular conduction may be slowed when horses are overdosed, with a prolongation of the QRS-complex noted. Ventricular arrhythmias may occur resulting in death with higher overdoses (5X). In humans, ephedrine (NOT epinephrine or norepinephrine) has been recommended to treat serious tolazoline-induced hypotension.

To Drug Monograph Index  To Ophthalmic Product Index

**Drug Interactions** - If large doses of tolazoline are given with either **norepinephrine** or **epinephrine**, a paradoxical drop in blood pressure can occur followed by a precipitous increase in blood pressure. Accumulation of acetaldehyde can occur if tolazoline and **alcohol** are given simultaneously.

**Doses** -
**Horses**:

For reversal of xylazine effects:

a) 4 mg/kg slow IV (4 ml/220 lb. of body weight); administration rate should approximate 1 ml/second. (Package Insert; Tolazine®—Lloyd Laboratories)

**Elephants:**

a)To reverse juvenile wild African elephants immobilized with ketamine-xylazine, tolazoline 0.5 mg/kg IV will be effective in about 3 minutes. Raath,J.P., 1993. **Chemical capture of the African elephant.** In: The Capture and care manual : capture, care, accommodation and transportation of wild African animals. Pretoria : Wildlife Decision Support Services : South African Veterinary Foundation, Pretoria pp. 484-511

b) To reverse xylazine give tolazoline at two times the xylazine dose. Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants.** In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441

c) As an antagonist to xylazine-ketamine 0.5 mg/kg IV. Allen,J.L. 1986. **Use of tolazoline as an antagonist to xylazine-ketamine-induced immobilization in African elephants.** American Journal of Veterinary Research 47:(4):781-783 **Abstract:** A group of 15 African elephants (Loxodonta africana) were immobilized with a combination of xylazine (0.2 mg/kg of body weight, IM) and ketamine (1 to 1.5 mg/kg of body weight, IM). Ten of the African elephants were allowed to remain recumbent for 30 minutes and the remaining 5 elephants, for 45 minutes before they were given tolazoline (0.5 mg/kg of body weight, IV). For the group of 15, the mean induction time (the time required from injection of the xylazine-ketamine combination until onset of recumbency) was 14.2 ± 4.35 minutes (mean ± SD), and standing time (the time required from the tolazoline injection until the elephant stood without stimulation or assistance) was 2.8 ± 0.68 minutes. All of the elephants were physically stimulated (by pushing, slapping, shouting) before they were given tolazoline, and none could be aroused. After tolazoline was given and the elephant was aroused, relapses to recumbency did not occur. Recovery was characterized by mild somnolence in an otherwise alert and responsive animal. Failure (no arousal) rates were 0% (95% confidence interval, 0 to 0.3085) for elephants given tolazoline after 30 minutes of recumbency and 100% for elephants that were not given tolazoline. There was no significant (P less than 0.05) difference in standing time 30 or 45 minutes after tolazoline injection.

**Monitoring Parameters/Client Information**- 1) Reversal effects (efficacy) 2) Adverse effects (see above). Because of the risks associated with the use of xylazine and reversal by tolazoline, these drugs should be administered and monitored by veterinary professionals only.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products**:

Tolazoline HCl Injection 100 mg/ml in 100 ml multi-dose vials; *Tolazine*® (Lloyd); (Rx). Approved for use in horses; not to be used in food-producing animals.

**Human-Approved Products**:

Tolazoline HCl Injection 25 mg/ml; *Priscoline®; HCl* (Novartis); (Rx)

To Drug Monograph Index To Ophthalmic Product Index

## TRIAMCINOLONE ACETONIDE

Note: For more information refer to the monograph: Glucocorticoids, General Information or to the manufacturer's product information.

**Chemistry** - Triamcinolone acetonide, a synthetic glucocorticoid, occurs as slightly odorous, white to cream-colored, crystalline powder with a melting point between 290 - 294°C. It is practically insoluble in water, very soluble in dehydrated alcohol and slightly soluble in alcohol. The commercially available sterile suspensions have a pH range of 5-7.5.

**Storage/Stability/Compatibility** - Triamcinolone acetonide products should be stored at room temperature (15-30°C); the injection should be protected from light.

**Doses -**
**Horses**:

For glucocorticoid effects:

a) 0.1 - 0.2 mg/kg IM or SQ; 3 - 6 mg subconjunctivally. (Robinson 1987)
b) 0.011 - 0.022 mg/kg PO *bid*;
0.011 - 0.022 mg/kg IM or SQ;
6 - 18 mg intra-articularly or intrasynovially, may repeat after 3-4 days; (Package inserts; *Vetalog*® *Powder and Injection*—Solvay)

**Dosage Forms/Preparations/Approval Status/Withdrawal Times** - All require a prescription (Rx).

**Veterinary-Approved Products**: Note: marketing status of oral preparations is in question.

Triamcinolone Tablets 0.5 mg, 1.5 mg; *Vetalog*® *Tablets* (Fort Dodge), generic. Approved for use in dogs and cats

Triamcinolone Acetonide Oral Powder 15 gram packets containing 10 grams of triamcinolone acetonide.; *Vetalog*® *Oral Powder* (Fort Dodge). Approved for use in horses.

Triamcinolone acetonide suspension for injection 2 mg/ml; 6 mg/ml ; *Vetalog*® *Parenteral Veterinary* (Fort Dodge); Generic. (Rx). Approved for use in dogs, cats, and horses.

**Human-Approved Products** include:

Triamcinolone Tablets 1 mg, 2 mg, 4 mg, 8 mg; *Aristocort*® (Fujisawa); Generic (Rx)

Triamcinolone Oral Syrup 4 mg/5ml *Kenacort*® (Apothecon); (Rx)

Triamcinolone Acetonide Sterile Suspension for injection 3 mg/ml, 10 mg/ml, 40 mg/ml; many tradenames; Generic, (Rx)

Many topical preparations are available, alone and in combination with other agents and inhaled products are also approved.

## TRIPELENNAMINE HCL

**Chemistry** - An ethylenediamine-derivative antihistamine, tripelennamine HCl occurs as a white, crystalline powder which will slowly darken upon exposure to light. It has a melting range of 188-192°C and $pK_a$s of 3.9 and 9.0. One gram is soluble in 1 ml of water or 6 ml of alcohol.

**Storage/Stability/Compatibility** - Store the injection at room temperature and protect from light; avoid freezing or excessive heat. Tablets should also be stored at room temperature in tight containers.

To Drug Monograph Index To Ophthalmic Product Index

**Pharmacology** - Antihistamines ($H_1$-receptor antagonists) competitively inhibit histamine at $H_1$ receptor sites. They do not inactivate or prevent the release of histamine, but can prevent histamine's action on the cell. Besides their antihistaminic activity, these agents also have varying degrees of anticholinergic and CNS activity (sedation). Tripelennamine is considered to have moderate sedative activity and minimal anticholinergic activity when compared to other antihistamines.

**Uses/Indications** - Antihistamines are used in veterinary medicine to reduce or help prevent histamine mediated adverse effects. Tripelennamine has been used as a CNS stimulant in "Downer cows" when administered slow IV.

**Pharmacokinetics** - The pharmacokinetics of tripelennamine have apparently not been thoroughly studied in domestic animals or humans.

**Contraindications/Precautions** - Tripelennamine is not recommended to be given IV in horses (see Adverse Effects).

**Adverse Effects/Warnings** - CNS stimulation (hyperexcitability, nervousness, & muscle tremors) lasting up to 20 minutes, has been noted in horses after receiving tripelennamine intravenously. Other effects seen (in all species), include CNS depression, incoordination, and GI disturbances.

Tripelennamine has been mixed with pentazocine and injected by human opiate addicts and drug abusers. Be alert for clients suggesting that this drug be dispensed for their animals.

**Overdosage** - Overdosage of tripelennamine reportedly can cause CNS excitation, seizures and ataxia. Treat symptomatically and supportively if symptoms are severe. Phenytoin (IV) is recommended in the treatment of seizures caused by antihistamine overdose in humans; barbiturates and diazepam are generally avoided.

**Drug Interactions** - Increased sedation can occur if chlorpheniramine is combined with **other CNS depressant drugs**. Antihistamines may partially counteract the anti-coagulation effects of **heparin** or **warfarin**.

**Laboratory Interactions** - Antihistamines can decrease the wheal and flare response to antigen skin testing. In humans, it is suggested that antihistamines be discontinued at least 4 days prior to testing.

**Doses** - It is recommended to warm the solution to near body temperature before injecting; give IM injections into large muscle areas.
**Horses**:

a) 1.1 mg/kg (2.5 ml per 100 lbs body weight) IM q6-12h *prn* (Package Insert; *Re-Covr*® - Solvay)
b) 1 mg/kg IM (Robinson 1987)

**Monitoring Parameters** -

1) Clinical efficacy and adverse effects

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Tripelennamine HCl for Injection (Veterinary) 20 mg/ml in 20 ml, 100 ml, and 250 ml vials; Generic (Phoenix) (Rx) Tripelennamine HCl injection is approved for use in cattle, horses, dogs, and cats. Treated cattle must not be slaughtered for food purposes for four days following the last treatment. Milk

To Drug Monograph Index To Ophthalmic Product Index

must not be used for food for 24 hours (2 milkings) after treatment. No specific tolerance for residues have been published

**Human-Approved Products**:

Tripelennamine HCl Oral Tablets 25 mg, 50 mg; *PBZ*® (Geigy);*Pelamine*® (Major); Generic; (Rx)

Tripelennamine HCl Extended-release tablets 100 mg; *PBZ-SR*® (Geigy); (Rx)

Tripelennamine HCl Elixir: 37.5 mg (equivalent to 25 mg HCl) per 5 ml in 473 mls; *PBZ*® (Geigy) (Rx)

**TSH - See Thyrotropin**

## TYLOSIN

**Chemistry** - A macrolide antibiotic related structurally to erythromycin, tylosin is produced from *Streptomyces fradiae*. It occurs as an almost white to buff-colored powder with a $pK_a$ of 7.1. It is slightly soluble in water and soluble in alcohol. Tylosin is considered to be highly lipid soluble. The tartrate salt is soluble in water. The injectable form of the drug (as the base) is in a 50% propylene glycol solution.

**Storage/Stability/Compatibility** - Unless otherwise instructed by the manufacturer, injectable tylosin should be stored in well-closed containers at room temperature. Tylosin, like erythromycin, is unstable in acidic (pH <4) media. It is not recommended to mix the parenteral injection with other drugs.

**Pharmacology** - Tylosin is thought to have the same mechanism of action as erythromycin (binds to 50S ribosome and inhibits protein synthesis) and exhibits a similar spectrum of activity. It is a bacteriostatic antibiotic. For more specific information on organisms that tylosin is usually active against, refer to the erythromycin monograph just prior to this one. Cross resistance with erythromycin occurs.

**Uses/Indications** - Although the injectable form of tylosin is approved for use in dogs and cats, it is rarely used parenterally in those species. Oral tylosin is sometimes recommended for the treatment of chronic colitis in small animals (see Doses), but controlled studies documenting its efficacy have not been performed. Tylosin is also used in clinically in cattle and swine for infections caused by susceptible organisms.

**Pharmacokinetics** - Tylosin tartrate is well absorbed from the GI tract, primarily from the intestine. The phosphate salt is less well absorbed after oral administration. Tylosin base injected SQ or IM is reportedly rapidly absorbed.

Like erythromycin, tylosin is well distributed in the body after systemic absorption, with the exception of penetration into the CSF. The volume of distribution of tylosin is reportedly 1.7 L/kg in small animals. Tylosin enters milk in concentrations of approximately 20% of those found in serum.

Tylosin is eliminated in the urine and bile apparently as unchanged drug. The elimination half life of tylosin is reportedly 54 minutes in small animals, 139 minutes in newborn calves and 64 minutes in calves 2 months of age or older.

**Contraindications/Precautions/Reproductive Safety** - Tylosin is contraindicated in patients hypersensitive to it or other macrolide antibiotics (*e.g.,* erythromycin). Most clinicians feel that tylosin is contraindicated in horses, as severe and sometimes fatal diarrheas may result from its use in that species. No information was located with regards to the reproductive safety of tylosin, but it is unlikely to have serious teratogenic potential.

**Adverse Effects/Warnings** - Most likely adverse effects with tylosin are pain and local reactions at intramuscular injection sites, and mild GI upset (anorexia, and diarrhea). Tylosin may induce severe diarrheas if administered orally to ruminants or by any route to horses. In swine, adverse effects reported include edema of rectal mucosa and mild anal protrusion with pruritis, erythema, and diarrhea.

**Overdosage/Acute Toxicity** - Tylosin is relatively safe in most overdose situations. The $LD_{50}$ in pigs is greater than 5 g/kg orally, and approximately 1 g/kg IM. Dogs are reported to tolerate oral doses of 800 mg/kg. Long-term (2 year) oral administration of up to 400 mg/kg produced no organ toxicity in dogs. Shock and death have been reported in baby pigs overdosed with tylosin, however.

**Drug Interactions** - Drug interactions with tylosin have not been well documented. It has been suggested that it may increase **digitalis glycoside** blood levels with resultant toxicity. It is suggested to refer to the erythromycin monograph for more information on potential interactions.

**Drug/Laboratory Interactions** - Macrolide antibiotics may cause falsely elevated values of **AST** (SGOT), and **ALT** (SGPT) when using colorimetric assays. Fluorometric determinations of **urinary catecholamines** can be altered by concomitant macrolide administration.

**Doses** -
**Cattle**:

For susceptible infections:

a) 17.6 mg/kg IM once daily. Continue treatment for 24 hours after symptoms have stopped, not to exceed 5 days. Do not inject more than 10 ml per site. Use the 50 mg/ml formulation in calves weighing less than 200 pounds. (Package insert; Tylosin Injection—TechAmerica)
b) For bronchopneumonia and fibrinous pneumonia in cattle associated with penicillin G-refractory C. pyogenes infections or other bacteria sensitive to tylosin and resistant to sulfas, penicillin G and tetracyclines: using Tylosin 200 mg/ml : 44 mg/kg IM q24h. Recommend a 21 day slaughter withdrawal at this dosage. (Hjerpe 1986)
c) 5 - 10 mg/kg IM or slow IV once daily; not to exceed 5 days. (Huber 1988a)
d) Tylosin base injectable: 10 mg/kg IM initially, then 6 mg/kg IM q8h (q8-12h in calves). (Baggot 1983)

**Elephants:**

a) 12 mg/kg /day IM for 5 days to treat acute mycoplasma infections. Schmidt, M: **Elephants** (Proboscidea). In: Fowler, M.E. (ed): Zoo and Wild Animal Medicine. 1986. Saunders, Philadelphia. pp.911-912.

**Monitoring Parameters** -

1) Clinical efficacy
2) Adverse effects

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Tylosin Injection 50 mg/ml, 200 mg/ml; *Tylan*® (Elanco), generic; (OTC) Approved for use in nonlactating dairy cattle, beef cattle, swine, dogs, and cats. Slaughter withdrawal = cattle 21 days; swine 14 days.

(Note: Although this author was unable to locate parenteral products approved for use in lactating dairy animals, one source (Huber 1988a) states that tylosin has a 72 hour milk withdrawal for dairy cattle, and 48 hour milk withdrawal in dairy goats and sheep.)

To Drug Monograph Index To Ophthalmic Product Index

Tylosin tartrate (approximately 4000 mg/teaspoonsful) in 100 g bottles; *Tylan®Soluble* (Elanco); (OTC) Approved for use in turkeys (not layers), chickens (not layers) and swine. Slaughter withdrawal swine = 2 days; chickens = 1 day; turkeys = 5 days.

There are many approved tylosin products for addition to feed or water for use in beef cattle, swine, and poultry. Many of these products also have other active ingredients included in their formulations.

**Human-Approved Products**: None.

## VITAMIN E/SELENIUM PK

**Chemistry** - Vitamin E is a lipid soluble vitamin that can be found in either liquid or solid forms. The liquid forms occur as clear, yellow to brownish red, viscous oils that are insoluble in water, soluble in alcohol and miscible with vegetable oils. Solid forms occur as white to tan-white granular powders that disperse in water to form cloudy suspensions. Vitamin E may also be known as alpha tocopherol. Selenium in commercially available veterinary injections is found as sodium selenite. Each mg of sodium selenite contains approximately 460 micrograms (46%) of selenium.

**Storage/Stability/Compatibility** - Vitamin E/Selenium for injection should be stored at temperatures less than 25°C (77°F).

**Pharmacology** - Both vitamin E and selenium are involved with cellular metabolism of sulfur. Vitamin E has antioxidant properties and, with selenium, it protects against red blood cell hemolysis and prevents the action of peroxidase on unsaturated bonds in cell membranes.

**Uses/Indications** - Depending on the actual product and species, vitamin E/selenium is indicated for the treatment or prophylaxis of selenium-tocopheral deficiency (STD) syndromes in ewes and lambs (white muscle disease), sows, weanling and baby pigs (hepatic necrosis, mulberry heart disease, white muscle disease), calves and breeding cows (white muscle disease), and horses (myositis associated with STD).

A vitamin E/selenium product (*Seletoc®*—Schering) is also indicated for the adjunctive treatment of acute symptoms of arthritic conditions in dogs, but its efficacy for this indication has been questioned.

**Pharmacokinetics** - After absorption, vitamin E is transported in the circulatory system via beta-lipoproteins. It is distributed to all tissues and is stored in adipose tissue. Vitamin E is only marginally transported across the placenta. Vitamin E is metabolized in the liver and excreted primarily into the bile. Pharmacokinetic parameters for selenium were not located.

**Contraindications/Precautions/Reproductive Safety** - Vitamin E/selenium products should only be used in the species in which they are approved. Because selenium can be extremely toxic, the use of these products promiscuously cannot be condoned.
When administering intravenously to horses, give slowly.

**Adverse Effects/Warnings** - Anaphylactoid reactions have been reported. Intramuscular injections may be associated with transient muscle soreness. Other adverse effects are generally associated with overdoses of selenium (see below).

**Overdosage/Acute Toxicity** - Selenium is quite toxic in overdose quantities, but has a fairly wide safety margin. Cattle have tolerated chronic doses of 0.6 mg/kg/day with no adverse effects (approximate therapeutic dose is 0.06 mg/kg). Symptoms of selenium toxicity include depression, ataxia, dyspnea, blindness, diarrhea, muscle weakness, and a “garlic” odor on the breath. Horses suffering from selenium

toxicity may become blind, paralyzed, slough their hooves, and lose hair from the tail and mane. Dogs may exhibit symptoms of anorexia, vomiting, and diarrhea at high dosages.

**Drug Interactions** - **Vitamin A** absorption, utilization and storage may be enhanced by vitamin E. Large doses of vitamin E may delay the hematologic response to **iron** therapy in patients with iron deficiency anemia. **Mineral oil** may reduce the absorption of orally administered vitamin E.

**Elephants:**

a) Dierenfeld,E.S. and Dolensek,E.P. 1988. **Circulating levels of vitamin E in captive Asian elephants (*Elephas maximus*)**. Zoo Biology 7(2):165-172 **Abstract:** Circulating levels of alpha-tocopherol (vitamin E) were examined via high-performance liquid chromatography in four female Asian elephants (*Elephas maximus*) at the New York Zoological Park between 1983 and 1987. Plasma vitamin E averaged 0.08 micrograms/ml in 1983, and was considered deficient. Over a four-year period of dietary supplementation ranging from 0.7 to 3.7 IU vitamin E/kg body mass (approximately 50 to 250 IU/kg diet as fed), mean plasma alpha-tocopherol increased to 0.6 micrograms/ml. Plasma and dietary vitamin E were found to be significantly correlated ($p < 0.025$) in these animals. Serum of plasma vitamin E measured in an additional 20 elephants from eight other zoological institutions in the United States and Canada averaged 0.5 microgram/ml, but values were not significantly correlated ($P > 0.05$) with calculated dietary levels of the vitamin. To achieve the mean value for circulating alpha-tocopherol in captive elephants (0.5 micrograms/ml), feed must provide at least 1.0, and more like 2.0 to 2.5 IU vitamin E/kg body mass (approximately 130 to 167 IU/kg diet).

b) Papas,A.M., Cambre,R.C., Citino,S.B., and Sokol,R.J. 1991. **Efficacy of absorption of various vitamin E forms by captive elephants and black rhinoceroses**. Journal of Zoo and Wildlife Medicine 22:(3):309-317 **Abstract:** A biochemical vitamin E deficiency may exist in captive elephants (*Elephas maximus* and *Loxodonta africana*) and black rhinoceroses (*Diceros bicornis*) because plasma alpha-tocopherol concentrations apparently are lower in these animals than in their free-ranging counterparts. Analysis of serum or plasma from 35 elephants and 11 black rhinoceroses from 11 zoological institutions and one private owner confirmed common occurrence and persistence of low circulating alpha-tocopherol levels. Concentrations averaged <0.3 micrograms/ml despite prolonged supplementation with D,L-alpha-tocopherol acetate, the most common vitamin E supplement for animal diets. Further experimental work demonstrated that supplementing the diet with D,L- or D-alpha-tocopherol acetate or D-alpha tocopherol to provide up to 62 IU/kg body weight (BW) in elephants and 23 IU/kg BW in black rhinoceroses increased circulating blood alpha-tocopherol by <0.2 micrograms/ml. Apparently, elephants and black rhinoceroses absorbed these fat-soluble or water-dispersible forms of vitamin E poorly. In contrast, the water-soluble form, D-alpha-tocopherol polyethylene glycol 1,000 succinate (TPGS) was absorbed well, as indicated by rapid increases in circulating blood alpha-tocopherol (0.3 to 1.9 micrograms/ml) from several-fold lower TPGS doses in the diet (4.8 or 6.6 IU/kg BW in elephants and 1.5 or 3.9 IU/kg BW in black rhinoceroses). There is a marked difference in the bioavailability of TPGS versus other vitamin E forms in captive elephants and black rhinoceroses, suggesting that there are major species differences in the utilization of various forms of vitamin E.

c) Dierenfeld,E.S., Traber-MG, Packer-L (ed.), and Fuchs-J, 1993. **Vitamin E status of exotic animals compared with livestock and domestics**. In: Vitamin E in health and disease. Marcel Dekker, Inc; New York; USA pp. 345-370 **Abstract:** Vitamin E deficiency has long been recognized as a health problem in zoo animals. This review focuses on 3 areas for which comparative data from livestock and domestic animals are particularly useful: pathological and clinical deficiency signs; plasma and tissue concentrations; and dietary evaluation. Comparative data for domestic horses and zoo Perissodactyla (e.g., rhinoceros, elephants), domestic ruminants and zoo Artiodactyla (e.g., camels, giraffes), domestic swine and non-human primates, domestic carnivores (dogs, cats) and exotic carnivores (e.g., lions, tigers) and domestic poultry and zoo avifauna (e.g., ostriches, parrots) are presented.

To Drug Monograph Index To Ophthalmic Product Index

d) Dierenfeld,E.S. 1994. **Vitamin E in exotics: effects, evaluation and ecology**. Journal of Nutrition. 124:(12 Suppl):2579S-2581S **Abstract:** The pathophysiology and lesions associated with vitamin E deficiency are similar between domestic and exotic species, and circulating plasma concentrations are also similar between comparable groups. However, many ecological variables must be considered for the most relevant comparisons. Tissue values of vitamin E, apart from plasma, are unknown for most exotics. Dietary vitamin E requirements of exotic species and domestics appear to differ; based on natural foodstuff analyses and clinical observations, between 50 and 200 mg vitamin E/kg DM are necessary to prevent vitamin E deficiency, 5- to 10-fold higher than current livestock recommendations.

e) Shrestha,S.P., Ullrey,D.E., Bernard,J.B., Wemmer,C., and Kraemer,D.C. 1998. **Plasma vitamin E and other analyte levels in Nepalese camp elephants (*Elephas maximus*).** Journal of Zoo and Wildlife Medicine 29:(3):269-278 **Abstract:** Plasma concentrations of α-tocopherol (vitamin E) and other analytes in Asian elephants (*Elephas maximus*) inn Nepal were determined during typical work camp management of the elephants. Elephants foraged for food for 4-6 hr each day under the control of mahouts and were also provided daily with cut forage and supplements of unhusked rice, cane molasses, and salt. Blood samples were taken monthly for 1 yr without chemical restraint from 26 female elephants in four camps. Elephants were 6-60+ yr of age. Mean (+/-SEM) α-tocopherol concentration was 0.77+/-0.047 μg/ml with a range of 0.23-1.57 μg/ml. Subadults had lower concentrations than did older elephants, and there were significant differences in mean concentrations from different camps and in mean monthly concentrations. Plasma α-tocopherol concentration appears to vary widely between individuals, and a single value of <0.3 μg/ml is not sufficient to diagnose incipient vitamin E deficiency. Mean (+/-SEM) plasma retinol (vitamin A) concentration was 0.0063 +/- 0.0003 μg/ml with a range of 0.01-0.12 μg/ml. Subadults had higher concentrations than did older elephants, and mean retinal values differed significantly among camps. Beta-carotene was not found in plasma. Twenty-five other analytes determined or derived were generally similar to those reported in other Asian and African (*Loxodonta africana*) elephants. Estimates of nutrient intake, based upon diet composition, suggested that dietary concentrations of zinc and sodium may have been marginal, but the absence of signs of any nutrient deficiencies indicates that dietary husbandry in these elephant camps was generally satisfactory.

**See also:**

Savage,A., Leong,K.M., Grobler,D., Lehnhardt,J., Dierenfeld,E.S., Stevens,E.F., and Aebischer,C.P. 1999. **Circulating levels of alpha-tocopherol and retinol in free-ranging African elephants (Loxodonta africana)**. Zoo Biology 18:(4):319-323

Stuart,R.L. 1997. **Vitamin E Supplementation in the Elephant**. The Elephant Managers Association Proceedings of the 18th Annual EMA Workshop, Fort Worth Zoological Park, Fort Worth Texas, November 1-4, 1997. Pages: 50-53

Sadler,W.C., Hopkins,D.T., Miller,R.E., Junge,R.E., Houston,E.W., Read,B., Kuehn,G., Gonzales,B., Miller,M., Kapustin,N., and Olson,D. 1994. **Vitamin E forms for elephants.** Proceedings American Association of Zoo Veterinarians. Pages: 360-370

Wallace,C., Ingram,K.A., Dierenfeld,E.S., and Stuart,R.L. 1992. **Serum vitamin E status of captive elephants during prolonged supplementation of micellized natural alpha-tocopherol**. Proc. Amer. Assoc. Zoo Vet.

Dolensek,E.P. and Combs,S.B. 1990. **Vitamin E deficiency in zoo animals**. Proc.4th Ann.Scholl Conf.Nutrition of Captive Wild Animals.

Papas,A.M., Cambre,R.V., Citino,S.B., Baer,D.J., and Wooden,G.R. 1990. **Species differences in the utilization of various forms of vitamin E**. Proc. Amer. Assoc. Zoo Vet. Pages: 186-190

To Drug Monograph Index To Ophthalmic Product Index

Dierenfeld,E.S. 1989. **Vitamin E in elephants -- A research update**. Proc.Ann.Elephant Workshop 10. Pages: 60-63

Ullrey,D.E. 1989. **Is vitamin E really the key to sexual satisfaction?** Proc.8th Ann.Scholl Conf.Nutrition of Captive Wild Animals. Pages: 49-57

Brush,P.J. and Anderson,P.H. 1986. **Levels of plasma alpha-tocopherol (Vitamin E) in zoo animals**. International Zoo Yearbook 24/25:316-321

**Monitoring Parameters** -

1) Clinical efficacy
2) Blood selenium levels. Normal values for selenium have been reported as: >1.14 micromol/L in calves, >0.63 micromol/L in cattle, >1.26 micromol/L in sheep, and >0.6 micromol/L in pigs. Values indicating deficiency are: <0.40 micromol/L in cattle, <0.60 micromol/L in sheep, and <0.20 micromol/L in pigs. Intermediate values may result in suboptimal production.
3) Optionally, glutathione peroxidase activity may be monitored

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times/Doses** (per manufacturer) -

**Veterinary-Approved Products**: **Vitamin E/Selenium Oral:**

*Equ-SeE* (one teaspoonful contains 1 mg selenium and 228 IU vitamin E) & *Equ-Se5E*® (one teaspoonful contains 1 mg selenium and approximately 1100 IU vitamin E); (Vet-a-Mix) (OTC) Approved for oral use in horses.

**Veterinary-Approved Products**: **Vitamin E/Selenium Injection:**

**Mu-Se**® (Schering); (Rx): Each ml contains: selenium 5 mg (as sodium selenite); Vitamin E 68 IU; 100 ml vial for injection. Approved for use in non-lactating dairy cattle and beef cattle. Slaughter withdrawal = 30 days.

**Dose**: For weanling calves: 1 ml per 200 lbs. body weight IM or SQ.
For breeding beef cows: 1 ml per 200 lbs. body weight during middle third of pregnancy and 30 days before calving IM or SQ.

**Bo-Se**® (Schering); (Rx): Each ml contains selenium 1 mg (as sodium selenite) & Vitamin E 68 IU; 100 ml vial for injection. Approved for use in calves, swine and sheep. Slaughter withdrawal = 30 days (calves); 14 days (lambs, ewes, sows, and pigs).

**Dose**: Calves: 2.5 - 3.75 mls/100 lbs body weight (depending on severity of condition and geographical area) IM or SQ.
Lambs (2 weeks of age or older): 1 ml per 40 lbs. body weight IM or SQ (1 ml minimum).
Ewes: 2.5 mls/100 lbs. body weight IM or SQ.
Sows and weanling pigs: 1 ml/40 lbs. body weight IM or SQ (1 ml minimum). Do not use on newborn pigs.

**L-Se**® (Schering); (Rx): Each ml contains: selenium 0.25 mg (as sodium selenite) and Vitamin E 68 IU in 30 ml vials. Approved for use in lambs and baby pigs. Slaughter withdrawal = 14 days.

**Dose**:Lambs: 1 ml SQ or IM in newborns and 4 ml SQ or IM in lambs 2 weeks of age or older
Baby Pigs: 1 ml SQ or IM.

**E-Se**® (Schering); (Rx): Each ml contains selenium 2.5 mg (as sodium selenite) and Vitamin E 68 IU in 100 ml vials. Approved for use in horses.

**Dose**: Equine: 1 ml/100 lbs. body weight slow IV or deep IM (in 2 or more sites; gluteal or cervical muscles). May be repeated at 5-10 day intervals.

To Drug Monograph Index To Ophthalmic Product Index

***Seletoc***® (Schering); (Rx): Each ml contains selenium 1 mg (as sodium selenite) and Vitamin E 68 IU in 10 ml vials. Approved for use in dogs.

**Dose**: Dogs: Initially, 1 ml per 20 pounds of body weight (minimum 0.25 ml; maximum 5 ml) SQ, or IM in divided doses in 2 or more sites. Repeat dose at 3 day intervals until satisfactory results then switch to maintenance dose. If no response in 14 days reevaluate. Maintenance dose: 1 ml per 40 lbs body weight (minimum 0.25 ml) repeat at 3-7 day intervals (or longer) to maintain.

Also available is a sustained-release selenium oral bolus (*Dura Se*®*-120*—Schering) that provides 3 mg of selenium per day for up to 4 months.

**Human-Approved Products**: There are no approved vitamin E/selenium products, but there are many products that contain either vitamin E (alone, or in combination with other vitamins ±minerals) or selenium (as an injection alone or in combination with other trace elements) available.

## WARFARIN SODIUM

**Chemistry** - A coumarin derivative, warfarin sodium occurs as a slightly bitter tasting, white, amorphous or crystalline powder. It is very soluble in water and freely soluble in alcohol. The commercially available products contain a racemic mixture of the two optical isomers.

**Storage/Stability/Compatibility** - Warfarin sodium tablets should be stored in tight, light-resistant containers at temperatures less than 40°C and, preferably, at room temperature. Warfarin sodium powder for injection should be protected from light and used immediately after reconstituting.

**Pharmacology** - Warfarin acts indirectly as an anticoagulant (it has no direct anticoagulant effect) by interfering with the action of vitamin $K_1$ in the synthesis of the coagulation factors II, VII, IX, and X. Sufficient amounts of vitamin $K_1$ can override this effect.

**Uses/Indications** - In veterinary medicine, warfarin is used primarily for the oral, long-term treatment (or prevention of recurrence) of thrombotic conditions, usually in cats, dogs or horses.

**Pharmacokinetics** - Warfarin is rapidly and completely absorbed in humans after oral administration; absorption data for veterinary species were not located.

After absorption, warfarin is highly bound to plasma proteins in humans, with approximately 99% of the drug bound. It is reported that there are wide species variations with regard to protein binding; horses have a higher free (unbound) fraction of the drug than do rats, sheep or swine. Only free (unbound) warfarin is active. While other coumarin and indandione anticoagulants are distributed in milk, in humans at least, warfarin does not enter milk.

Warfarin is principally metabolized in the liver to inactive metabolites which are excreted in the urine and in the bile (and then reabsorbed and excreted in the urine). The plasma half-life of warfarin may be several hours to several days, depending on the patient (and species?).

**Contraindications/Precautions/Reproductive Safety** - Warfarin is contraindicated in patients with preexistent hemorrhagic tendencies or diseases, those undergoing or contemplating eye or CNS surgery, major regional lumbar block anesthesia, or surgery of large, open surfaces. It should not be used in patients with active bleeding from the GI, respiratory or GU tract. Contraindications also include aneurysm, acute nephritis, cerebrovascular hemorrhage, blood dyscrasias, uncontrolled or malignant hypertension, hepatic insufficiency, pericardial effusion and visceral carcinomas.

To Drug Monograph Index To Ophthalmic Product Index

Warfarin is embryotoxic, can cause congenital malformations and is considered contraindicated during pregnancy. If anticoagulant therapy is required during pregnancy, most clinicians recommend using low-dose heparin.

**Adverse Effects/Warnings** - The principal adverse effect of warfarin use is dose-related hemorrhage, which may be manifested by signs or symptoms of anemia, thrombocytopenia, weakness, hematomas and ecchymoses, epistaxis, hematemesis, hematuria, melena, hematochezia, hemathrosis, hemothorax, intracranial and/or pericardial hemorrhage, and death.

**Overdosage/Acute Toxicity** - Acute overdosages of warfarin may result in life-threatening hemorrhage. In dogs and cats, single doses of 5 - 50 mg/kg have been associated with toxicity. It must be remembered that a lag time of 2-5 days may occur before signs and symptoms of toxicity occur and animals must be monitored and treated accordingly.

Cumulative toxic doses of warfarin have been reported as 1 - 5 mg/kg for 5-15 days in dogs and 1 mg/kg for 7 days in cats.

If overdosage is detected early, prevent absorption from the gut using standard protocols. If symptoms are noted, they should be treated with blood products and vitamin $K_1$ (phytonadione). Refer to the phytonadione monograph for more information.

**Drug Interactions** - A multitude of drugs have been documented or theorized to interact with warfarin. The following drugs may increase the anticoagulant response of warfarin: **allopurinol, amiodarone, anabolic steroids, chloral hydrate, chloramphenicol, cimetidine, clofibrate, co-trimoxazole (trimethoprim/sulfa), danazol, dextrothyroxine sodium, diazoxide, diflunisal, disulfiram, erythromycin, ethacrynic acid, fenoprofen, glucagon, ibuprofen, indomethicin, isoniazid, ketoprofen, meclofenamic acid (meclofenamate), metronidazole, miconazole, nalidixic acid, oral neomycin, pentoxyfilline, phenylbutazone, propoxyphene, propylthiouracil, quinidine, and salicylates**. The following drugs may decrease the anticoagulant response of warfarin: **barbiturates (phenobarbital, etc.), carbamazepine, corticosteroids, corticotropin, griseofulvin, mercaptopurine, estrogen-containing products, rifampin, spironolactone, sucralfate, and vitamin K**. Should concurrent use of any of the above drugs with warfarin be necessary, enhanced monitoring is required. It is also recommended to refer to other references on drug interactions for more specific information.

**Drug/Laboratory Interactions -** Warfarin may cause falsely decreased **theophylline** values if using the Schack and Waxler ultraviolet method of assay.

**Doses -**
**Horses**:

As an anticoagulant:

a) 30 - 75 mg/450 kg body weight PO. (Robinson 1987)
b) Initially, 0.018 mg/kg PO once daily and increase dose by 20% every day until baseline PT is doubled. Final dose rates may be from 0.012 mg/kg to 0.57 mg/kg daily. (Vrins, Carlson, and Feldman 1983)

**Monitoring Parameters** - Note: The frequency of monitoring is controversial, and is dependent on several factors including dose, patient's condition, concomitant problems, etc. See the *Dosage* section above for more information.

1) While Prothrombin Times (PT) are most commonly used to monitor warfarin, PIVKA (proteins induced by vitamin K antagonists) has been suggested as being more sensitive.
2) Platelet counts and hematocrit (PCV) should be done periodically
3) Occult blood in stool and urine; other observations for bleeding

To Drug Monograph Index To Ophthalmic Product Index

4) Clinical efficacy

**Client Information** - Clients must be counseled on both the importance of administering the drug as directed and also to immediately report any signs or symptoms of hemorrhage.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None.

**Human-Approved Products**:

Warfarin Sodium Tablets (scored) 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, 10 mg; *Coumadin*® (DuPont), (Rx)

Warfarin Sodium Powder for Injection lyophilized 2 mg in 5 mg vials; *Coumadin*® (DuPont); (Rx)

A method of suspending warfarin tablets in an oral suspension has been described (Enos 1989). To make 30 ml of a 0.25 mg/ml suspension: Crush three 2.5 mg tablets in a mortar and pestle. Add 10 ml glycerin to form a paste. Then 10 ml of water; and q.s. to 30 ml with dark corn syrup (*Karo*®). Warm gently. Shake well and use within 30 days.

## XYLAZINE HCL * (ADVERSE EFFECT REPORTED)

**Chemistry** - Xylazine HCl is a alpha$_2$-adrenergic agonist structurally related to clonidine. The pH of the commercially prepared injections is approximately 5.5. Dosages and bottle concentrations are expressed in terms of the base.

**Storage/Stability/Compatibility** - Do not store above 30°C (86°F). Xylazine is reportedly compatible in the same syringe with several compounds, including: acepromazine, buprenorphine, butorphanol, chloral hydrate, and meperidine.

**Pharmacology** - A potent alpha$_2$-adrenergic agonist, xylazine is classified as a sedative/analgesic with muscle relaxant properties. Although xylazine possesses several of the same pharmacologic actions as morphine, it does not cause CNS excitation in cats, horses or cattle, but causes sedation and CNS depression. In horses, the visceral analgesia produced has been demonstrated to be superior to that produced by meperidine, butorphanol or pentazocine.

Xylazine causes skeletal muscle relaxation through central mediated pathways. Emesis is often seen in cats, and is also seen occasionally in dogs receiving xylazine. While thought to be centrally mediated, neither dopaminergic blockers (*e.g.,* phenothiazines) or alpha-blockers (yohimbine, tolazoline) block the emetic effect. Xylazine does not cause emesis in horses, cattle, sheep or goats. Xylazine depresses thermoregulatory mechanisms and either hypothermia or hyperthermia is a possibility depending on ambient air temperatures.

Effects on the cardiovascular system include an initial increase in total peripheral resistance with increased blood pressure followed by a longer period of lowered blood pressures (below baseline). A bradycardic effect can be seen with some animals developing a second degree heart block or other arrhythmias. An overall decrease in cardiac output of up to 30% may be seen. Xylazine has been demonstrated to enhance the arryhthmogenic effects of epinephrine in dogs with or without concurrent halothane.

Xylazine's effects on respiratory function are usually clinically insignificant, but at high dosages, it can cause respiratory depression with decreased tidal volumes and respiratory rates and an overall decreased minute volume. Brachycephalic dogs and horses with upper airway disease may develop dyspnea.

To Drug Monograph Index To Ophthalmic Product Index

Xylazine can induce increases in blood glucose secondary to decreased serum levels of insulin. In non-diabetic animals, there appears to be little clinical significance associated with this effect.
In horses, sedatory signs include a lowering of the head with relaxed facial muscles and drooping of the lower lip. The retractor muscle is relaxed in male horses, but unlike acepromazine, no reports of permanent penile paralysis has been reported. Although, the animal may appear to be thoroughly sedated, auditory stimuli may provoke arousal with kicking and avoidance responses.

With regard to the sensitivity of species to xylazine definite differences are seen. Ruminants are extremely sensitive to xylazine when compared with horses, dogs, or cats. Ruminants generally require approximately 1/10th the dosage that is required for horses to exhibit the same effect. In cattle (and occasionally cats and horses), polyuria is seen following xylazine administration, probably as a result of decreased production of vasopressin (anti-diuretic hormone, ADH). Bradycardia and hypersalivation are also seen in cattle and are diminished by pretreating with atropine. Swine, require 20-30 times the ruminant dose and therefore, xylazine is not routinely used in this species.

**Uses/Indications** - Xylazine is approved for use in dogs, cats, horses, deer, and elk. It is indicated in dogs, cats and horses to produce a state of sedation with a shorter period of analgesia, and as a preanesthetic before local or general anesthesia. Because of the emetic action of xylazine in cats, it is occasionally used to induce vomiting after ingesting toxins.

**Pharmacokinetics** - Absorption is rapid following IM injection, but bioavailabilities are incomplete and variable. Bioavailabilities of 40-48% in the horse, 17-73% in the sheep, and 52-90% in the dog have been reported after IM administration.

In horses, the onset of action following IV dosage occurs within 1-2 minutes with a maximum effect 3-10 minutes after injection. The duration of effect is dose dependent but may last for approximately 1.5 hours. The serum half-life after a single dose of xylazine is approximately 50 minutes in the horse and recovery times generally take from 2-3 hours.

In dogs and cats, the onset of action following an IM or SQ dose is approximately 10-15 minutes, and 3-5 minutes following an IV dose. The analgesic effects may persist for only 15-30 minutes, but the sedative actions may last for 1-2 hours depending on the dose given. The serum half-live of xylazine in dogs has been reported as averaging 30 minutes. Complete recovery after dosing may take from 2-4 hours in dogs and cats.

Xylazine is not detected in milk of lactating dairy cattle at 5 & 21 hours post-dose, but the FDA has not approved the use of this agent in dairy cattle and no meat or milk withdrawal times have been specified.

**Contraindications/Precautions** - Xylazine is contraindicated in animals receiving epinephrine or having active ventricular arrhythmias. It should be used with extreme caution in animals with preexisting cardiac dysfunction, hypotension or shock, respiratory dysfunction, severe hepatic or renal insufficiency, preexisting seizure disorders, or if severely debilitated. Because it may induce premature parturition, it should generally not be used in the last trimester of pregnancy, particularly in cattle.

Be certain of product concentration when drawing up into syringe, especially if treating ruminants. Do not give to ruminants that are dehydrated, have urinary tract obstruction, or are debilitated. It is not approved for any species to be consumed for food purposes.
Horses have been known to kick after a stimulatory event (usually auditory); use caution. Avoid intra-arterial injection; may cause severe seizures and collapse. The manufacturers warn against using in conjunction with other tranquilizers.

To Drug Monograph Index  To Ophthalmic Product Index

**Adverse Effects/Warnings** - Emesis is generally seen within 3-5 minutes after xylazine administration in cats and occasionally in dogs. To prevent aspiration, do not induce further anesthesia until this time period has lapsed. Other adverse effects listed in the package insert (*Gemini*®, Butler) for dogs and cats include: muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, and increased urination in cats.

Dogs may develop bloat from aerophagia which may require decompression. Because of gaseous distention of the stomach, xylazine's use before radiography can make test interpretation difficult.

Adverse effects listed in the package insert (*AnaSed*®, Lloyd) for horses include: muscle tremors, bradycardia with partial A-V block, reduced respiratory rate, movement in response to sharp auditory stimuli, and sweating (rarely profuse). Additionally, large animals may become ataxic following dosing and caution should be observed.

Adverse reactions reported in cattle include salivation, ruminal atony, bloating and regurgitation, hypothermia, diarrhea, and bradycardia. The hypersalivation and bradycardia may be alleviated by pretreating with atropine. Xylazine may induce premature parturition in cattle.

**Overdosage** - In the event of an accidental overdosage, cardiac arrhythmias, hypotension, and profound CNS and respiratory depression may occur. Seizures have also been reported after overdoses. There has been much interest in using alpha-blocking agents as antidotes or reversal agents to xylazine. Yohimbine or tolazoline have been suggested to be used alone and in combination to reverse the effects of xylazine or speed recovery times. A separate monograph for yohimbine is available which discusses suggested doses, etc.

To treat the respiratory depressant effects of xylazine toxicity, mechanical respiratory support with respiratory stimulants (*e.g.,* doxapram) have been recommended for use.

**Drug Interactions** - The use of **epinephrine** with & without the concurrent use of halothane concomitantly with xylazine may induce the development of ventricular arrhythmias.
The combination use of **acepromazine** with xylazine is generally considered to be safe, but there is potential for additive hypotensive effects and this combination should be used cautiously in animals susceptible to hemodynamic complications. **Other CNS depressant agents (barbiturates, narcotics, anesthetics**, **phenothiazines**, etc.) may cause additive CNS depression if used with xylazine. Dosages of these agents may need to be reduced.
A case report of a horse developing colic-like symptoms after **reserpine** and xylazine has been reported. Until more is known about this potential interaction, use together of these two agents together should be avoided. The manufacturers warn against using xylazine in conjunction with other tranquilizers.

**Doses** -
**Horses**:

a) 1.1 mg/kg IV; 2.2 mg/kg IM. Allow animal to rest quietly until full effect is reached. (Package Insert; *Rompun*® - Miles)
b) Sedative/analgesic for colic: 0.3 - 0.5 mg/kg IV; repeat as necessary (Muir 1987)
c) Prior to guaifenesin/thiobarbiturate anesthesia: 0.55 mg/kg IV; Prior to ketamine induction: 1.1 mg/kg IV; In combination with opioid/tranquilizers (all IV doses):

1) xylazine 0.66 mg/kg; meperidine 1.1 mg/kg
2) xylazine 1.1 mg/kg; butorphanol 0.01 - 0.02 mg/kg
3) xylazine 0.6 mg/kg; acepromazine 0.02 mg/kg

Note: the manufacturers state that xylazine should not be used in conjunction with tranquilizers (Thurmon and Benson 1987)

To Drug Monograph Index To Ophthalmic Product Index

**Elephants:**

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

a) Xylazine 100-200 mg/metric ton for Asian elephants. Extreme aggressiveness, musth, painful conditions, and ambient disturbances may necessitate higher doses. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Tranquilization and translocation of elephants.** Journal of Indian Veterinary Association Kerala 7:(3):42-46.

Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1992. **Tranquilization and translocation of elephants.** In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 176 **Abstract: (Full text):** A total of 140 captive rogue tuskers were successfully tranquilized and translocated during the period for April 1979 to December 1988. Most of the animals were those used in festivals or in lumbering operations. The requests handled by the tranquilization team were of urgent nature and no kunkies were available to assist the operation. Hence the animals were tranquilized retaining certain amount of ambulatory property and not allowing the animals to assume recumbency. After ascertaining complete sedation which took nearly 45 minutes after darting the limbs were noosed were polypropylene ropes and pulled by volunteers numbering from 15 to 20 on each rope on the forelimb. The animals were also given oral and percussion commands and coaxed to move. Animals could be moved on an average of 100 meters to be tied in a safe tethering area. The chemical used at first was nicotine and was subsequently replaced by xylazine alone or its combinations for better margin of safety. The combination of xylazine with acepromazine and ketamine was discarded due to photosensitization of elephants and subsequent skin lesions on the back of the elephants. The dose of xylazine varied from 100 to 120 mg/ton body weight. The data show that 85% of the cases were attended while the bulls were in premusth or post-musth period indicating lack of sufficient precaution taken by the mahouts.

b) 0.10-0.11 mg/kg xylazine IM for Asian elephants; can be combined with acepromazine or ketamine; the dose of individual drugs can be reduced up to 50% when combinations are used. Nayar,K.N.M., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Management of surgical affections in captive elephants.** Journal of Indian Veterinary Association Kerala 7:(3):55-59

c) Xylazine at a dose of 100-300 mg in adult Asian elephants (approximately 4-10 mg/ 100 kg body weight) injected slowly intravenously resulted in good sedative, analgesic, and muscle relaxing effects in 21 Asian elephants undergoing blood collection, biopsies and ultrasound examinations. The author advises that yohimbine or atipamezole be readily available in case of overdose or inadvertent human exposure (1mg/kg can be lethal in man. Rietschel,W., Hildebrandt,T., Goritz,F., and Ratanakorn,P. 2001. **Sedation of Thai Working Elephants with Xylazine and Atipamezole as a Reversal.** A Research Update on Elephants and Rhinos; Proceedings of the International Elephant and Rhino Research Symposium, Vienna, June 7-11, 2001. Pages: 121-123

d) In Asian elephants: xylazine alone (0.1 mg/kg) or in combination with ketamine (1.25: 1 ratio). Sarma,K.K. and Pathak,S.C. 2001. **Cardio vascular response to xylazine and Hellabrunn mixture with Yohimbine as reversal agent in Asian elephants.** Indian Veterinary Journal 78:(5):400-492 **Abstract:** Xylazine (0.1 mg/kg body weight) produced highly significant bradycardia and hypotension in recumbent Asian elephants, with a peak depression observed at the 30th minute for heart rate and 30th minute in the mean arterial pressure (MAP). Ketamine (1.25 : 1 ratio with xylazine) mildly marginalised the

To Drug Monograph Index To Ophthalmic Product Index

bradycardia, but remarkably improved the MAP. Yohimbine, used to reverse the sedation produced by xylazine did not appear to influence these parameters to any appreciable levels.

e) Xylazine at dosages of 0.18-0.33 mg/kg (total doses 600-1000 mg) was used to sedate 3 African elephants to load into a trailer a distance of about 50 m away. The procedure was accomplished but the sedation was rated as fair. Ramsay,E. 2000. **Standing sedation and tranquilization in captive African elephants** (*Loxodonta africana*). Proc. Am. Assoc. Zoo Vet. Pages: 111-114

f) * **Adverse effect**: A 27 year-old male Asian elephant with mild bilateral corneal opacities was laid in lateral recumbency, injected with 150 mg xylazine slowly via the caudal auricular vein and then allowed to stand. After 2.5 minutes he tilted his head upwards and backwards in a tentative gait. At 4-5 minutes he trumpetted loudly and started to shake his head vigorously, followed by complete delirium. After 10 minutes of violent excitement, he gradually became normal but his degree of sedation was minimal. An additional 50 mg of xylazine was given IV and the elephant became profoundly sedated. He was reversed with 60 mg yohimbine IV. The author suggests that the elephant's visual impairment may have caused the reaction. Sarma,K.K. 1999. **Bizarre behaviour of an elephant during xylazine anaesthesia.** Indian Veterinary Journal 76:(11):1018-1019

g) Intravenous xylazine (33-72 µg/kg) was titrated to achieve standing sedation with responsiveness to voice commands in a 5000 kg male Asian elephant sedated on 3 occasions for treatment of a foot abscess. Partial reversal with atipamezole made the animal more responsive in cases of heavy sedation. Honeyman,V.L., Cooper,R.M., and Black,S.R. 1998. **A protected contact approach to anesthesia and medical management of an Asian elephant (*Elephas maximus*).** Proceedings AAZV and AAWV Joint Conference. Pages: 338-341

h) Xylazine doses ranging from 100-550 mg with a mean of 0.209 mg/kg body weight were used to capture 8 wild Asian elephants. Bosi,E.J., Kilbourn,A.M., Andau,M., and Tambing,E. 1997. **Translocation of wild Asian elephants (Elephas maximus) in Sabah, Malaysia.** Proceedings American Association of Zoo Veterinarians. Pages: 302 **Abstract:** The East Malaysian State of Sabah is believed to be home to about 1000 wild Asian elephants (Elephas maximus). Some forest habitat has been lost through agricultural development. In some cases, elephants are stranded in small pockets of forest which are unable to sustain them. The Wildlife Department of Sabah has adopted a policy of capturing and translocating these animals to wildlife forest reserves. The capture of these wild animals is made possible using chemicals such as Immobilon® (etorphine HCl and acepromazine maleate) and Xylazine-100 (xylazine HCl). The reversal agents are Revivon (Diprenorphine) and Reverzine (Yohimbine), respectively. A recent capture and translocation exercise carried out involving eight wild elephants employed xylazine hydrochloride. The dose of xylazine used was calculated based on the diameter of the front footprint which provides information on body dimensions when actual weights are not available. Xylazine doses used ranged from 100-550 mg with a mean of 0.209 mg/kg body weight. Sedation was observed within 26 min after the darting. The animals were then shackled and tethered. The time for the capture operations ranged from 27-110 mins, with a mean of 72 min. Xylazine is used again during the loading of the animals onto the lorries. It is an effective sedative for wild elephants which can be adjusted or reversed. The choice and used of this drug depends entire on the ability to track the animal after darting and the ability to maneuver the captive elephants into suitable locations for tethering prior to loading. Heavy machinery is required to load the animals, unlike most other wild Asian elephant translocations were trained elephants are used to facilitate loading.

i) Captive Asian elephants: For sedation: 0.04-0.08 mg/kg (180-360 mg total dose); For immobilization 0.15-0.20 mg/kg alone or 0.12 mg/kg xylazine in combination with 0.33 mg/kg ketamine.

Captive African elephants: For sedation: 0.08-0.10 mg/kg (100-640 mg total dose);

To Drug Monograph Index To Ophthalmic Product Index

For immobilization (opiates are preferred): 0.15-0.20 mg/kg xylazine;
For babies and juveniles: 0.14 mg/kg xylazine in combination with 1.14 mg/kg ketamine. Fowler,M.E., 1995. **Elephants**. In: Restraint and handling of wild and domestic animals. Iowa State University Press, Ames, Iowa, USA pp. 265-269

j) Adult 700 mg; juvenile-adult 200-600mg; baby-juvenile 20-160 (species not specified); adult Asian elephant for translocation 150-2850 mg. Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants.** In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441. Author's (Mikota) note: The animal category and drug dose column headings for xylazine are misaligned in this reference and may cause confusion. The doses listed here have been correctly matched to their respective age categories. Regarding the Asian elephant dose, also note that in the original source (Lahiri-Choudhury, 1992), 2850 mg represents a combination of xylazine and ketamine. It does not represent a high end dose of xylazine alone. In this comparative study, 2850 mg was the maximum given to an individual elephant (over the time period that included capture and translocation, not as a single dose) and the maximum dose used during 24 hours.

k) 100 mg/ton is an ideal dose for Asian elephants. Appayya,M.K. and Khadri,S.S.M.S., 1992. **Chemical capture of wild elephants and their translocation carried out in Karnataka state.** In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 107-112

l) In a comparison of Asian elephant capture and translocation techniques, 400 mg xylazine was the maximum single dose used in Malaysia (tusker over 9'6") and 150 mg was the maximum dose used in West Bengal (tusker 8'2"). Maximum total on a single elephant were 2100 mg over 4 days (Malaysia) and 1525 mg (West Bengal). Maximum during 24 hours was 1500 mg (Malaysia) and 925 mg (West Bengal). Lahiri-Choudhury,D.K., 1992. **Translocation of wild elephants.** In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 91-106

m) Xylazine, administered IM was used to induce surgical anesthesia in 8 Asian elephants. A dose of 150 mg in a 1500 kg baby tusker and a dose of 400 mg in a 3000 kg tusker resulted in standing immobilization. Recumbent immobilization was achieved with doses of 400 mg (3500 kg tuskers) and 450 mg (4000 kg tusker), and with combinations of 350 mg xylazine + 350 mg ketamine (3000 kg cow), 300 mg xylazine + 150 mg acepromazine (2500 kg cow) and 350 mg xylazine + 150 mg acepromazine (3000 kg cow). Induction occurred in 10-15 minutes and duration of anesthesia varied from 30-60 minutes and provided sufficient analgesia for a variety of surgical procedures. Nayar,K.N.M., Radhakrishnan,K., Chandrasekharan,K., Cheeran,J.V., Ravindran,S., and George,P.O., 1992. **Anaesthesia for surgical manipulations in the elephant.** In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 156-158 Abstract: Anaesthesia using chloral hydrate, thiopentone sodium, xylazine and ketamine was induced in ten elephants. The effects, duration of induction and anaesthesia were recorded. Post anaesthesia complications were not encountered in any of the animals. Surgical manipulations could be carried out under anaesthesia induced with these drugs.

n) A mixture containing 100-150 mg xylazine and 50-100 mg ketamine injected intravascularly to the laterally recumbent Asian elephant produced quick, safe and dependable analgesia, anesthesia, and muscular relaxation. Surgical operations like tusk extraction, bullet extraction, umbilical and pleural herniorraphy, trunk

To Drug Monograph Index To Ophthalmic Product Index

injury, extensive wound repair, etc. were performed in 53 elephants. Pathak,S.C. 1991. **Xylazine-ketamine anesthesia in Indian elephant (Elephas maximus indicus).** - trial on 53 clinical cases. International Seminar on Veterinary Medicine in Wild and Captive Animals, Nov. 8-10, Bangalore, India. Pages: 21 **Abstract:** Veterinarians are often required to attend and undertake surgery on elephants. Unless the animal is deeply sedated or anesthetized certain works become impractical. Xylazine has proved to be a good sedative and analgesic in elephants. This drug is not freely available in India and is costly. The drug is usually used by intramuscular route but to reduce the dose it has been used intravenously. Intravenous use may be risky for its bradycardia effect and fall in cardiac output. Ketamine, on the other hand, has no depressant effect on the cardiovascular and respiratory system but produces muscular tremor and stiffness of the skeletal muscle. Combination of Xylazine and Ketamine minimizes the undesirable aspects of both the drugs. A mixture containing 100-150 mg xylazine and 50-100 mg ketamine injected intravascularly to the laterally recumbent elephant produced quick, safe and dependable analgesia, anesthesia, and muscular relaxation. Surgical operations like tusk extraction, bullet extraction, umbilical and pleural herniorraphy, trunk injury, extensive wound repair, etc. were performed in 53 elephants. Recovery followed without excitement and untoward effect based on the observations of this trial on clinical cases, combination of Xylazine and Ketamine is recommended in elephant.

o) A dose of 0.16 mg/kg was adequate to produce sedation, analgesia, and muscle relaxation to perform a ventral herniorrhaphy in an Asian elephant. Pathak,S.C., Saikia,J., Lahon,D.K., Deka,K.N., Barua,S.K., Dewan,J.N., and Vety,A.H. 1990. **Attempted ventral herniorrhaphy in an Asian elephant (*Elephas maximus*) using xylazine sedation.** Journal of Zoo and Wildlife Medicine 21:(2):234-235 **Abstract:** Ventral herniorrhaphy in a female Asian elephant (*Elephas maximus*) under xylazine hydrochloride sedation was attempted. A dose of 0.16 mg/kg body weight was adequate to produce sedation, analgesia, and muscle relaxation for the procedure. The postoperative management of the surgical wound was difficult and resulted in the failure of the surgery.

p) An African elephant weighing 650 kg was premedicated with 0.27 mg/kg ketamine and 0.23 mg/kg xylazine IM followed 20 minutes later by etorphine. Welsch,B., Jacobson,E.R., Kollias,G.V., Kramer,L., Gardner,H., and Page,C.D. 1989. **Tusk extraction in the African elephant (*Loxodonta africana*).** Journal of Zoo and Wildlife Medicine 20:(4):446-453 **Abstract:** Unilateral dentoalveolar abscesses and/or tusk fractures were identified and tusk extractions performed in seven 3.5-21-yr-old African elephants (*Loxodonta africana*) of both sexes weighing 650-3,000 kg. Following immobilization with etorphine hydrochloride or carfentanil citrate, six of seven elephants were intubated and maintained on a 1-1.5% halothane in oxygen mixture; one elephant was maintained in lateral recumbency by multiple i.v. injections of etorphine. All elephants were positioned with the affected tusk up. For one elephant, two surgical procedures were required to remove the tusk. In six of seven elephants, the tusks were sectioned transversely and the tusk wall thinned by enlarging the pulp cavity with carbide burs. In those tusks with remaining pulp, the pulp was removed with stainless steel rods and hooks. Next, the tusk was sectioned longitudinally into three or four segments using a wood saw within the pulp chamber. bone gouges, osteotomes, and a mallet were used to free the outer epithelial and alveolar attachments from the tusk. Starting with the smallest segment, the sections were removed using long screwdriver-shaped stainless steel rods. The alveolar chamber was then periodically flushed postsurgically with a dilute organic iodine solution. For six of seven elephants, complete granulation of the alveolar chamber was evident by 4 mo postsurgery; the seventh elephant showed partial healing with granulation tissue at 2 mo following surgery.

q) Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing juvenile African elephants during a 45-minute transport period before administration of general anesthesia. Heard,D.J., Kollias,G.V., Webb,A.I., Jacobson,E.R., and Brock,K.A. 1988. **Use of halothane to maintain anesthesia induced with etorphine in juvenile African elephants**. Journal of the American Veterinary Medical Association 193:254-256 **Excerpts:** Sixteen 3- to 5-year-old African elephants were anesthetized one or more times for a total of 27 diagnostic and surgical procedures. Xylazine (0.1 ± 0.04 mg/kg of body weight, mean ± SD) and ketamine (0.6 ± 0.13 mg/kg) administered IM induced good chemical restraint in standing

juvenile elephants during a 45-minute transport period before administration of general anesthesia. After IM or IV administration of etorphine (1.9 ± 0.56 micrograms/kg), the mean time to lateral recumbency was 20 ± 6.6 and 3 ± 0.0 minutes, respectively. The mean heart rate, systolic blood pressure, and respiration rate during all procedures was 50 ± 12 beats/min, 106 ± 19 mm of Hg, and 10 ± 3 breaths/min, respectively. Cardiac arrhythmias were detected during 2 procedures. In one elephant paroxysmal ventricular tachycardia was detected and the procedure terminated when the arrhythmia failed to stabilize after multiple doses of lidocaine (1 mg/kg, IV). In another elephant, second degree atrioventricular block returned to normal sinus rhythm after IV administration of atropine (0.04 mg/kg).

In one elephant, low mean blood pressure (54 mm of Hg) responded to reduction in halothane (vaporizer setting 1 to 0.75%) and slow infusion of dobutamine HCl ((250 mg/1,000 ml) given to effect. The systolic blood pressure increased to 90 mm of Hg and remained high with a continuous infusion of dobutamine (5 µg/kg/min).

Immediately after induction in another elephant, profound respiratory depression (< 1 breath / minute) and palpably weak arterial pulse were identified. Intravenous administration of diprenorphine at half the recommended reversal dose resulted in improvement of respiration and palpable arterial pulse, without the elephant developing signs of complete anesthetic reversal.

Alterations in systolic blood pressure, ear flapping, and trunk muscle tone were useful for monitoring depth of anesthesia. Results indicated that halothane in oxygen was effective for maintenance of surgical anesthesia in juvenile African elephants after induction with etorphine. Note: A correction appeared in a later volume 193(6): p.721

r) A group of 15 African elephants (Loxodonta africana) were immobilized with a combination of xylazine (0.2 mg/kg of body weight, IM) and ketamine (1 to 1.5 mg/kg of body weight, IM). Allen,J.L. 1986. **Use of tolazoline as an antagonist to xylazine-ketamine-induced immobilization in African elephants.** American Journal of Veterinary Research 47:(4):781-783 **Abstract:** A group of 15 African elephants (Loxodonta africana) were immobilized with a combination of xylazine (0.2 mg/kg of body weight, IM) and ketamine (1 to 1.5 mg/kg of body weight, IM). Ten of the African elephants were allowed to remain recumbent for 30 minutes and the remaining 5 elephants, for 45 minutes before they were given tolazoline (0.5 mg/kg of body weight, IV). For the group of 15, the mean induction time (the time required from injection of the xylazine-ketamine combination until onset of recumbency) was 14.2 ± 4.35 minutes (mean ± SD), and standing time (the time required from the tolazoline injection until the elephant stood without stimulation or assistance) was 2.8 ± 0.68 minutes. All of the elephants were physically stimulated (by pushing, slapping, shouting) before they were given tolazoline, and none could be aroused. After tolazoline was given and the elephant was aroused, relapses to recumbency did not occur. Recovery was characterized by mild somnolence in an otherwise alert and responsive animal. Failure (no arousal) rates were 0% (95% confidence interval, 0 to 0.3085) for elephants given tolazoline after 30 minutes of recumbency and 100% for elephants that were not given tolazoline. There was no significant (P less than 0.05) difference in standing time 30 or 45 minutes after tolazoline injection.

s) .08 mg/kg given IM (up to 0.15 mg/kg in an excited animal). Causes first degree heart block and is contraindicated in cases of known heart disease. The administration of atropine (4 to 5 mg/ 100 kg) should be administered to elephants that lie down following xylazine to prevent hypostatic congestion and cardiodepressant effects. Xylazine can be give IV at 0.04 mg/kg, however, the induction may not be as smooth and the elephant may risk falling. Schmidt,M.J., 1986. **Proboscidea (Elephants).** In: Fowler,M.E. (Editor), Zoo and wild animal medicine. W.B. Saunders, Philadelphia,PA, USA pp. 884-923. Mikota note: No species differences listed.

t) Twenty-two juvenile African elephants were given a combination of xylazine (mean +/- SD = 0.14 +/- 0.03 mg/kg of body weight) and ketamine (1.14 +/- 0.21 mg/kg) as a single

IM injection. Jacobson,E.R., Allen,J., Martin,H., and Kollias,G.V. 1985. **Effects of yohimbine on combined xylazine-ketamine-induced sedation and immobilization in juvenile African elephants.** Journal of the American Veterinary Medical Association 187:(11):1195-1198 **Abstract:** Twenty-two juvenile African elephants were given a combination of xylazine (mean +/- SD = 0.14 +/- 0.03 mg/kg of body weight) and ketamine (1.14 +/- 0.21 mg/kg) as a single IM injection; one elephant was immobilized twice, 77 days apart. After injection, 14 elephants were immobilized, 4 were sedated deeply, 2 were sedated moderately, and 2 were sedated minimally. Immobilized elephants had a mean immobilization time of 11.6 +/- 6.9 minutes. At the conclusion of a variety of clinical procedures, 12 of the 14 elephants immobilized with a single dose combination of xylazine and ketamine were given yohimbine (0.13 +/- 0.03 mg/kg) IV, and the remaining 2 elephants were allowed to recover spontaneously; the elephants given yohimbine had a mean standing time of 2.4 +/- 1.1 minutes. Of the 8 sedated elephants, 5 were given an additional dose of combined xylazine (0.08 +/- 0.03 mg/kg), and ketamine (0.61 +/- 0.19 mg/kg) IM, and 1 elephant was given ketamine (0.47 mg/kg) IV. After injection, 4 of the 8 elephants were recumbent laterally within 17 minutes and 2 remained standing, under deep sedation. Seven of the 8 elephants were given yohimbine (0.13 +/- 0.03 mg/kg) IV; all were ambulatory in 2 minutes. Results indicated that yohimbine may be useful in controlling duration of xylazine-ketamine sedation and immobilization in juvenile African elephants.

u) An Asian elephant (approx 3500 kg) was given three doses of xylazine over the course of approximately 1 hour 20 minutes (4-5 times the usual dose). Xylazine was antagonized with 4-aminopyridine and yohimbine. Three hours and 40 minutes after reversal, 1000 mg of xylazine given IM resulted in the death of the elephant. Although this elephant was scheduled for euthanasia, the author suggests that following reversal, additional doses of xylazine should not be given for 24 hours. Schmidt,M.J. 1983**. Antagonism of xylazine sedation by yohimbine and 4-aminopyridine in an adult Asian elephant (*Elephas maximus*).** Journal of Zoo Animal Medicine 14:94-97 **Abstract:** Heavy xylazine sedation was successfully antagonized by intravenous injection of yohimbine and 4-aminopyridine (4-AP) in an adult female Asian elephant (*Elephas maximus*) prior to euthanasia. A total xylazine dose of 1,200 mg intramuscularly plus 600 mg intravenously (approximately 0.33 mg/kg body weight) was given resulting in heavy sedation. After 50 minutes of deep recumbent sedation, 425 mg yohimbine and 1,000 mg of 4-AP were administered intravenously. Xylazine sedation was antagonized and the elephant was up and walking around within 5 minutes of antagonist administration. The elephant remained standing for other 3 hours; at which point euthanasia was performed.

v) Doses of 100 to 300 mg of a 10% solution of xylazine satisfactorily sedated 6 Asian elephants ranging from 150 to 255 cm shoulder height. At these dosages, all animals were sedated in the standing position. Bongso,T.A. 1980. **Sedation of the Asian elephant with xylazine.** Journal of the American Veterinary Medical Association 177:(9):783 **Abstract: (Full text):** Doses of 100 to 300 mg of a 10% solution of xylazine satisfactorily sedated 6 elephants ranging from 150 to 255 cm shoulder height. At these dosages, all animals were sedated in the standing position. The time taken to produce the initial signs of sedation ranged from 10+4 to 20+4 minutes, and the effects lasted from 60+8 to 100+15 minutes. The time taken from injection to complete recovery ranged from 360+31 to 540+21 minutes. Recovery was uncomplicated. Repeated administration of as much as 7 injections per animal at intervals of 3 to 4 days had no adverse effects. Disturbances during induction delayed the onset of action of the drug –also see *T.A. Bongso in Vet Rec, 105, (November 10, 1979): 442.*

**See also:**

Sharma S.P. 1997. **Surgical treatment of gunshot wounds under xylazine and ketamine anaesthesia in an elephant: clinical case report.** Indian Veterinary Journal 74:(11):973-974

Aik,S.S. 1992. **Preliminary observations on the training of Burmese elephants using xylazine.** New Zealand Veterinary Journal 40:(2):81-84 **Abstract:** A traditional elephant training method was chosen to be modified by the use of xylazine as a sedative and muscle relaxant. Three elephant calves with different

degrees of tameness were trained using xylazine. The drug was helpful in the training process. Xylazine made restraint of the elephants much easier and safer. During training, repeated doses of xylazine were used to prevent beatings, the wounds worsening and to pacify the elephants. The tamest elephant calf was punished less and took less time to be trained than the others. It is concluded that it is important to play with elephant calves to win their acceptance of man.

Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K., 1992. **Transportation of elephants by rail.** In: Silas,E.G., Nair,M.K., and Nirmalan,G. (Editors), The Asian Elephant: Ecology, Biology, Diseases, Conservation and Management (Proceedings of the National Symposium on the Asian Elephant held at the Kerala Agricultural University, Trichur, India, January 1989). Kerala Agricultural University, Trichur, India pp. 120-12

Lance,W.R. 1991. **New pharmaceutical tools for the 1990's.** Proceedings of the American Association of Zoo Veterinarians 354-359

Morton,D.J. and Kock,M.D. 1991. **Stability of hyaluronidase in solution with etorphine and xylazine.** J.Zoo and Wildlife Medicine 22:(3):345-347 **Abstract:** During capture of free-living wildlife, stress is potentially the greatest problem encountered. For this reason, reduction in induction time during immobilization is of paramount importance. Hyaluronidase reduces induction times, although no reports have assessed stability of the enzyme in drug mixtures used for chemical capture. This report presents information on the stability of hyaluronidase in combination with etorphine and xylazine, one of the most common drug mixtures used in chemical immobilization of wildlife. Hyaluronidase activity remains high for at least 48 hr, provided storage temperatures can be maintained at less than or equal to 30º C. Storage at greater than or equal to 40ºC is associated with rapid loss of enzyme activity in the mixture.

Jacobson,E.R. 1988. **Chemical restraint and anesthesia of elephants.** Proc.Ann.Elephant Workshop 9. Pages: 112-119

Heard,D.J., Jacobson,E.R., and Brock,K.A. 1986. **Effects of oxygen supplementation on blood gas values in chemically restrained juvenile African elephants.** Journal of the American Veterinary Medical Association 189:(9):1071-1074 **Abstract:** Arterial oxygen and carbon dioxide tensions were determined in sedated immature African elephants and in elephants immobilized with etorphine hydrochloride or with an etorphine-ketamine combination. For manipulative and surgical procedures, the Hudson demand value was used for oxygen supplementation during 6 procedures, and insufflation was used during 2 procedures. The Hudson demand value was more effective than insufflation in sustaining adequate arterial oxygenation.

Kock,N., Kock,M., Arif,A., and Wahid,M.N.S.A. 1984. **Immobilization techniques and complications associated with a bull Indian elephant (*Elephas maximus indicus*) during musth.** Proc.Am.Assoc.Zoo Vet. Pages: 68-74 **Summary:** An Asian bull in musth (estimated weight 4500 kg) was immobilized six times. Three drugs were used either alone or in combination. A mixture of etorphine and acetylpromazine (Immobilon®) was used effectively on three occasions at an average dose of 0.48 ml/1000kg. Xylazine (0.1 mg/kg) used alone was ineffective on two occasions and was supplemented with Immobilon. When Immobilon was used after the xylazine, the dose was reduced to 0.2 ml / 1000 kg. (Kock et.al. 1984). (Author's (Mikota) note: xylazine dose given as mg/kg and etorphine dose given as ml in original article).

Jacob,V., Cheeran,K., Chandrasekharan,K., and Radhakrishnan,K. 1983. **Immobilization of elephant in musth using xylazine hydrochloride.** 7th Annual Symposium of the Indian Society of Veterinary Surgeons. Pages: 62

Fowler,M.E. 1981. **Problems with immobilizing and anesthetizing elephants.** Proceedings of the American Association of Zoo Veterinarians 87-91

Bongso,T.A. 1980. **Use of xylazine for the transport of elephants by air.** Vet Rec 107:(21):492

To Drug Monograph Index To Ophthalmic Product Index

Schmidt,M.J. 1975. **The use of xylazine in captive Asian elephants.** Proc.Am.Assoc.Zoo Vet. Pages: 1-11

Schmidt,M.J. 1975. **A preliminary report on the use of rompun in captive Asian elephants.** Journal of Zoo Animal Medicine 6:13-21

**Monitoring Parameters** - 1) Level of anesthesia/analgesia; 2) Respiratory function; cardiovascular status (rate, rhythm, BP if possible); 3) Hydration status if polyuria present

**Client Information** - Xylazine should only be used by individuals familiar with its use.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -
**Veterinary-Approved Products**:

*Rompun*® (Bayer) *Gemini*® (Butler); *AnaSed*® (Lloyd);*Sedazine*® (Fort Dodge) (Rx) Approved for use (depending on strength) in dogs, cats, horses, deer, and elk.

While xyalzine is not approved for use in cattle in the USA, at labeled doses in Canada it reportedly has been assigned withdrawal times of 3 days for meat and 48 hours for milk. FARAD has reportedly suggested a withdrawal of 7 days for meat and 72 hours for milk for extra-label use in the USA.

**Human-Approved Products**: None

## YOHIMBINE HCL

**Chemistry** - A Rauwolfia or indolealkylamine alkaloid, yohimbine HCl has a molecular weight of 390.9. It is chemically related to reserpine.

**Storage/Stability/Compatibility** - Yohimbine injection should be stored at room temperature (15-30°C); (*Antagonil*®-store in refrigerator), and protected from light and heat.

**Pharmacology** - Yohimbine is an alpha$_2$-adrenergic antagonist that can antagonize the effects of xylazine. Alone, yohimbine increases heart rate, blood pressure, causes CNS stimulation and antidiuresis, and has hyperinsulinemic effects. By blocking central alpha$_2$-receptors, yohimbine causes sympathetic outflow (norepinephrine) to be enhanced. Peripheral alpha$_2$-receptors are also found in the cardiovascular system, genitourinary system, GI tract, in platelets, and adipose tissue.

**Uses/Indications** - Yohimbine is indicated to reverse the effects of xyalzine in dogs, but it is being used clinically in several other species as well. Yohimbine may be efficacious in reversing some of the toxic effects associated with other agents as well (*e.g.,* amitraz), but additional research must be performed before additional recommendations for its use can be made.

**Pharmacokinetics** - The pharmacokinetics of this drug have been reported in steers, dogs, and horses (Jernigan et al. 1988). The apparent volume of distribution (steady-state) is approximately 5 L/kg in steers, 2 - 5 L/kg in horses, and 4.5 L/kg in dogs. The total body clearance is approximately 70 ml/min/kg in steers, 35 ml/min/kg in horses, and 30 ml/min/kg in dogs. The half-life of the drug is approximately 0.5 - 1 hours in steers, 0.5 - 1.5 hours in horses, and 1.5 - 2 hours in dogs.

Yohimbine is believed to penetrate the CNS quite readily and when used to reverse the effects of xylazine, onset of action generally occurs within 3 minutes. The metabolic fate of the drug is not known.

**Contraindications/Precautions/Reproductive Safety** - Yohimbine is contraindicated in patients hypersensitive to it. In humans, yohimbine is contraindicated in patients with renal disease. Yohimbine

To Drug Monograph Index To Ophthalmic Product Index

should be used cautiously in patients with seizure disorders. When used to reverse the effects xyalzine, normal pain perception may result.
Safe use of yohimbine in pregnant animals has not been established.

**Adverse Effects/Warnings** - Yohimbine may cause transient apprehension or CNS excitement, muscle tremors, salivation, increased respiratory rates, and hyperemic mucous membranes. Adverse effects appear to be more probable in small animals than in large animals.

**Overdosage/Acute Toxicity** - Dogs receiving 0.55 mg/kg (5 times recommended dose) exhibited symptoms of transient seizures and muscle tremors.

**Drug Interactions** - Little information is available, use with caution with other alpha$_2$-adrenergic antagonists or other drugs that can cause CNS stimulation. In humans, yohimbine is recommended not to be used with antidepressants or other mood-altering agents.

**Doses -**
**Horses:**

For xylazine reversal:

a) 0.075 mg/kg IV (Gross and Tranquilli 1989)

**Elephants:**

For xylazine reversal:
a) 0.125 mg/kg. Cheeran,J.V., Chandrasekharan,K., and Radhakrishnan,K. 2002. **Tranquilization and translocation of elephants.** Journal of Indian Veterinary Association Kerala 7:(3):42-46

b) 0.05mg/kg yohimbine (route not specified) was effective in reversing ketamine-xylazine in 6 adult Asian elephants when administered 40 minutes after sedation. Sarma,K.K. and Pathak,S.C. 2001. **Cardio vascular response to xylazine and Hellabrunn mixture with Yohimbine as reversal agent in Asian elephants.** Indian Veterinary Journal 78:(5):400-492 **Summary:** Xylazine (0.1 mg/kg body weight) produced highly significant bradycardia and hypotension in recumbent Asian elephants, with a peak depression observed at the 30th minute for heart rate and 30th minute in the mean arterial pressure (MAP). Ketamine (1.25 : 1 ratio with xylazine) mildly marginalised the bradycardia, but remarkably improved the MAP. Yohimbine, used to reverse the sedation produced by xylazine did not appear to influence these parameters to any appreciable levels.

c) Yohimbine (60-72 µg/kg IV) was used to reverse xylazine in 3 African elephant immobilizations. Ramsay,E. 2000. **Standing sedation and tranquilization in captive African elephants (*Loxodonta africana*).** Proc. Am. Assoc. Zoo Vet. Pages: 111-114

d) Yohimbine is given at 0.5 times the xylazine dose. Kock,R.A., Morkel,P., and Kock,M.D., 1993. **Current immobilization procedures used in elephants.** In: Fowler,M.E. (Editor), Zoo and Wild Animal Medicine Current Therapy 3. W.B. Saunders Company, Philadelphia, PA, USA pp. 436-441

e) 50-250 mg in Asian elephants. e) Atapattu,N. 1991. **Antagonism of xylazine induced sedation and immobilization in wild elephant (Elephas maximus maximus).** International Seminar on Veterinary Medicine in Wild and Captive Animals, Nov. 8-10, Bangalore, India. Pages: 20 **Abstract:** Xylazine HCL has been the drug of choice for sedation of elephants. Sedated animals recover on its own after few hours. But there had been number of deaths in immobilized elephants after Xylazine induced sedation. Yohimbine HCL was tried on 10 wild elephants to antagonize Xylazine induced sedation. An initial dose of 50 mg of Yohimbine HCL was administered intravenously followed by a singular dose intramuscularly, similar doses were repeated in half an hour intervals. All the elephants recovered from Xylazine induced sedation after

To Drug Monograph Index To Ophthalmic Product Index

the treatment of Yohimbine HCL. The dose of Yohimbine HCL varied from 50 mg to 250 mg to complete recovery. The recommended dose of 0.13mg/kg had no significance on the body weight. The physical state of the animals, the dose of Xylazine HCL administered and other stress factors were more significant in deciding the dose of YohimbineHCL. All these animals were monitored for a period of one month and found their behaviour is recumbent laterally within 17 minutes and 2 remained standing, under deep sedation. Seven of the 8 elephants were given yohimbine (0.13 +/- 0.03 mg/kg) IV; all were ambulatory in 2 minutes. Results indicated that yohimbine may be useful in controlling duration of xylazine-ketamine sedation and immobilization in juvenile African elephants.

f) Yohimbine in combination with 4-aminopyridine reversed heavy xylazine sedation in an adult Asian elephant. See abstract below (Schmidt, 1983). Schmidt,M.J. 1983. **Antagonism of xylazine sedation by yohimbine and 4-aminopyridine in an adult Asian elephant (*Elephas maximus*).** Journal of Zoo Animal Medicine 14:94-97 **Summary:** Heavy xylazine sedation was successfully antagonized by intravenous injection of yohimbine and 4-aminopyridine (4-AP) in an adult female Asian elephant (*Elephas maximus*) prior to euthanasia. A total xylazine dose of 1,200 mg intramuscularly plus 600 mg intravenously (approximately 0.33 mg/kg body weight) was given resulting in heavy sedation. After 50 minutes of deep recumbent sedation, 425 mg yohimbine and 1,000 mg of 4-AP were administered intravenously. Xylazine sedation was antagonized and the elephant was up and walking around within 5 minutes of antagonist administration. The elephant remained standing for other 3 hours; at which point euthanasia was performed.

**Monitoring Parameters** -

1) CNS status (arousal level, etc.)
2) Cardiac rate; rhythm (if indicated), blood pressure (if indicated and practical)
3) Respiratory rate

**Client Information** - This agent should be used with direct professional supervision only.

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**:

Yohimbine Sterile Solution for Injection 2 mg/ml in 20 ml vials *Yobine*® (Lloyd); (Rx) Approved for use in dogs.

Yohimbine HCl Sterile Solution for Injection 5 mg/ml in 20 ml vials; *Antagonil*® (Wildlife Labs); (Rx) Approved for use in deer.

**Human-Approved Products**: Oral 5.4 mg tablets are available, but would unlikely to be of veterinary benefit.

**Zolazepam - see Tiletamine/Zolazepam**

## ZINC ACETATE
## ZINC SULFATE

**Chemistry** - Zinc acetate occurs as white crystals or granules. It has a faint acetous odor and effloresces slightly. One gram is soluble in 2.5 ml of water and in 30 ml of alcohol.

Zinc sulfate occurs as a colorless granular powder, small needles, or transparent prisms. It is odorless but has an astringent metallic taste. 1.67 grams are soluble in one ml of water. Zinc sulfate is insoluble in alcohol and contains 23% zinc by weight.

To Drug Monograph Index To Ophthalmic Product Index

**Storage/Stability/Compatibility** - Store zinc acetate crystals in tight containers. Unless otherwise recommended by the manufacturer, store zinc sulfate products in tight containers at room temperature.

**Pharmacology** - Zinc is a necessary nutritional supplement; it is required by over 200 metalloenzymes for proper function. Enzyme systems that require zinc include alkaline phosphatase, alcohol dehydrogenase, carbonic anhydrase and RNA polymerase. Zinc is also necessary to maintain structural integrity of cell membranes and nucleic acids. Zinc dependent physiological processes include sexual maturation and reproduction, cell growth and division, vision, night vision, wound healing, immune response, and taste acuity.
When administered orally, large doses of zinc can inhibit the absorption of copper.

**Uses/Indications** - Zinc sulfate is used systemically as a nutritional supplement in a variety of species. Oral zinc acetate has been shown to reduce copper toxicity in susceptible dog breeds (Bedlington Terriers, West Highland White Terriers) with hepatic copper toxicosis. Zinc sulfate is also used topically as an astringent and as weak antiseptic both for dermatologic and ophthalmic conditions.

**Pharmacokinetics** - About 20-30% of dietary zinc is absorbed, principally from the duodenum and ileum. Bioavailability is dependent upon the food in which it is present. Phytates can chelate zinc and form insoluble complexes in an alkaline pH. Zinc is stored mostly in red and white blood cells, but is also found in the muscle, skin, bone, retina, pancreas, liver, kidney and prostate. Elimination is primarily via the feces, but some is also excreted by the kidneys and in sweat. Zinc found in feces may be reabsorbed in the colon.

**Contraindications/Precautions/Reproductive Safety** - Zinc supplementation should be carefully considered before administering to patients with copper deficiency.
No documented adverse effects associated with zinc therapy during pregnancy apparently exist, but neither have adequate, well-controlled studies been performed.

**Adverse Effects/Warnings** - Large doses may cause GI disturbances. Hematologic abnormalities may occur with large doses, particularly if a coexistent copper deficiency exists.

**Overdosage/Acute Toxicity** - Signs associated with overdoses of zinc, include hemolytic anemia, hypotension, jaundice, vomiting and pulmonary edema. Suggestions for treatment of overdoses of oral zinc, include removing the source, dilution with milk or water and chelation therapy using edetate calcium disodium (Calcium EDTA). Refer to that monograph for possible doses and usage information.

**Drug Interactions** - Large doses of zinc can inhibit **copper** absorption in the intestine. If this interaction is desirable, separate copper and zinc supplements by at least two hours. **Penicillamine** and **ursodiol** may potentially inhibit zinc absorption; clinical significance is not clear. Zinc salts may chelate oral **tetracycline** and reduce its absorption; separate doses by at least two hours. Zinc salts may reduce the absorption of some fluroquinolones (*e.g.,* **enrofloxacin**).

**Doses** -
**Dogs**:

For zinc-related dermatoses:

a) Rapidly growing dogs: 10 mg/kg day PO of zinc sulfate. (Willemse 1992)
b) For zinc-responsive dermatoses found in Siberian huskies, Alaskan malamutes, Great Danes, and Doberman pinschers: Zinc sulfate: 10 mg/kg PO with food either once daily or divided q12h. Alternatively, zinc methionine: 2 mg/kg PO once daily. Correct any dietary imbalances (high calcium and phytate). Lifetime therapy usually required. If vomiting occurs, lower dose or give with food.

To Drug Monograph Index To Ophthalmic Product Index

For syndrome seen in puppies: Dietary corrections alone usually resolve the syndrome, but zinc supplementation as above, can expedite process. Some puppies require supplementation until maturity. (Kwochka 1994)

**Cats:**

For adjunctive therapy of severe hepatic lipidosis:

a) 7 -10 mg/kg PO once daily, in B-Complex mixture if possible. (Center 1994)

**Elephants:**

a) an Asian elephant with skin lesions responded to 2 g zinc carbonate /day. Schmidt,M.J. 1989. **Zinc deficiency, presumptive secondary immune deficiency and hyperkeratosis in an Asian elephant: A case report**. Proc.Am.Assoc.Zoo Vet. Pages: 23-31. **Abstract:** Zinc deficiency in an Asian elephant caused a secondary immune deficiency, and skin lesions which included superinfected vesiculobullae above the toenails and hyperkeratosis on the extensor surfaces of both elbows and on the tail. The elephant responded to therapy with an immune stimulant drug, but the chronic recurring skin lesions did not heal until after zinc supplementation was added to the diet. Additional excerpt: Dramatic improvement was noted within two weeks after the elephant was started on 2 g zinc carbonate per day. Lesions resolved by eight weeks. Subsequently, the dietary zinc level was adjusted from 21.56 mg/kg of feed to 53.6 mg/kg of feed on a dry matter basis.

**Monitoring Parameters/Client Information** - See above

**Dosage Forms/Preparations/FDA Approval Status/Withholding Times** -

**Veterinary-Approved Products**: None (for systemic use).
Several vitamin/mineral supplements contain zinc, however.

**Human-Approved Products**:

Zinc Acetate is available from chemical supply houses.

Zine Sulfate Injection: 1 mg/ml (as sulfate) in 10 & 30 ml vials; 5 mg/ml in 5 & 10 ml vials; 1 mg/ml (as 2.09 mg chloride) in 10 ml vials; *Zinca-Pak*® (Smith & Nephew SoloPak); generic, (Rx)

Zinc Sulfate Oral Tablets 66 mg (15 mg zinc); 110 mg (25 mg zinc); 200 mg (45 mg zinc); *Zinc 15*® (Mericon);*Orazinc*® (Mericon); Generic; (OTC)

Zinc Sulfate Oral Capsules 220 mg (50 mg zinc); *Orazinc*® (Mericon), *Verazinc*® (Forest), *Zinc-220*® (Alto), *Zincate*® (Paddock), generic; (Rx or OTC depending on product)

Zinc sulfate is also available in topical ophthalmic preparations.

## ZUCLOPENTHIXOL

**CAUTION!** Sedative and anesthetic drug dosages for African elephants often vary from those for Asian elephants. Do not assume that the recommendations for one species can be applied to the other. Significant variation may also occur between individual elephants. Higher doses may be needed in wild or excited animals. Unless otherwise specified, doses refer to captive elephants. The information provided here should be used as a guideline only. Consultation with experienced colleagues is advised.

**Elephants:**

To Drug Monograph Index To Ophthalmic Product Index

a) An Asian elephant (approx. 3750 kg) in dystocia was given 480 mg zuclopenthixol per os. An additional 400 mg was given 5 hours later and a vaginal vestibulotomy was performed under local anesthesia. Schaftenaar,W. 1996. **Vaginal vestibulotomy in an Asian elephant (*Elephas maximus*)**. Proceedings American Association of Zoo Veterinarians. Pages: 434-439 **Abstract:** Due to its dimensions, dystocia in elephants presents a difficult problem. This paper describes the delivery of a dead calf by surgical intervention. A vestibulotomy was performed under local anesthesia. Complications in wound healing resulted in a permanent fistula of the vestibulum. The difficulties in decision making and the interpretation of clinical signs are discussed.

To Drug Monograph Index To Ophthalmic Product Index

# Ophthalmic Products Index

**Note:** The following information is from an earlier version of Plumb's Veterinary Drug Handbook. Please consult the most current version for additional drugs or updated information.

The following section lists the majority of veterinary-labeled ophthalmic topical products and some of the more commonly used human-labeled products in veterinary medicine. It was written in cooperation with Dennis K. Olivero, DVM, DACVO to whom I would like to express my gratitude. Drugs are listed by therapeutic class. All doses (in italics) are from Dr. Olivero, unless otherwise noted.

For additional information, an excellent review on veterinary ophthalmic pharmacology and therapeutics can be found in the chapter by A. Regnier and P.L. Toutain in: *Veterinary Ophthalmology*, 2nd Edition; Kirk N. Gelatt, Editor; Lea & Febiger, Philadelphia, 1991. 765 pp




To Drug Monograph Index  To Ophthalmic Product Index

## Glaucoma, Topical Agents

Note: Generally, once acute congestive primary glaucoma is noted in one eye it is treated as an emergency using mannitol/glycerin systemically, a systemic carbonic anhydrase inhibitor, a miotic and then surgery is considered for lasting control of intraocular pressure. The following topical drugs are used "in general" as a preventative measure to prevent the occurrence of primary glaucoma in the unaffected eye. Topical ocular antihypertensive medications are sometimes employed for pressure control with secondary glaucomas also.

### TIMOLOL MALEATE (OPHTHALMIC)

**Indications/Pharmacology -** Timolol maleate is used primarily to prevent the development of primary glaucoma in the contralateral eye of a dog which has developed primary glaucoma in one eye. It only reduces intraocular pressure 3-10 mmHg and, therefore is of minimal usefulness in patients requiring treatment of primary acute congestive glaucoma. Timolol's mechanism of action: decreases cyclic-AMP synthesis in non-pigmented ciliary epithelium resulting in decreased aqueous humor production. It may also cause slight miosis in dogs and cats.

**Suggested Dosage/Precautions/Adverse Effects** - One drop twice daily of the 0.5% solution. The 0.25% concentration has minimal efficacy in animals and is not worth using. While problems have rarely been noted in veterinary medicine, ophthalmic beta blockers should be used with caution in patients with bronchoconstrictive disease or congestive heart failure.

**Dosage Forms/Preparations/FDA Approval Status -**

Veterinary-Approved Products: None

Human-Approved Products: Timolol Maleate 0.25% (see dosage above) or 0.5% solution in 2.5, 5, 10, and 15 ml Ocumeter® bottles; *Timoptic*® (MSD); (Rx)

### METIPRANOLOL

**Indications/Pharmacology** - Metipranolol HCl can be used as a substitute for timolol maleate (see above). Metipranolol is a nonselective beta blocking agent and reduces intraocular pressure minimally in animals by decreasing cyclic-AMP synthesis in the ciliary body. Pilot studies have suggested that metipranolol is as effective as timolol maleate, but is significantly less expensive. Metipranolol has been useful in the author's (DKO) clinic for the management of primary open angle glaucoma in cats.

**Suggested Dosage/Precautions/Adverse Effects** - One drop twice daily of the 0.3% solution. While problems have rarely been noted in veterinary medicine, ophthalmic beta blockers should be used with caution in patients with bronchoconstrictive disease or congestive heart failure.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary Labeled Products:** None

**Human-Approved Products:** 0.3% Metipranolol Solution in 2, 5, & 10 ml *OptiPranolol*® (Bausch & Lomb); (Rx)

### LEVOBUNOLOL HCL

To Drug Monograph Index To Ophthalmic Product Index

**Indications/Pharmacology** - Levobunolol HCl is a beta1 and beta2 blocking agent similar to timolol and metipranolol above but without the potential for myocardial depression or airway constriction noted rarely in veterinary medicine and occasionally in human patients. Levobunolol is used in humans with glaucoma responsive to beta adrenergic blocking agents but who suffer cardiac and respiratory side effects associated with timolol.

**Suggested Dosage/Precautions/Adverse Effects** - One drop twice daily of the 0.5% concentration. Miosis may develop in veterinary patients after application of topical beta blocking antiglaucoma medications.

**Dosage Forms/Preparations/FDA Approval Status-**

**Veterinary Labeled Products:** None

**Human-Approved Products:** Levobunolol HCl 0.25% or 0.5% solution in 5, 10, & 15ml. *Betagan*® (Allergan); (Rx)

## PILOCARPINE HCL

**Indications/Pharmacology** - Pilocarpine is a miotic agent that is used in the treatment of primary glaucoma only. Pilocarpine causes the ciliary body muscle to constrict placing posteriorly directed tension on the base of the iris to mechanically pull open the iridocorneal angle structures. By causing miosis, it may prevent closure of the iridocorneal angle by preventing excess iris tissue from peripherally compromising the outflow of aqueous humor.

The lacrimal glands of dogs and cats are predominately under parasympathetic stimulation. Pilocarpine was used in the 1970's and early 1980's as a stimulant of tear production, delivered either topically or by applying it (the eyedrop preparation) on the food of dogs with keratoconjunctivitis sicca. Toxicity problems with excessive salivation, vomiting and diarrhea complicated its use. It does not directly address the issue of autoimmunity thought to be the etiopathogenesis behind most cases of keratoconjunctivitis sicca in the dog. The popularity of treatment of KCS with ophthalmic cyclosporine ointment has been associated with a decline in the use of pilocarpine for this disease.

**Suggested Dosage/Precautions/Adverse Effects** - One drop in affected eye(s) 3 times daily. Usually 1% or 2% is most commonly used in veterinary medicine. Pilocarpine can cause local irritation initially. In humans, this irritation reportedly diminishes after 3 days of therapy. It may also cause inflammation of the uveal tract, especially with repeated applications and can cause hyphema. Pilocarpine should not be used in secondary glaucoma cases. With repeated use, pilocarpine may cause systemic effects (vomiting, diarrhea, and increased salivation).

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Pilocarpine HCl Ophthalmic Solution 0.25%, 0.5%, 1%, 2%, 3%, 4%, and 6% (in addition there are 8% and 10% solutions and a 4% gel is available from Alcon) in 15 ml and 30 ml containers. There are many products and trade names associated with pilocarpine, including I*sopto Carpine*® (Alcon), *Ocu-Carpine*® (Iomed), *Piloptic*® (Optopics), *Pilostat*® (Bausch and Lomb) and many generically labeled products. All are Rx.

See also the epinephrine monograph for information on epinephrine/pilocarpine fixed dose combination products.

## DEMECARIUM (OPHTHALMIC)

**Indications/Pharmacology** - Demecarium is a potent carbamate inhibitor that may reduce intraocular pressures for up to 48 hours in canines. Demecarium reversibly inhibits anticholinesterase thereby causing miosis. Demecarium is generally used in preventive management of the contralateral eye in patients after the diagnosis of an acute congestive crisis of primary glaucoma in the other eye. It is not used in secondary glaucoma. Demecarium has the advantage of once or twice daily dosing.

**Suggested Dosage/Precautions/Adverse Effects** - One drop once or twice daily. Demecarium is contraindicated during pregnancy. Because of additive effects, demecarium should be used with caution with

other cholinesterase inhibitors (e.g., carbamate/organophosphate antiparasiticides), or succinylcholine. Demecarium may cause local inflammation and systemic adverse effects (vomiting, diarrhea, increased salivation, cardiac effects) are possible, particularly with high dosages or in very small dogs.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Demecarium 0.125% or 0.25% in 5 ml dropper bottles, *Humorsol*® (Merck); (Rx). Do not freeze and protect from heat.

## EPINEPHRINE, TOPICAL

**Indications/Pharmacology** - Epinephrine (usually in combination with pilocarpine due to epinephrine's mydriatic effects) is usually used as a preventative measure to prevent glaucoma in the unaffected eye. Epinephrine acts on both alpha and beta adrenergic receptors, thereby causing conjunctival decongestion, transient mydriasis (less so in cats) and decreased IOP (intraocular pressure). Decreased IOP is probably due primarily to increased aqueous humor outflow, but decreased aqueous humor production may occur secondary to vasoconstriction.

**Suggested Dosage/Precautions/Adverse Effects** - One drop 2-3 times daily in the unaffected eye. Epinephrine may cause ocular discomfort upon instillation.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Epinephrine (HCl) 0.25%, 0.5%, 1% & 2% in 10 or 15 ml btls.; *Epifrin*® (Allergan), *Glaucon*® (Alcon); (Rx)

Epinephrine (Borate) 0.5%, 1% & 2% in 7.5 ml btls; *Eppy/N*® (Pilkington/Barnes-Hind), *Epinal*® (Alcon); (Rx)

Epinephrine Bitartrate 1% in combination with Pilocarpine HCl (either 1%, 2%, 3%, 4% or 6%) *E-Pilo-1*® (2, 3, etc.) (Iolab); *P1*(2, 3, etc.)*E1* (Alcon); (Rx)

## DORZOLAMIDE HCL

**Indications/Pharmacology** - Dorzolamide is often used in the contralateral eye of a dog with primary glaucoma to prevent development of bilateral disease. It is also an excellent agent to consider for most secondary glaucomas in dogs and cats because it has no effect on pupil size. Like the related oral carbonic anhydrase inhibitors (dichlorphenamide or *Daranide*®, methazolamide or *Neptazane*®), dorzolamide decreases aqueous humor production by the ciliary body epithelium by altering pH and affecting the $H^+/Na^+$ active transport exchange mechanism. Oral carbonic anhydrase inhibitors cause numerous systemic side effects such as metabolic acidosis and panting, diarrhea, vomiting, anorexia and others, all of which can be avoided with topical carbonic anhydrase inhibitors.

**Suggested Dosage/Precautions/Adverse Effects** - One drop three times daily is the standard treatment frequency, adjusted based on clinical response. Dorzolamide may cause stinging upon topical application.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:** Dorzolamide HCl 2% 5, 10, 15ml; *Trusopt*® (Merck); (Rx)

## LATANOPROST (OPHTHALMIC)

**Indications/Pharmacology** - Latanoprost is a prostaglandin $F_2$alpha analogue which reduces intraocular pressure by increasing aqueous humor outflow via the uveoscleral outflow mechanism. The major outflow mechanism in animals and people is through the iridocorneal angle termed the conventional outflow mechanism. A species variable alternative pathway directly across the surface of the iris into the iridal venous supply accounts for some outflow in people and animals. The horse apparently has the highest uveoscleral outflow of the domestic species studied. Latanoprost dramatically increases uveoscleral outflow and is an

exciting agent for glaucoma patients because this medication directly increases alternative drainage of aqueous humor, which logically would seem superior to reducing production or attempting to increase outflow through a failing conventional outflow system. Latanoprost is marketed for once daily usage in people and clinical studies show reduced effectiveness when once daily treatment is exceeded. In the author's clinic (DKO) with limited cases, the intraocular pressure reduction associated with the use of this agent has been impressive and can exceed even that possible with oral or topical carbonic anhydrase inhibitors. Latanoprost has been used in veterinary ophthalmology to treat primary and secondary glaucomas although clinicians should assess the possibility of profound miosis associated with the use of this medication in their secondary glaucoma cases.

**Suggested Dosage/Precautions/Adverse Effects** - One drop is applied in the PM. Latanoprost may cause topical irritation. Conjunctival hyperemia is commonly noted in patients using this medication. A direct stimulation of iris melanocytes results in excess melanin production in the iris of people using this medication, causing a dark brown color change to the iris. Profound miosis is noted with the use of latanoprost in dogs and cats.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products:** None

**Human-Approved Products:** Latanoprost 0.005% 2.5 ml; *Xalantan*® (Pharmacia & Upjohn) (Rx). Store under refrigeration until use; at room temp for 6 weeks after opened.

## Vasoconstrictors/Mydriatics

### PHENYLEPHRINE HCL

**Indications/Pharmacology** - Phenylephrine is used to differentiate conjunctival vascular injection (blanches with phenylephrine application) versus deep episcleral injection (blanches incompletely) associated with uveitis, glaucoma, or scleritis. It is also used prior to conjunctival surgery to reduce hemorrhage and in combination with atropine prior to cataract or other intraocular surgeries which require maximal pupillary dilation. Phenylephrine can be used to confirm the diagnosis of Horner's syndrome. Dilution of 2.5% phenylephrine solution with saline (1:10) produces a 0.25% solution. Normal eyes will not demonstrate mydriasis in response to this low concentration of phenylephrine. Third order Horner's syndrome of greater than two weeks duration is associated with receptor up regulation and therefore a response to 0.25% phenylephrine is noted. In this way, the diagnosis of Horner's is confirmed and a suggestion as to whether or not the condition is 2nd or 3rd order in nature.

In dogs, maximum mydriasis persists for about 2 hours and effects may last for up to 18 hours. Phenylephrine has significant alpha adrenergic effects (vasoconstriction and pupillary dilation) and minimal effects on beta receptors. When used alone, phenylephrine is reportedly not efficacious in the cat unless used with other mydriatics.

**Suggested Dosage/Precautions/Adverse Effects** - For diagnosis and characterization of Horner's syndrome: Apply 0.25% solution (see above) in both eyes. If there is a response in the miotic eye; 3rd order. If no response, apply 2.5% solution; if there is a response in both eyes it confirms Horner's and probably is 2nd order.

For treatment of Horner's Syndrome: Treatment is indicated only if patient experiences visual difficulty because third eyelid is elevated over pupil; then given on an as needed basis with an average duration of effect of 3-6 hours.

Prior to cataract or intraocular surgery: 2.5% or 10% given every 15 minutes for two hours. Monitor for hypertension and/or cardiac arrhythmia in small patients especially when using the 10% solution.

Local discomfort may occur after instillation and chronic use may lead to inflammation. In some species (cat, rabbit, humans) transient stromal clouding may occur if used when corneal epithelium is damaged.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Phenylephrine HCl 0.12% in 15 ml or 20 ml bottles (OTC)

To Drug Monograph Index To Ophthalmic Product Index

Phenylephrine HCl 2.5% in 2, 5 or 15 ml bottles (Rx)

Phenylephrine HCl 10% available in 1, 2, 5 or 15 ml bottles (Rx). Available generically and under several proprietary names. A well known trade name is *Neo-Synephrine*® (Sanofi Winthrop). A viscous form of the 10% is also available.

## Cycloplegic Mydriatics

### ATROPINE SULFATE (OPHTHALMIC)

**Indications/Pharmacology** - Atropine, when used topically on the eye, acts by blocking the cholinergic responses of the sphincter muscle of the iris and the ciliary body to cause mydriasis (pupillary dilation) and accommodation paralysis (cycloplegia). Atropine may be useful in the control of pain secondary to corneal and uveal disease; to maximally dilate the pupil prior to intraocular surgery; to dilate the pupil and prevent pupillary block in glaucoma and uveitis. In the dog, atropine causes maximal mydriasis in about 1 hour and it may persist for up to 120 hours. Cats also show a delayed onset of action and mydriasis may persist for up to 144 hours (dose dependent). Atropine is particularly long acting in horses.

Atropine may be used in combination with 10% phenylephrine to achieve mydriasis and cycloplegia in cases of anterior uveitis.

**Suggested Dosages/Precautions/Adverse Effects** - Ointments or drops are routinely used in dogs. One percent is commonly used, but 2% solutions may be required in severe cases of uveitis. Ointments are generally used in cats to prevent hypersalivation associated with the bitter taste of this medication. Dosage frequencies are variable depending on the condition and its severity. Commonly, atropine is given as one drop 2-3 times a day until pupillary dilation is achieved and once daily thereafter to maintain this response.

Atropine may precipitate acute, congestive primary glaucoma in dogs predisposed to primary glaucoma; do not use in primary glaucoma. Repeated topical application prior to surgery can result in systemic atropine toxicosis (mania, hyperthermia, etc.). Salivation may result in dogs as well as cats (see above) secondary to the bitter taste.

Reportedly, very frequent treatment with atropine may induce colic in horses secondary to systemic absorption and atropine's vagal parasympathetic effects. However, clinically this effect is only rarely noted.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:**

Atropine Sulfate Ophthalmic Ointment 10 mg/gm (1%) in 3.5 gm tubes; *Atrophate*® (Schering-Plough); (Rx)

**Human-Approved Products:**

Atropine Sulfate Ophthalmic Ointment 5 mg/gm (0.5%), 10 mg/gm (1%) in 3.5 gm tubes; Generic and various trade names; (Rx)

Atropine Sulfate Ophthalmic Solution 0.5%, 1%, and 2% in unit dose droppers; 2, 5, & 15 ml bottles; Generic and various trade names; (Rx)

### TROPICAMIDE (OPHTHALMIC)

**Indications/Pharmacology** - Tropicamide, like atropine, causes mydriasis and cycloplegia, but has more mydriatic than cycloplegic activity. Tropicamide has a more rapid onset (maximum mydriasis in 15-30 minutes) of action and a shorter duration of action (pupil returns to normal in 6-12 hours in most animals) than does atropine, thereby making it more useful for funduscopic examinations. In dogs, intraocular pressure is apparently not affected by tropicamide.

**Suggested Dosages/Precautions/Adverse Effects** - Once or twice application to eye, prior to exam. Following cataract surgery: apply 2-3 times daily to keep pupil constantly changing in size and reduce formation of synechiae associated with prolonged pupillary dilation (atropine). Note: a current trend away from the use of mydriatics after intraocular surgery has developed in recognition of immediate postoperative pressure elevations in some animals following surgery.

Tropicamide is less effective in pain control (cycloplegia) than atropine.

To Drug Monograph Index To Ophthalmic Product Index

Tropicamide may cause salivation, particularly in cats and may also sting when applied. Tropicamide may precipitate acute congestive glaucoma in predisposed patients.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary Approved Products:** None

**Human-Approved Products:** Tropicamide Solution 0.5% and 1% in 2 ml & 15 ml bottles; *Mydriacyl*® (Alcon), *Opticyl*® (Optopics), *Tropicacyl*® (Akorn), Generic; (Rx)

## Topical Anesthetics

### PROPARACAINE HCL (OPHTHALMIC)

**Indications/Pharmacology** - Proparacaine is a rapid acting topical anesthetic useful for a variety of ophthalmic procedures including tonometry (intraocular pressure measurement), relief of corneal pain to facilitate examination, biopsy/sample collection, and to distinguish between corneal and uveal pain. Proparacaine primarily anesthetizes the cornea; with limited penetration into conjunctiva. Anesthesia is of short duration (5-10 minutes).

**Suggested Dosages/Precautions/Adverse Effects**- Usual dose is 1 - 2 drops prior to examination or procedure. For prolonged procedures only requiring local anesthesia; may repeat 1 drop doses every 5-10 minutes for 5-7 doses.

Topical anesthetics should not be used to treat painful eye disease. Prolonged use may retard wound healing and cause corneal epithelial ulcers. Because the blink reflex may be suppressed, the eye should be protected from external injury during use. Repeated use may lead to rapid development of tolerance. Local allergic-type reactions have been rarely reported in humans.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:**

Proparacaine HCl Solution 0.5% in 15 ml bottles; *Ophthaine*® (Solvay); (Rx)

Protect from light. Refrigerate.

**Human-Approved Products:**

Proparacaine HCl Solution 0.5% in 2 & 15 ml bottles; *Ophthetic*® (Allergan), *Alcaine*® (Alcon), *Ophthaine*® (Squibb), *AK-Taine*® (Akorn), Generic; (Rx)

Protect from light. Some products should be refrigerated; check label.

## Non-Steroidal Antiinflammatory Agents

### FLURBIPROFEN SODIUM (OPHTHALMIC)

**Indications/Pharmacology** - Flurbiprofen is a non-steroidal anti-inflammatory agent that probably acts by inhibiting the cyclo-oxygenase enzyme system, thereby reducing the biosynthesis of prostaglandins. Prostaglandins may mediate certain kinds of ocular inflammation. They may disrupt the blood-aqueous humor barrier, cause vasodilation, increase intraocular pressure and leukocytosis, and increase vascular permeability. Prostaglandins may also cause iris sphincter constriction (miosis) independent of cholinergic mechanisms. Flurbiprofen can inhibit this intraocular miosis and may also be useful in the management of uveal inflammation (usually in addition to topical steroids).

**Suggested Dosages/Precautions/Adverse Effects** - Prior to surgery: One drop 4 times at 20 minute intervals.

Because flurbiprofen may be as immunosuppressive as topical corticosteroids, it should not be used in patients with infected corneal ulcers. By blocking prostaglandin synthesis, arachidonic acid metabolites may be shunted into leukotriene pathways and this effect may result in a transient increase in intraocular pressure commonly noted after intraocular surgery. Postoperative pressure spikes following cataract surgery have been the subject of much study in recent years and a general trend away from the use of flurbiprofen prior to cataract surgery has resulted from these studies.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

To Drug Monograph Index To Ophthalmic Product Index

Flurbiprofen Sodium 0.03% Solution in 2.5, 5 & 10 ml btls; *Ocufen*® (Allergan); (Rx)

### KETOROLAC TROMETHAMINE (OPHTHALMIC)

**Indications/Pharmacology** - Ketorolac tromethamine is a pyrrolol-pyrrole nonsteroidal anti-inflammatory agent that inhibits prostaglandin formation. Prostaglandins mediate inflammation within the eye by disrupting the blood-aqueous barrier, inducing vasodilation and increasing intraocular pressure. Prostaglandins may also cause iris sphincter constriction (miosis) independent of cholinergic mechanisms. Ketorolac tromethamine is marketed for use before cataract extraction in human patients (to prevent miosis during surgery) and for control of post surgical inflammation, especially following cataract surgery. It is also approved for management of conjunctivitis associated with seasonal allergy in people. In veterinary medicine, ketorolac tromethamine is primarily used to control surgical or nonsurgical uveitis particularly in cases with concurrent corneal infection when topical corticosteroids are contraindicated or in diabetic patients, especially smaller patients, adversely affected by systemic uptake of topically applied corticosteroids. Nonsteroidal agents like ketorolac tromethamine can be combined with topical steroids in patients with severe uveal inflammation.

**Suggested Dosages/Precautions/Adverse Effects** - Prior to surgery: One drop 4 times at 20 minute intervals. One drop four times daily following cataract surgery or for treatment of uveitis or for management of allergic conjunctivitis.

The manufacturer indicates that ketorolac tromethamine does not enhance the spread of preexisting corneal fungal, viral or bacterial infections in animals models. Ketorolac tromethamine does not in and of itself induce postoperative pressure elevation other then that which frequently follows cataract extraction in people and animals.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Ketorolac Tromethamine Solution 0.5% 3, 5, 10 ml; *Acular*® (Allergan); (Rx)

### DICLOFENAC SODIUM (OPHTHALMIC)

**Indications/Pharmacology** - Diclofenac sodium is a phenylacetic acid that inhibits cyclooxygenase, inhibiting prostaglandin synthesis. Diclofenac sodium topical solution reduces inflammation following cataract extraction in people and counteracts photophobia in humans having refractive corneal surgery. In veterinary medicine, diclofenac sodium is used for treatment of uveitis following surgery on the eye or other causes of uveitis especially when corneal infection is suspected or in diabetic patients whose insulin regulation could be altered by the systemic uptake of topical corticosteroids. Diclofenac can be combined with topical corticosteroids for better control of uveitis in animals when the condition is severe.

**Suggested Dosages/Precautions/Adverse Effects** - Prior to surgery: One drop 4 times at 20 minute intervals. One drop four times daily following cataract surgery or for the treatment of uveitis. Caution should be used when applying any anti-inflammatory agent on the cornea in the face of corneal stromal infection because of the positive role inflammation plays in the immune response to microbial invasion of tissue. A stinging sensation is noted in 15% of people using this medication.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:** Diclofenac Sodium 0.1% in 2.5, 5 ml; *Voltaren*® (Ciba Vision); (Rx)

## Antiinflammatory Mast Cell Stabilizers

### Lodoxamine Tromethamine (Ophthalmic)

**Indications/Pharmacology** - Lodoxamine tromethamine is a mast cell stabilizer that inhibits Type I hypersensitivity responses by preventing antigen mediated histamine release. Lodoxamine stabilizes mast

cells by blocking calcium influx into the cell upon antigen recognition, thereby blocking histamine release. Lodoxamine has no intrinsic vasoconstrictor, antihistaminic, cyclooxygenase inhibition or other anti-inflammatory properties. Lodoxamine is used in people for management of conjunctivitis associated with seasonal allergy and other histamine mediated disorders. In veterinary medicine, lodoxamine tromethamine has been used in horses and small animal patients with presumed allergic conjunctivitis.

**Suggested Dosages/Precautions/Adverse Effects** - Prior to surgery: One drop 2-4 times daily. A stinging sensation is noted in a low percentage of people using this medication.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:** Lodoxamine Tromethamine 0.1% 10ml; *Alomide*® (Alcon); (Rx)

### CROMOLYN SODIUM (OPHTHALMIC)

**Indications/Pharmacology** - Cromolyn sodium is a mast cell stabilizing agent that blocks release of histamine and slow-reacting substance of anaphylaxis from mast cells following antigen recognition. Similar to lodoxamine tromethamine, cromolyn sodium has no intrinsic vasoconstrictor, antihistaminic, cyclooxygenase inhibition or other anti-inflammatory properties. Mast cell stabilizing agents are most useful in animal patients suffering from allergic conjunctivitis.

**Suggested Dosages/Precautions/Adverse Effects** - Prior to surgery: One drop 2-6 times daily. A stinging sensation is noted in a low percentage of people using this medication.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:** Cromolyn Sodium 4% in 2.5, 10ml; *Crolom*® (Bausch & Lomb); (Rx)

## CORTICOSTEROIDS, TOPICAL

(see also Antibiotic & Corticosteroid Combinations)

**Indications/Dosages/Precautions -** Topical corticosteroids are used to treat diseases of the eye involving the conjunctiva, sclera, cornea, and anterior chamber. Penetration of topically applied corticosteroids into the eyelids is poor as is penetration to the posterior segment of the eye. Corticosteroid-responsive conditions affecting these areas are usually managed with systemically administered agents (with or without adjunctive topically applied medications).

Conjunctivitis in animals is often treated symptomatically, particularly during the first occurrence of the condition for any particular patient. Antibiotic agents with hydrocortisone or dexamethasone, or antibiotic agents alone initially, are used for conjunctivitis in the dog and the horse. Allergic and eosinophilic conjunctivitis are rare diagnoses in the cat. Topically applied corticosteroids should not be used to treat conjunctivitis in cats. Herpes virus is the most common feline conjunctival pathogen and topically applied steroids can induce prolonged disease, steroid dependency and corneal complications including ulcerative keratitis and/or corneal sequestrum formation.

Inflammatory conditions of the canine sclera and episclera include episcleritis, scleritis, nodular granulomatous episclerokeratitis, Collie granuloma and others. Potency and penetration of corticosteroid agents is important in the management of these conditions. Dexamethasone sodium phosphate ointment is often employed and the relatively reduced penetration of the fibrous ocular tunics of this medication compared with that of 1% prednisolone acetate ophthalmic suspension is made up for by increased contact time of the ointment form of this drug and by the increased potency of dexamethasone (30X cortisone) relative to prednisolone (4-5X cortisone). Dexamethasone products alone (without antibiotics) are becoming increasingly scarce in the marketplace and because of this, dexamethasone is often used in combination with an antibiotic for availability reasons only. Four times daily treatment is often the initial frequency with tapering paralleled to clinical response. Topical treatment is often used following subconjunctival injection of corticosteroid agents into or adjacent to the lesion (if focal). Systemic steroid treatment is usually not necessary.

To Drug Monograph Index  To Ophthalmic Product Index

Nonulcerative inflammatory conditions of the cornea of animals include chronic superficial keratitis (pannus) of the German Shepherd and other breeds, eosinophilic keratitis of the cat and certain, often poorly understood, keratopathies of the equine, including Onchocerca related keratitis. German Shepherd pannus may be better managed using cyclosporine ophthalmic solution or ointment with or without concurrent topical steroids initially followed by long term management with cyclosporine ophthalmic alone (see cyclosporine ophthalmic). Eosinophilic keratitis is often treated with subconjunctival corticosteroids in addition to topical 0.1% dexamethasone ophthalmic ointment or solution or 1% prednisolone acetate ophthalmic suspension 4 times daily, tapering the dosage frequency based on clinical response. Recent research reveals that eosinophilic keratitis may be an unusual immune response to latent feline herpes virus in the corneal stroma, calling into question the value of topical steroids in the management of a disease with an infectious etiology. Equine keratopathies are treated with 0.1% dexamethasone ointment 4 times daily with tapering of the treatment frequency based on the clinical response.

Corticosteroids are also used to manage anterior uveal inflammatory disease of companion animals. In small animals, 1% prednisolone acetate ophthalmic suspension is generally used for this purpose because of superior penetration into the anterior segment of the eye in comparison with dexamethasone products. The frequency of treatment depends on the severity of the condition. Severe anterior uveitis can be treated with subconjunctival corticosteroids given in combination with hourly topical corticosteroids with reevaluation performed again 24 hours after beginning treatment. Moderate to mild uveitis and that found following surgery of the anterior segment is often treated initially at the QID level with tapering based on clinical response. Anterior uveitis in animals can often be associated with an underlying systemic infectious or neoplastic condition in animals. Clinicians are advised to evaluate the patient for generalized infectious or neoplastic conditions prior to or concurrent with a course of corticosteroid antiinflammatory therapy, particularly if the condition dictates systemic treatment with these agents in combination with subconjunctival and topical treatment. Uveitis in the equine species is often treated with either 1% prednisolone acetate ophthalmic suspension or with 0.1% dexamethasone ointment. Many clinicians prefer to use the ointment because of increased contact time and potency and the logistics of frequent treatment of this species. 1% prednisolone acetate can be passed through a subpalpebral lavage catheter very frequently to treat equine patients with anterior uveitis when necessary.

*Pred Forte*®, *Econopred Plus*® or generic 1% prednisolone acetate ophthalmic suspension are the prednisolone products most used by veterinary ophthalmologists. There are few indications for *Econopred*® or *Pred Mild*® in veterinary ophthalmology.

Inflammatory condition of the posterior segment require systemic treatment because of poor penetration of topically applied agents.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Prednisolone Acetate Drops: 0.12% Suspension *Pred Mild*® (Allergan); 0.125% Suspension *Econopred*® (Alcon); 1% Suspension; *Econopred Plus*® (Alcon); *Pred Forte*® (Allerga_n; Generic; (Rx)

Prednisolone Sodium Phosphate Drops: 0.125% Solution (various manufacturers); 1% Solution (various); (Rx)

Combination of Prednisolone (0.25%) and Atropine (1%) Drops: *Mydrapred*® (Alcon) in 5 ml bottles; (Rx)

Also available: Fluorometholone or Medrysone drops.

Other routes of administration: Systemically administered corticosteroids (usually orally) may be indicated for non-infectious inflammatory ocular conditions and following intraocular surgery. Subconjunctival steroids are useful in anterior segment inflammatory disease and following cataract surgery and intraocular glaucoma surgery. Subconjunctival steroids may be absorbed systemically and should be used with caution in patients with endocrinopathies (e.g., diabetes mellitus) or infectious diseases.

To Drug Monograph Index To Ophthalmic Product Index

## Antibiotics, Single and Combination Agents

**Indications/Pharmacology/General Use Considerations** - Topical antibiotic agents are commonly used to treat conjunctivitis and ulcerative keratitis complicated by bacterial infection of the corneal stroma. These agents are also used to prevent infection following surgery of the eyelids, conjunctiva, cornea, and the anterior segment. Conjunctivitis in animals is a common clinical entity. Because in most instances the condition does not threaten vision, it is often treated symptomatically with antibiotic agents or antibiotic agents in combination with topical steroids (see antibiotic/corticosteroid combination agents). Conjunctivitis is an exclusion diagnosis in animals, ruling out other causes for ocular discomfort and discharge, including anterior uveitis, glaucoma and inflammatory disease of the sclera, episclera and cornea. Triple antibiotic products (neomycin, bacitracin and polymyxin B) are often employed for this purpose, with or without hydrocortisone, because these drugs are not used systemically and because the combination of antibiotics is broad spectrum. Triple antibiotic or triple antibiotic HC is often used in dogs 4 times daily for 1 to 2 weeks for conjunctivitis. Chronic or recurrent cases of conjunctivitis would indicate further diagnostic evaluation to determine an underlying cause. Tetracycline ophthalmic ointment is often used QID in cats for nonspecific or undiagnosed conjunctivitis. The rationale for this treatment is the efficacy of tetracycline for Chlamydia spp. and Mycoplasma spp., two infectious agents reported to cause conjunctivitis in the cat. Antibiotic agents with corticosteroids should not be used for the treatment of conjunctivitis in the cat. The majority of cases are related to primary or recurring infection with feline herpes virus and recent evidence indicates that topical or systemic steroid therapy can potentially prolong the duration of the viral infection and result in corneal complications in cases which otherwise may have remained a conjunctival infection. Triple antibiotic with or without hydrocortisone is often used to treat conjunctivitis in the equine species. Sensitivity to triple antibiotic in dogs and cats has been noted and is reportedly the result of neomycin allergy, as is noted in people.

Antibiotic therapy for corneal disease varies from prophylactic therapy to prevent infection to treatment of established corneal infections. Following an acute superficial injury to the cornea in the dog, cat or horse, treatment with triple antibiotic ointment or drops 4 times daily is usually sufficient to prevent bacterial infection of the corneal stroma. Reevaluation of the patient 24-48 hours after the injury is indicated. Progressive edema, pain, and white opacification of the cornea (cellular infiltrate) would suggest that the antibiotic protocol (agent and frequency) has failed to prevent bacterial infection.

Established bacterial infection of the corneal stroma is managed medically or surgically depending on the depth of infection. Ulcerative keratitis with bacterial infection causing deterioration of 50-75% of the stromal thickness is usually treated with conjunctival or corneal grafting in addition to antibiotic therapy. This is done to introduce immune system components and a blood supply to the cornea (conjunctival graft) in addition to replacing lost stromal tissue. Conjunctival grafting will usually stabilize stromal deterioration secondary to bacterial infection but carries the disadvantage of permanent opacification of the cornea in the site of previous ulcerative keratitis (unless other surgeries are performed). Aggressive medical management with topical antibiotic agents is often successful in controlling corneal infection which involves 75% or less of the depth of the cornea. The slit lamp biomicroscope is used by ophthalmologists at referral centers and specialty clinics to determine the depth of corneal involvement.

Clinical signs of bacterial infection of the corneal stroma includes increasing pain, progressive corneal opacity, hypopyon, and the development of a progressively expanding indentation or crater in the surface of the cornea. Cytology is indicated in the management of such patients. Gram staining is usually not necessary. Cocci noted with Dif-Quick® or related stains are considered to be gram positive cocci. Those cocci forming chains are considered to be Streptococcus organisms. Those cocci of variable size and shape and forming grape clusters are considered to be Staphylococcal organisms. Rods are considered to be gram negative organisms and Pseudomonas spp. is suspected. A degree of suspicion for fungal keratitis should be maintained while evaluating cytologic material collected from the cornea of the horse. Fungal hyphae stain dark blue with Dif-Quick® type stains. Culture and sensitivity tests are informative but the information is available at a time when the efficacy of the antibiotic therapy chosen has already been established. In 24-48 hours the case will show signs of improvement, indicating efficacy of the therapeutic protocol or the condition will have advanced and surgery will be under consideration. Sensitivities are relatively meaningless because aggressive medical treatment can result in corneal drug concentrations several times the MIC and sometimes

beyond that considered toxic on a systemic basis. The use of eyedrops rather than ointments is recommended for aggressive medical management protocols.

Cytologic evaluation of material from the cornea will dictate antibiotic selection for aggressive medical management of corneal ulcers. Cocci are often treated with frequent application of triple antibiotic drops. Gentamicin has limited spectrum for Streptococci spp. and would not be a first choice agent when cocci forming chains are noted on cytologic evaluation of material from an infected corneal ulcer. Gentamicin has efficacy for some Staphylococcal spp. Chloramphenicol is also an antibiotic available for treatment of gram positive infections of the cornea. Gram negative infections of the cornea are often treated with gentamicin, tobramycin or the quinolones. Several studies indicate that a bacterial infection of the corneal stroma that responds to tobramycin is usually as responsive to gentamicin applied frequently making the newer aminoglycoside and quinolone antibiotics rarely necessary. These agents are reserved for very specific instances of stromal infection with highly resistant organisms and should not be considered for prophylactic treatment. Applied very frequently, bactericidal concentrations of either triple antibiotic or gentamicin ophthalmic solutions can be achieved in the corneal stroma making these two agents effective for the vast majority of corneal infections in companion animals. Relative penetration of antibiotic agents into the cornea is irrelevant during the treatment of ulcerative keratitis. All agents are water soluble (eye drops) and would penetrate the corneal stroma similarly. Penetration of various antibiotic agents into the cornea is a consideration when the corneal epithelium is intact as is often noted with the development of stromal abscessation in equines.

Aggressive medical management protocols involve hourly or q30 minute application of topical antibiotics. Sometimes two agents are used with synergistic properties (for example an aminoglycoside and a cephalosporin). One agent is applied on the hour and the other on the half hour. Single agents are usually applied hourly. The case is reevaluated 18-24 hours after initiation of the treatment regimen. Increased patient comfort, reduced corneal edema and no increase in the depth or width of the corneal ulcer are signs of efficacy of the selected treatment plan. In some cases at 24 hours and most cases by 30 hours, the peripheral "rim" of the corneal ulcer will fail to take on fluorescein stain, indicating early epithelialization of the corneal ulcer. It is the author's (DKO) impression that epithelialization of the ulcer will not occur until the stromal infection has been arrested. Cytologic evaluation of material collected from the cornea can be repeated to evaluate efficacy of the drug(s) selected. Clinical improvement signals the clinician to begin reducing treatment frequency slowly over the next two days, working towards the QID level. Long term aggressive medical management is not recommended because several agents, especially the aminoglycosides, are epitheliotoxic and prolonged once per hour treatment likely would delay healing rather than improve the case.

Aggressive medical management usually requires hospitalization in an intensive care unit for careful treatment and monitoring of the case. The advantage of aggressive medical management is reduced opacity in the cornea in comparison with conjunctival grafting. This is associated with an improved visual result, particularly if the injury is central. Medical management is usually less expensive than surgical treatment. General anesthesia is not necessary for aggressive medical management. Although aggressive medical management may result in halting further bacterial deterioration of stromal tissue in very deep corneal ulcers, reepithelialization of Descemet's membrane or a thin layer of corneal stroma interposed between Descemet's membrane and the corneal epithelium leaves the cornea dangerously thin. Minor trauma to the eye could result in rupture of the cornea across this area and loss of the anterior chamber.

Post surgical prophylactic medical treatment usually involves triple antibiotic agents because of their broad spectrum and because they are not agents used systemically. Four times daily treatment is recommended. Ointments are commonly used after surgery of the eyelids, conjunctiva or cornea. Eyedrops are usually used following surgery of the cornea or anterior segment. Bacterial infection of the anterior chamber alone is uncommon. Bacterial endophthalmitis carries a poor prognosis for saving vision or the globe in animals and is usually managed surgically in people. Gentamicin is sometimes used for prophylactic therapy of the equine species because of a greater number of gram negative organisms in the environment of this species, although the aminoglycosides would not be a first choice agent for prophylactic medical treatment of small animals. Tobramycin and the quinolones would not be considered for prophylactic treatment following surgery performed under sterile conditions.

To Drug Monograph Index To Ophthalmic Product Index

**Indications/Pharmacology** - A broad spectrum antibiotic, chloramphenicol has the ability to cross the corneal barrier and enter the anterior chamber. However, there are very few infections that occur in the anterior chamber and if bacteria are actually present there, the blood ocular barrier is lost and systemically administered antibiotics can achieve therapeutic levels.

Because of the potential toxicity associated with chloramphenicol to humans, chloramphenicol's use in veterinary ophthalmology is becoming less widespread. It may be useful, however, in treating cats with suspected Mycoplasma or chlamydia conjunctivitis.

**Suggested Dosages/Precautions/Adverse Effects** - For prophylaxis following surgery or for cats with Mycoplasma or chlamydial conjunctivitis: One drop (or 1/4 inch strip if using ointment) four times daily. For established corneal infection: Application may be very frequent (up to hourly).

Chloramphenicol exposure in humans has resulted in fatal aplastic anemia. For this reason, this drug should be used with caution in veterinary patients and some ophthalmologists avoid its use entirely. Clients should be cautioned to use appropriate safeguards when applying the drug and avoiding contact with drops or solutions after application.

Labels state to not use longer than 7 days in cats, but *tid* application of ointment for 21 days to cats did not cause toxicity. Must not be used in any food producing animal.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:**

Chloramphenicol 1% Ophthalmic Ointment in 3.5 gm; *Bemacol*®-(Pfizer); *Chlorbiotic*®-(Schering); *Chloricol*® (Evsco); Generic; (Rx)

Chloramphenicol 0.5% Ophthalmic Drops in 7.5 ml btls tubes; *Chlorasol*®-(Evsco); (Rx). Refrigerate until dispensed.

Approved for use in dogs and cats.

**Human-Approved Products:**

Chloramphenicol 1% Ophthalmic Ointment in 3.5 gm tubes; *Chloromycetin*® (Parke Davis); *Chloroptic*® (Allergan); Generic (Rx)

Chloramphenicol 0.5% Ophthalmic Drops in 7.5 ml btls tubes; *Chloroptic*® (Allergan); Generic; (Rx). Refrigerate until dispensed.

## CIPROFLOXACIN (OPHTHALMIC)
## NORFLOXACIN (OPHTHALMIC)
## OFLOXACIN (OPHTHALMIC)

**Indications/Pharmacology** - These fluroquinolone ophthalmic antibiotics are primarily useful for established gram negative corneal infections. They are not recommended for prophylactic use prior to or after surgery. See the main enrofloxacin/ciprofloxacin monograph for additional pharmacologic information.

**Precautions/Adverse Effects** - Ciprofloxacin may cause crusting or crystalline precipitates in the superficial portion of corneal defects. Other potential adverse effects with quinolones include: conjunctival hyperemia, bad taste in mouth, itching foreign body sensation, photophobia, lid edema, tearing keratitis and nausea. Allergic reactions have been reported with quinolone eye preps.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Ciprofloxacin 3 mg/ml drops in 2.5 & 5 ml btls; *Ciloxan*® (Alcon); Rx

Norfloxacin 3 mg/ml drops in 5 ml btls; *Chibroxin*® (Merck); Rx

Ofloxacin 3 mg/ml drops in 5 ml btls; *Ocuflox*® (Allergan); Rx

## GENTAMICIN (OPHTHALMIC
## TOBRAMYCIN (OPHTHALMIC)

To Drug Monograph Index  To Ophthalmic Product Index

**Indications/Pharmacology** - The aminoglycosides are excellent drugs for gram negative or staphylococcal corneal infections. With frequent application, clinicians can establish corneal drug levels far in excess of MIC for most organisms without exceeding toxic systemic levels. Therefore, MIC reports may not be meaningful. Because of the high levels attainable, gentamicin usually exhibits similar efficacy to tobramycin, except in certain resistant gram-negative infections (e.g., Pseudomonas aeruginosa).

For serious gram negative or staphylococcal corneal ulcer infections, some ophthalmologists use cefazolin eye drops (compounded preparation) in combination with gentamicin or tobramycin. Synergism may result.

**Precautions/Adverse Effects** - Hypersensitivity, and localized ocular toxicity (lid itching, swelling and conjunctival erythema) have been reported rarely. Mydriasis and conjunctival paresthesias may also occur.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:**

Gentamicin Ophthalmic Ointment 3 mg/g in 3.5 gm tubes; *Gentocin*® (Schering); (Rx). Approved for use in dogs and cats.

Gentamicin Ophthalmic Drops 3 mg/ml in 5 ml btls *Gentocin*® (Schering); (Rx). Approved for use in dogs and cats.

**Human-Approved Products:**

Gentamicin Ophthalmic Ointment 3 mg/g in 3.5 gm tubes; *Garamycin*® (Schering); *Genoptic*® (Allergan); various; (Rx)

Gentamicin Ophthalmic Drops 3 mg/ml in 5 ml btls *Garamycin*® (Schering); *Genoptic*® (Allergan); various; (Rx)

Tobramycin Ophthalmic Ointment 3 mg/g in 3.5 gm tubes; *Tobrex*® (Alcon); (Rx)

Tobramycin Ophthalmic Drops 3 mg/ml in 5 ml btls *Tobrex*® (Alcon); (Rx)

### TETRACYCLINE (OPHTHALMIC)

**Indications/Pharmacology** - The tetracyclines are most useful in cats for the treatment Chlamydial and Mycoplasma conjunctivitis as well as nonspecific or symptomatic therapy for undiagnosed (causative organism not determined) conjunctivitis in cats. While its use in dogs and horses is questionable, it may be useful in goats for Chlamydial/Mycoplasma keratoconjunctivitis.

Tetracycline is often used to "back into" the diagnosis of herpes virus conjunctivitis in cats. Since the majority of conjunctivitis cases in cats are caused by herpes virus (approx. 90%) and the bulk of the remainder are caused either by Chlamydia or Mycoplasma, if the cat fails to respond to tetracycline, the cause is most likely due to herpes virus.

**Suggested Dosages/Precautions/Adverse Effects** - For Chlamydial/Mycoplasma keratoconjunctivitis: Apply 4 times daily. Dramatic improvement should be noted in 3-4 days, but treatment should continue for 3-4 weeks for Chlamydia to break the reproductive cycle of this organism.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Tetracycline HCl Ointment 10 mg/g in 3.75 g tubes *Achromycin*® (Storz/Lederle); (Rx)

Tetracycline HCl Suspension 10 mg/ml in 4 ml btls *Achromycin*® (Storz/Lederle); (Rx)

Other available ophthalmic antibiotics: Chlortetracycline: *Aureomycin*® (Storz Lederle); Bacitracin (alone); Erythromycin Ointment; Polymyxin B powder for solution; Sodium Sulfacetamide.

## ANTIBIOTIC COMBINATIONS (OPHTHALMIC)

**Indications/Pharmacology** - These combination products exhibit a broad-spectrum of activity and are considered the first choice for symptomatic treatment of conjunctivitis in dogs and for prophylactic treatment of small animals prior to or after eye surgery. These agents are also used prophylactically for corneal injuries/wounds.

To Drug Monograph Index To Ophthalmic Product Index

**Suggested Dosages/Precautions/Adverse Effects** - Usually applied 4 times daily to prevent infection and up to every 30 minutes in established corneal infections. See individual product label information and the information noted previously.

Neomycin has been reported to cause allergic reactions in dogs and cats, particularly after prolonged usage.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:**

Ointments:

Bacitracin zinc 400 units/Neomycin 3.5 mg/Polymyxin B Sulfate 10,000 Units per gram in 3.5 gm tubes *Mycitracin*® (Upjohn) (Note: contains 500 mg bacitracin/gm); *Neobacimyx*® (Schering); *Trioptic-P*® (Pfizer); *Vetropolycin*® (Pitman-Moore); Generic. All are Rx and approved for dogs and cats.

Oxytetracycline HCl 5 mg/Polymyxin B Sulfate 10,000 U/gm in 3.5 gm tubes *Terramycin*® *Ophthalmic Ointment* (Pfizer); OTC. Approved for use in dogs, cats, sheep, cattle, and horses.

Drops:

Neomycin 3.5 mg/Polymyxin B Sulfate 10,000 Units per ml: *Optiprime*®-(Syntex); Rx. Approved for use in dogs.

**Human-Approved Products:**

There are a wide variety of human-labeled ophthalmic combination products available. Most are a combination of bacitracin/neomycin/polymyxin B. However, there are variations of this theme (e.g., gramicidin in place of bacitracin in topical solutions-Neosporin® Ophthalmic Solution). All these products require a prescription.

## ANTIBIOTIC & CORTICOSTEROID COMBINATIONS

**Indications/Pharmacology** - There are three basic categories of these products that are routinely used in veterinary medicine; antibiotic combinations with hydrocortisone, antibiotic combinations with dexamethasone, and individual antibiotics (e.g., gentamicin or chloramphenicol) with a steroid.

Antibiotic combinations with hydrocortisone (ointment or solution) are used in dogs and horses for conjunctivitis as nonspecific therapy after ruling out other causes for red painful eyes, including glaucoma and anterior uveitis. They generally are applied 4 times daily and then on a tapering schedule based on the response to therapy. The hydrocortisone is relatively weak as an antiinflammatory agent and is not effective for intraocular inflammatory disease such as anterior uveitis. The relative penetration and potency of hydrocortisone in these preparations makes them relatively ineffective for immune mediated extraocular disease including scleritis, episcleritis and or nodular granulomatous episclerokeratitis. Anterior uveitis is statistically more common in horses than simple conjunctivitis and the steroid in these agents would not be helpful in improving the clinical signs of immune mediated uveitis.

Antibiotic combinations with dexamethasone are valuable for use in cases of more severe canine or equine conjunctivitis, nonulcerative keratitis and for immune-mediated scleral or corneal conditions such as chronic superficial keratitis (German Shepherd pannus), feline eosinophilic keratitis, scleritis, episcleritis and nodular granulomatous episclerokeratitis. For these conditions the antibiotic agent is not necessary but dexamethasone-only products are not always available. These medications are also used in the equine species with equine uveitis because the ointment forms persist on the cornea longer than drops and because they are less expensive than prednisolone acetate ophthalmic suspensions.

Single agent antibiotic (gentamicin) and potent steroid (betamethasone) combination products (e.g., *Gentocin Durafilm*®) are commonly used in veterinary medicine. However, there are few instances in veterinary ophthalmology in which a very potent corticosteroid agent and an aminoglycoside antibiotic are necessary in combination. Simple conjunctivitis in dogs and horses is adequately treated with antibiotic combinations with hydrocortisone. Avoid use of this agent in cats with conjunctivitis for the reasons noted below.

**Suggested Dosages/Precautions/Adverse Effects** - See individual product label information and the information noted above.

To Drug Monograph Index To Ophthalmic Product Index

Avoid use of antibiotic/steroid combination agents in cats with conjunctivitis as the most common cause of conjunctivitis in the cat is primary or recurring infection with exposure to, or reactivation of, latent feline herpes virus. Recent research indicates that topical steroids increase the length of the typical course of feline herpes virus related conjunctivitis and/or keratitis and can induce corneal involvement in cases which might otherwise have remained confined to conjunctiva. Corneal sequestration has been noted to occur in cats with herpes virus conjunctivitis after treatment with topical steroids. Recommended treatment for feline herpes virus conjunctivitis is tetracycline ointment *QID* during active disease, as this drug is effective against Mycoplasma and chlamydia (other causes of infectious conjunctivitis in the cat).

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products:**

Triple Antibiotic Ointments with Hydrocortisone:

Bacitracin zinc 400 units/Neomycin 3.5 mg/Polymyxin B Sulfate 10,000 Units & Hydrocortisone acetate 1% per gram in 3.5 gm tubes *Neobacimyx H*® (Schering); *Trioptic-S*® (Pfizer); *Vetropolycin HC*®- (Pitman-Moore); Generic. All are Rx and approved for dogs and cats.

Other Antibiotic/Steroid Ointments:

Neomycin Sulfate 5 mg & Prednisolone 2 mg (0.2%) per gram in 3.5 gram tubes *(Optisone*®-Evsco); (Rx). Approved for use in dogs and cats.

Neomycin Sulfate 5 mg & Isoflupredone acetate 1 mg (0.1%) per gram in 3.5 & 5 gram tubes *Neo-Predef*® *Sterile Ointment*® (Upjohn); (Rx). Approved for use in horses, cattle, dogs and cats.

Chloramphenicol 1% and Prednisolone acetate 2.5 mg (0.25%) in 3.5 gm tubes; *Chlorasone*® (Evsco) (Rx). Approved for use dogs and cats.

Drops:

Gentamicin Ophthalmic Drops 3 mg/ml & Betamethasone acetate 1 m/ml in 5 ml btls *Gentocin Durafilm*® (Schering); (Rx). Approved for use in dogs.

**Human-Approved Products:**

There are a wide variety of human-labeled ophthalmic antibiotic/steroid combination products available. Some of the more commonly used combinations include:

Ointments:

Bacitracin/Neomycin/Polymyxin B and Hydrocortisone *Cortisporin*® (BW)
Neomycin/Polymyxin B & Dexamethasone *Maxitrol*® (Alcon); (Rx)
Neomycin and Dexamethasone *NeoDecadron*® (Merck); (Rx)

Drops:

Neomycin/Polymyxin B and Hydrocortisone *Cortisporin*® (BW, etc.); (Rx)
Neomycin/Polymyxin B & Dexamethasone *Maxitrol*® (Alcon); (Rx)
Neomycin and Dexamethasone *NeoDecadron*® (Merck); (Rx)

## Antifungals (Ophthalmic)

Fungal keratitis is a serious corneal disease, most commonly reported in the horse. The species selectivity of this disease is related to the environment of this animal, which is often contaminated with fungal elements. An increased incidence of fungal keratitis in people was directly related to the development of multiple topical steroid agents for treatment of eye diseases. In the horse, many cases of fungal keratitis are noted in association with prior treatment of conjunctival and/or corneal diseases with topical steroid agents. Aspergillus is the most common cause of fungal keratitis in the horse, although there is a great deal of variation in fungal isolates from the cornea depending upon geographical location. Studies in people and anecdotal reports from veterinarians suggest that fungal keratitises due to Fusarium organisms are more resistant to therapy than are those caused by aspergillus. Most studies in the equine suggest that about 50% of cases of fungal keratitis in the horse result in perforation of the corneal and enucleation of the eye. Medical and surgical therapy (keratectomy, corneal debridement, and conjunctival grafting) are used to treat such cases with the goals of therapy including arresting infection, mechanical removal of organisms from the cornea, and support of the cornea. All antifungal agents available for use in the equine suffer from poor penetration into the corneal stroma. Conjunctival grafting may further hinder drug penetration as a trade off to improving vascular

availability to the cornea and mechanical support. Pathologic specimens from horses with fungal keratitis indicate that fungal organisms, unlike bacterial organisms, have a propensity to multiply deep in the stroma, directly adjacent to Descemet's membrane, making corneal penetration an important issue. Because the prognosis for return of vision and saving the globe in cases of fungal keratitis cases is guarded and because treatment is labor intensive, referral to teaching or other hospitals for 24 hour care and observation is recommended.

## NATAMYCIN (OPHTHALMIC)

**Indications/Pharmacology** - Natamycin is a semisynthetic polyene antibiotic. Natamycin is poorly water soluble and will not penetrate the intact corneal epithelium. Natamycin is the only antifungal agent approved for use on the eye and the only commercially available eye drug for treatment of fungal keratitis.

**Suggested Dosages/Precautions/Adverse Effects** - The product comes as a thick white suspension which complicates the use of subpalpebral lavage apparatus for frequent treatment of the cornea of the horse. The drug tends to plug up the tubing systems used for medication. It will cause dramatic swelling and pain in the upper eyelid if it leaks out of the tubing into the subcutaneous tissues of the eyelid. Corneal penetration is poor and the medication is very expensive. Fungal keratitis cases are treated aggressively with hourly or bi-hourly treatment the first 1 to 3 days and gradual reduction in treatment frequency with signs of clinical improvement. Cytology and repeated cultures of the cornea are used to indicate treatment effectiveness. Worsening of the corneal edema and cellular infiltration can be a sign of treatment response. This is thought to be due to antigenic release associated with killing of fungal organisms (like the pulmonary response noted in dogs with institution of antifungal therapy for blastomycosis, etc.). Four to six weeks of treatment is not uncommon for fungal keratitis cases.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Natamycin Ophthalmic Suspension 5% in 15 ml btls *Natacyn*® (Alcon); (Rx)

## MICONAZOLE (OPHTHALMIC)

**Indications/Pharmacology** - Miconazole is a broad spectrum imidazole antifungal agent with some antibacterial activity. Miconazole will penetrate the intact corneal epithelium. Topical miconazole therapy has been a favorite first choice agent for treatment of fungal keratitis in the horse by veterinary ophthalmologists for several years. Miconazole may be delivered by subconjunctival route, but with some local irritation, and topical use is the most commonly employed treatment method.

**Suggested Dosages/Precautions/Adverse Effects** - Miconazole is formulated at 10 mg/ml for IV use in humans. It can be directly taken from the glass ampule for IV use and applied to the cornea of horses. It is a clear solution readily delivered through subpalpebral lavage apparatus systems. The medication is significantly less expensive compared with natamycin and its corneal penetration is more favorable, although still less than optimal. Treatment is generally delivered hourly or bi-hourly during the first several days of treatment. Once clinical improvement is noted and cytology specimens and repeated cultures indicate eradication of fungal organisms, the treatment frequency is gradually reduced. Most fungal keratitis cases are treated 4 to 6 weeks.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Miconazole Injection 10 mg/ml in 20 ml glass ampules *Monistat-i.v.*® (Janssen); Rx

## SILVER SULFADIAZINE (OPHTHALMIC)

**Indications/Pharmacology** - Silver Sulfadiazine Cream is a broad spectrum agent which covers bacteria (gram positive and negative) and fungal agents. It has been used extensively in people suffering from skin burns. It is nontoxic to the skin, conjunctiva and cornea and has been used in the last several years for cases

of fungal keratitis. Particularly good results have been noted in cases of superficial keratitis prior to development of advanced disease. Clinical response is better when used early in the course of the disease. Treatment with silver sulfadiazine is considered non-conventional in people. It is gaining in popularity in the treatment of equine fungal keratitis by veterinary ophthalmologists. For medico-legal reasons, in very expensive horses in which litigation may be an issue, treatment with more conventional therapy (Natamycin) may be indicated first, or consideration can be given to signed consent regarding treatment with Silver Sulfadiazine. The initial response to this drug has been promising, however.

**Suggested Dosages/Precautions/Adverse Effects** - The commercially available product is a cream, but can be delivered into the conjunctival sac using a tuberculin syringe, without the needle. A typical treatment dose is 0.2 ml drawn into a syringe. It will not pass through standard sized subpalpebral lavage catheters, although it may be administered through large medication administration systems using red rubber feeding tubes passed through the lid, with variable results getting the medication to pass through the tube. It is probably best applied manually. The cream sticks well to the cornea which probably improves effectiveness, similar to natamycin, as compared to miconazole. Treatment regimes are similar to the other antifungal agents with very frequent applications necessary during the early phases of the treatment and reduction in therapy based upon clinical response. Daily debridement of the necrotic corneal stroma and epithelium will improve penetration of the drug and the clinical response.

The medication is inexpensive and is available from any pharmacy, but it is not labeled for use in eyes. The label (package insert) specifically states "not to be used in eyes" so liability for use in eyes rests solely with the prescribing veterinarian and some pharmacists may be unwilling to dispense this medication for ophthalmic use.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Silver Sulfadiazine Topical (not an ophthalmic product) 10 mg per gram in a water miscible cream base. Available in 20, 50, 400, and 1000 g containers; *Silvadene*®-(Marion); *Flint SSD*® (Flint); Rx

## Antivirals (Ophthalmic)

Antiviral drugs are used most commonly in clinical practice for the treatment of feline ocular herpes virus infections. Simple acute conjunctivitis is best managed with symptomatic antibiotic therapy alone (i.e., tetracycline treatment). The development of concurrent corneal disease, however, indicates that consideration should be given to the use of antiviral drugs. Persistent cases of conjunctivitis in the cat due to feline herpes virus infection may also benefit from treatment with topical antiviral drugs.

### TRIFLURIDINE (TRIFLUOROTHYMIDINE)

**Indications/Pharmacology** - Trifluridine (trifluorothymidine; *Viroptic*®) is a pyrimidine nucleoside analog. It is structurally related to 2-deoxythymidine, the natural precursor of DNA synthesis. Trifluridine is poorly absorbed by the cornea and is virostatic. *Viroptic*® interrupts viral replication by substituting in "nonsense" pyrimidine analogues. For this reason, a competent surface immunity is necessary to resolve ocular disease, with or without antiviral therapy. A recent in vitro study in which several strains of feline herpes virus were collected from the United States and were used to infect kidney epithelial cells showed that trifluridine was more effective at lower concentrations compared with several other agents. For this reason, trifluridine is often the first choice drug employed in the treatment of feline herpes virus ocular disease. Antiviral agents have also been used in the treatment of superficial punctate keratitis in the horse, thought to be associated with equine herpes virus-2 (EHV-2) infection of the cornea.

**Suggested Dosages/Precautions/Adverse Effects** - Trifluridine must be applied very frequently. The author (DKO) recommends treatment every 2 hours (waking hours) during the first 2 days of therapy to establish effective corneal drug levels. After this time, treatment 4-6 times daily is indicated. Because trifluridine is virostatic and not viricidal, treatment 1 week beyond the resolution of clinical signs is recommended, to prevent a rebound effect associated with poor surface immunity in combination with residual active viral agents.

To Drug Monograph Index To Ophthalmic Product Index

Anecdotally, improvement with antiviral agents is noted in about 50% of cats in which the treatment is employed. In some cats the ocular disease persists despite treatment with antiviral agents. It is not certain if these are truly cases of feline herpes virus infection or other disease as the confirmation of feline herpes virus infection is exceedingly difficult in practice, (except in the acute disease with respiratory and ocular involvement, because of the logistics of viral isolation tests for doctors in clinical practice (usually only available at major institutions or referral centers) and because of the high degree of false negatives with herpes virus FA tests and with available polymerase chain reaction (DNA amplification) technology). Chronic conjunctivitis in the cat seems to be the most resistant to treatment with antiviral agents.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Trifluridine Ophthalmic Solution 1% in 7.5 ml btls *Viroptic*® (B-W); (Rx)

## Agents for Keratoconjunctivitis Sicca

Keratoconjunctivitis sicca (KCS) is a common ocular disorder in dogs. Recent research efforts indicate that KCS in dogs is an immune mediated disease. It is similar to Sjogren's Syndrome in humans except we do not recognize a connective tissue disorder in the dog compared to this disease in people (man-dry eye, dry mouth, and connective tissue disorder like rheumatoid arthritis; dogs just dry eye). Immune mediated lacrimal adenitis can result in complete destruction of tear producing glands in dogs. Glandular fibrosis produces absolute sicca and these cases may be better managed with a parotid duct transposition surgery because there may be little remaining gland tissue to treat.

### CYCLOSPORINE (OPHTHALMIC)

**Indications/Pharmacology** - Cyclosporine is a polypeptide agent first isolated from a fungus. The agent interferes with interleukin synthesis by T lymphocytes and in so doing has been employed extensively in people following major organ transplantation to prevent immune rejection. Cyclosporine is extremely hydrophobic and was originally compounded by pharmacists in virgin olive oil or purified corn oil for the topical application to dogs with keratoconjunctivitis sicca. Topical cyclosporine is now commercially available as a 0.2% ointment (*Optimmune*®-Schering). The mechanism of action of cyclosporine in the treatment of keratoconjunctivitis sicca is still not fully understood, although it has been employed in the treatment of KCS in dogs for several years. It stimulates increased tear production in normal dogs and for this reason it is thought to have a direct stimulatory effect on the tear gland. It may do this acting as a prolactin analog, fitting onto lacrimal prolactin receptors. Its interleukin blocking effects likely are the major mechanism of action. Halting local inflammatory mediator production appears to arrest self perpetuating lacrimal adenitis resulting in resumption of normal or improved tear production after several weeks of therapy. Cyclosporine in the cornea, appears to have the ability to lessen granulation and pigment development. This property appears to be unrelated to its tear producing ability.

The reported success rate of alleviating the signs of KCS in dogs with treatment with cyclosporine is 75-85%. Some studies indicate that the higher the Schirmer value prior to starting therapy, the more likely that the dog will be well managed with cyclosporine drops alone. Absolute sicca may be associated with extensive fibrosis of the tear glands, leaving little tissue for stimulation or repair.

Cyclosporine is effective in the management of German Shepherd Pannus or chronic superficial keratitis in the dog. This condition is an immune disease of the cornea and likely is interleukin mediated. Cyclosporine may be preferred for the treatment of pannus because of the lack of systemic side effects noted in dogs with chronic topical administration of cyclosporine. Chronic topical corticosteroid treatment is associated with biochemical changes in the blood of large and small dogs.

Cyclosporine has been tried in the management of the rare case of keratoconjunctivitis sicca in the cat. Dry eye in cats is usually associated with herpes virus destruction of lacrimal epithelial cells and or stenosis of the ductules or openings of the ductules due to chronic viral conjunctivitis. Preliminary results have not been promising. Topical cyclosporine often aggravates ophthalmic herpes virus infections in people.

Cyclosporine has not shown promising effects in the management of feline eosinophilic keratitis, a condition now thought to be related to chronic stromal herpes virus infection in cats.

**Suggested Dosages/Precautions/Adverse Effects** - Cyclosporine is initiated generally as the first course of therapy for confirmed dry eye cases in the dog. The topical half life of cyclosporine is about 8 hours and most canine cases of KCS are managed with twice daily therapy with 0.2% ointment (*Optimmune*®). Three times a day therapy has been employed during the initial phases of treatment in more difficult or slow responding cases. For some uncertain reason (reversal of lacrimal adenitis‡ reorganization of lacrimal epithelial cell function‡ formation of secretory granules‡ tear production) 3-8 weeks of therapy are necessary before a dramatic increase in the Schirmer tear test becomes evident. Patients are generally maintained for life on cyclosporine ophthalmic once or twice daily depending on the response. Discontinuation of therapy is usually associated with the return of clinical signs of KCS within a few days. Reinstitution of therapy at this time, is usually associated with an almost immediate return of tear production (versus the initial lag phase noted). This likely is related to the degree of inflammatory disease noted with short discontinuation of therapy versus that present initially, prior to the diagnosis of KCS.

If tear production is very low, cyclosporine is often used in combination with artificial tears during the initial phases of therapy. Once tear production is improved, artificial tears can generally be removed completely or their frequency reduced in the treatment plan. After treatment is initiated, reevaluation of tear production in one month is recommended. If ulcerative keratitis complicates keratoconjunctivitis sicca in the dog, more frequent evaluation is necessary. Cyclosporine, although an immunomodulating agent, is considered safe in the face of ulcerative keratitis, with concurrent antibiotic therapy. Caution is advised, however.

When cyclosporin is delivered topically, no systemic toxicity has been noted in dogs given this drug chronically. This is probably associated with the poor absorption of this drug across the GI tract and because it is delivered to the eye at very low concentrations which even if 100% absorbed, when divided over the body weight of the dog is well below even the therapeutic dose. Advanced detection methods have made it possible to measure trace levels of cyclosporine in the blood of dogs being topically treated for dry eye. The clinical implications of this finding is uncertain at this time.

**Dosage Forms/Preparations/FDA Approval Status** - *Optimmune*® ointment is the approved formulation of topical cyclosporine for the management of dry eye in dogs. Compounding of topical cyclosporine drops was popular before the introduction, approval, and marketing of *Optimmune*® ointment. Clinicians persistently using compounded formulations of cyclosporine eye drops may be outside of expected ethical and legal standards of practice except under very specific situations. The use of commercially available ophthalmic products instead of compounded medications is highly recommended. Optimmune® is first applied 2 or 3 times daily and frequency of daily application is adjusted based on clinical response.

**Veterinary-Approved Products:**

Cyclosporine Ophthalmic Ointment 0.2%; *Optimmune*® (Schering-Plough); (Rx)

**Human-Approved Products:**

Orphan products are available for human uses.

## ARTIFICIAL TEAR PRODUCTS;OCULAR LUBRICANTS

**Indications/Pharmacology** - Artificial tear solutions are aqueous isotonic, pH buffered viscous solutions that serve as a lubricant for dry eyes and associated eye irritation due to dry eye syndromes. They are often useful adjuncts in keratoconjunctivitis sicca in dogs early in cyclosporine therapy.

Ocular lubricants are white petrolatum-based products that serve to lubricate and protect eyes. They are particularly useful during anesthetic procedures where animals' eyes may remain open and during which time tear production is dramatically reduced.

**Dosage Forms/Preparations/FDA Approval Status -**

**Veterinary-Approved Products:** None

**Human-Approved Products:**

To Drug Monograph Index To Ophthalmic Product Index

There are a plethora of products available with a variety of formulations and trade names. All are OTC. Some commonly known products include:Artificial Tear Products (Methylcellulose-based): *Adsorbotear*® (Alcon); *Comfort Tears*® (Pilkington Barnes Hind); *Isopto-Tears*® (Alcon); *Tears Naturale*® (Alcon); *Lacril*® (Allergan)

Artificial Tear Products (Polyvinyl Alcohol-based): *Hypotears*® (Iolab); *Liquifilm Tears* (Allergan); *Tears Plus*® (Allergan)

Artificial Tear Products (Glycerin-based): *Dry Eye Therapy*® (Bausch & Lomb); *Eye Lube A* (Optopics)

Ocular Lubricants (Petrolatum-based): *Lacri-Lube*® *S.O.P.* (Allergan); *Akwa Tears*® (Akorn)

### OPHTHALMIC IRRIGANTS ARTIFICIAL TEAR PRODUCTS;OCULAR LUBRICANTS

**Indications/Pharmacology** - Sterile isotonic solutions are used for flushing the nasolacrimal system and for removing debris from the eye. They are also used to remove excess stain after diagnostic staining of the cornea. Sterile lactated Ringer's solution (LRS) is well tolerated by the surface of the eye as is a balanced salt solution (BSS). Extraocular irrigating solutions may contain preservatives. Intraocular irrigating solutions (used during surgical procedures) do not contain preservatives and also contain electrolytes that are required for normal cell function.

**Suggested Dosages/Precautions/Adverse Effects** - Extraocular: Use to flush eye as necessary; control rate of flow by exerting pressure on bottle. Intraocular: Refer to both established practices for each surgical procedure as well as the specific manufacturers' recommendations.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:**

*Eye Rinse*® (Butler); (OTC): Contains: water, boric acid, zinc sulfate, glycerin, camphor. Note: This product is not labeled to be used as an irrigant per se, but as an aid in cleaning the eye and removing eye stains.

**Human-Approved Products:**

Common trade name products for extraocular irrigation: *AK-Rinse*® (Akorn), *Blinx*® (Pilkington Barnes Hind), *Collyrium for Fresh Eyes Eye Wash*® (Wyeth-Ayerst), *Dacriose*® (Iolab), *Eye Irrigating Solution*® (Rugby), *Eye-Stream*® (Alcon), *Eye Wash*® (several manufacturers), *Eye Irrigating Wash*® (Roberts Hauck), *Irrigate Eye Wash*® (Optopics), *Optigene*® (Pfeiffer), *Star-Optic Eye Wash*® (Stellar), *Visual-Eyes* ® (Optopics). All are OTC.

Common trade name products for intraocular irrigation: Note: Most of these products contain Balanced Salt Solution (BSS) = NaCl 0.64%, KCl 0.075%, $CaCl_2 \cdot 2H_2O$ 0.048%, $MgCl_2 \cdot 6H_2O$ 0.03%, Na acetate trihydrate 0.39%, sodium citrate dihydrate 0.17%, sodium hydroxide and/or hydrochloric acid to adjust pH, and water: Balanced Salt Solution (various manufacturers), *BSS*® (Alcon), *Iocare Balanced Salt Solution*® (Iolab); All are Rx.

BSS + solutions that also contain dextrose, glutathione, bicarbonate, phosphate are also available as: *BSS Plus*® (Alcon) and *AMO Endosol Extra*® (Allergan); All are Rx.

## Diagnostics

### FLUORESCEIN SODIUM

**Indications/Pharmacology** - Fluorescein sodium is a yellow water soluble dye. It is used most commonly to delineate full thickness loss of corneal epithelium. In this instance it will stain the corneal stroma. The epithelium is not stained because its outer lipid cell membrane repels the stain. Descemet's membrane will not stain with fluorescein stain and this is used to indicate descemetocele formation, an ocular emergency.

Fluorescein stain is applied to the precorneal tear film in dogs and cats and the break-up of this stain with time, as observed through a slit lamp biomicroscope using a cobalt blue light source, is used to determine the tear film break-up time (normal 19s), an indicator of tear film quality.

Fluorescein stain is applied to the tear film of dogs to determine patency of the nasolacrimal outflow system. The normal wait time is 2-5 minutes in dogs and up to 10 minutes in cats. A positive test indicates

patency of the system. A negative test is not indicative of disease as the test is negative in a large percentage of normal animals. Fluorescein stain, then, can be added to irrigating solution to flush the nasolacrimal system, making detecting the irrigation solution at the nose more obvious during flushing of the system.

**Suggested Dosages/Precautions/Adverse Effects** - Fluorescein stain is applied by dropping a drop of irrigating solution onto the sterile strip and then allowing the drop to fall on the eye. The strip should not contact the cornea or it will cause false positive stain retention at the site of contact with the epithelial cells. After a few seconds, the excess fluorescein is irrigated from the eye, staining areas of full thickness epithelial loss.

Conjunctival or corneal epithelial cells for fluorescent antibody testing should be collected prior to application of fluorescein stain, which can cause a false positive test for several days after application of the stain.

Fluorescein may rarely cause hypersensitivity reactions. Temporary staining of fur and skin may result. Do not use during intraocular surgery.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:** Sterile strips of paper impregnated with fluorescein sodium are the most commonly used form in veterinary medicine. Solutions (2%) of fluorescein are available, however they are not popular following one study indicating that Pseudomonas is readily grown in such solutions. Injectable products are also available (for ophthalmic angiography), but are not routinely used in veterinary medicine.

Fluorescein Sodium Strips 0.6 mg *Ful-Glo*® (Barnes Hind); 1 mg *Fluorets*® (Akorn), *Fluor-I-Strip*®-*A.T.* (W-A); 9 mg *Fluor-I-Strip*® (W-A); All Rx.

## ROSE BENGAL

**Indications/Pharmacology** - Rose Bengal is a vital stain and stains dead epithelial cells and mucus. Full thickness loss of the corneal epithelium is not necessary (only dead cells need be present) to obtain Rose Bengal stain uptake. It does not stain epithelial defects and does not pass into intercellular spaces.

Rose Bengal stain is most commonly employed in the detection of the presence of viral keratitis in the cat. Because feline herpes virus tends to infect one cell, moving then to an adjacent cell (causing the so called dendritic tracts in the cornea) without full thickness loss of corneal epithelium initially, Rose Bengal is an ideal diagnostic agent for this infection. Rose Bengal can also be used to detect damaged corneal epithelium on the dorsal cornea in early cases of keratitis sicca. Rose Bengal stain is virucidal although no information is available relative to its use as a therapeutic agent.

**Suggested Dosages/Precautions/Adverse Effects** - Rose Bengal is applied as a solution (1-2 drops in conjunctival sac before examination) or from an impregnated strip (saturate tip of strip with sterile irrigating solution; touch bulbar conjunctiva or lower fornix with moistened strip; cause patient to blink several times to distribute the stain).

Rose Bengal is apparently toxic to the cornea and conjunctiva and should be thoroughly flushed from the eye after use to prevent irritation. Hypersensitivity reactions are possible. May stain clothing.

**Dosage Forms/Preparations/FDA Approval Status** -

**Veterinary-Approved Products:** None

**Human-Approved Products:**

Rose Bengal Solution 1% in 5 ml dropper bottles (Akorn); Rx

Rose Bengal Strips 1.3 mg per strip; *Rosets*® (Akorn), Generic (Barnes-Hind); R

To Drug Monograph Index To Ophthalmic Product Index

# APPENDICES

## TABLES OF PARENTERAL FLUIDS

(Not a complete listing; includes both human and veterinary-approved products)

**DEXTROSE/ELECTROLYTE COMBINATIONS**

| Solution | $D_5$ in Ringer's | $D_{2.5}$ in half-strength Lactated Ringers | $D_5$ in Lactated Ringers | Normosol®-M w/$D_5$; Plasma-Lyte 56 w/$D_5$ | Plasma-Lyte® 148 and $D_5$ | Normosol®-R and $D_5$ |
|---|---|---|---|---|---|---|
| **Dextrose** (g/L) | 50 | 25 | 50 | 50 | 50 | 50 |
| **Calories** (kCal/L) | 170 | 89 | 179 | 170 | 190 | 185 |
| **$Na^+$** (mEq/L) | 147 | 65.5 | 130 | 40 | 140 | 140 |
| **$K^+$** (mEq/L) | 4 | 2 | 4 | 13 | 5 | 5 |
| **$Ca^{++}$** (mEq/L) | 4.5 | 1.4 | 2.7 | | | |
| **$Mg^{++}$** (mEq/L) | | | | 3 | 3 | 3 |
| **$Cl^-$** (mEq/L) | 156 | 54 | 109 | 40 | 98 | 98 |
| **Gluconate** (mEq/L) | | | | | 23 | 23 |
| **Lactate** (mEq/L) | | 14 | 28 | | | |
| **Acetate** (mEq/L) | | | | 16 | 27 | 27 |
| **Osmolarity** (mOsm/L) | 562 | 263 | 527 | 368 (363) | 547 | 552 |
| **Available as:** | 500 & 1000 ml | 250, 500 & 1000 ml | 250, 500 & 1000 ml | 500 & 1000 ml | 500 & 1000 ml | 500 & 1000 ml |

To Drug Monograph Index To Ophthalmic Product Index

## Dextrose/Saline Combinations

| Solution | $Na^+$ (mEq/L) | $Cl^-$ (mEq/L) | Dextrose (g/L) | Calories (kCal/L) | Osmolality (mOsm/L) | Available as: |
|---|---|---|---|---|---|---|
| $D_{2.5}$ & 0.45% NaCl | 77 | 77 | 25 | 85 | 280 | 250, 500, & 1000 ml |
| $D_5$ & 0.11% NaCl | 19 | 19 | 50 | 170 | 290 | 500 & 1000 ml |
| $D_5$ & 0.2% NaCl | 34 | 34 | 50 | 170 | 320 | 250, 500, & 1000 ml |
| $D_5$ & 0.33% NaCl | 56 | 56 | 50 | 170 | 365 | 250, 500, & 1000 ml |
| $D_5$ & 0.45% NaCl | 77 | 77 | 50 | 170 | 405 | 250, 500, & 1000 ml |
| $D_5$ & 0.9% NaCl | 154 | 154 | 100 | 170 | 560 | 250, 500, & 1000 ml |
| $D_{10}$ & 0.45% NaCl | 77 | 77 | 100 | 340 | 660 | 1000 ml |
| $D_{10}$ & 0.9% NaCl | 154 | 154 | 100 | 340 | 815 | 500 & 1000 ml |

## Dextrose Solutions

| Solution | Dextrose (g/L) | Calories (kCal/L) | Osmolality (mOsm/L) | Available as: |
|---|---|---|---|---|
| Dextrose 2.5% | 25 | 85 | 126 | 250, 500, & 1000 ml |
| Dextrose 5% | 50 | 170 | 253 | 10, 25, 50, 100, 130, 150, 250, 400, 500, 1000 ml |
| Dextrose 10% | 100 | 340 | 505 | 250, 500, & 1000 ml |
| Dextrose 20% | 200 | 680 | 1010 | 500 & 1000 ml |
| Dextrose 25% | 250 | 850 | 1330 | in 10 ml syringes |
| Dextrose 30% | 300 | 1020 | 1515 | 500 & 1000 ml |
| Dextrose 38.5% | 385 | 1310 | 1945 | 1000 ml |
| Dextrose 40% | 400 | 1360 | 2020 | 500 & 1000 ml |
| Dextrose 50% | 500 | 1700 | 2525 | 50, 250, 500, & 1000 ml |
| Dextrose 60% | 600 | 2040 | 3030 | 500 & 1000 ml |
| Dextrose 70% | 700 | 2380 | 3535 | 250, 500, & 1000 ml |

To Drug Monograph Index  To Ophthalmic Product Index

## Electrolyte Combination Injections

| Solution | Ringer's Injection | Lactated Ringer's Injection (LRS ) | Plasma-Lyte® 56 | Plasma-Lyte® R | Plasma-Lyte A; Normosol®-R pH 7.4 | Isolyte® S pH 7.4 |
|---|---|---|---|---|---|---|
| **$Na^+$** (mEq/L) | 147 | 130 | 40 | 140 | 140 | 141 |
| **$K^+$** (mEq/L) | 4 | 4 | 13 | 10 | 5 | 5 |
| **$Ca^{++}$** (mEq/L) | 4 | 3 | | 5 | | |
| **$Mg^{++}$** (mEq/L) | | | 3 | 3 | 3 | 3 |
| **$Cl^-$** (mEq/L) | 156 | 109 | 40 | 103 | 98 | 98 |
| **Gluconate** (mEq/L) | | | | | 23 | 23 |
| **Lactate** (mEq/L) | | 28 | | 8 | | |
| **Acetate** (mEq/L) | | | 16 | 47 | 27 | 29 |
| **Osmolarity** (mOsm/L) | 310 | 272 | 111 | 312 | 294 (295) | 295 |
| **Available as:** | 250, 500, 1000 ml | 250, 500, 1000, 5000 ml | 500 & 1000 ml | 1000 ml | 500, 1000, & 5000 ml | 500 & 1000 ml |

## Sodium Chloride Injections

| Solution | Sodium (mEq/L) | Chloride (mEq/L) | Osmolality (mOsm/L) | Available as: |
|---|---|---|---|---|
| **Sodium Chloride 0.2%** | 34 | 34 | 69 | 3 ml |
| **Sodium Chloride 0.45% (Half-Normal Saline)** | 77 | 77 | 155 | 3, 5, 500, and 1000 ml |
| **Sodium Chloride 0.9% (Normal Saline )** | 154 | 154 | 310 | 1, 2, 2.5. 3, 4, 5, 10, 20, 25, 30, 50, 100, 130, 150, 250, 500, & 1000 ml |
| **Sodium Chloride 3%** | 513 | 513 | 1030 | 500 ml |
| **Sodium Chloride 5%** | 855 | 855 | 1710 | 500 ml |

To Drug Monograph Index  To Ophthalmic Product Index

# Abbreviations Used In Prescription Writing

A warning; and the strange case of S.I.D.: Although prescription abbreviations are used throughout this reference and they are fairly well recognized, they do increase the potential for mistakes to occur. When writing a prescription, this author recommends writing out the directions in plain English and avoiding the use of abbreviations entirely. If abbreviations are to be used, definitely avoid q.d., q.o.d., and s.i.d. because they can be easily confused with other abbreviations.

S.I.D. is virtually unknown to health professionals outside of veterinary medicine and the vast majority of pharmacists have never seen it used. S.I.D. should be eliminated from all veterinary usage.

| | |
|---|---|
| a.c. | before meals |
| a.d. | right ear |
| a.s. | left ear |
| a.u. | both ears |
| amp. | ampule |
| b.i.d. | twice a day |
| c. | with |
| cap. | capsule |
| cc | cubic centimeter |
| disp. | dispense |
| g or gm | gram |
| gtt(s). | drop(s) |
| h. | hour |
| h.s. | at bedtime |
| IM | intramuscular |
| IP | intraperitoneal |
| IV | intravenous |
| lb. | pound |
| m2 | meter squared |

To Drug Monograph Index  To Ophthalmic Product Index

| | |
|---|---|
| mg. | milligram |
| ml. | milliliter |
| o.d. | right eye |
| o.s. | left eye |
| o.u. | both eyes |
| p.c. | after meals |
| p.o. | by mouth |
| p.r.n. | as needed |
| q. | every |
| q4h, etc | every 4 hours |
| q.i.d. | four times a day |
| q.o.d. | every other day |
| q.s. | a sufficient quantity |
| q4h | every 4 hours, etc. |
| s.i.d. | once a day |
| Sig: | directions to pt. |
| stat | immediately |
| SubQ, SQ, SC, Subcut | subcutaneous |
| susp. | suspension |
| t.i.d. | three times a day |
| tab | tablet |
| Tbsp. | tablespoon (15 ml) |
| tsp. | teaspoon (5 ml) |
| Ut dict. | as directed |

To Drug Monograph Index  To Ophthalmic Product Index

# Conversion Tables

WEIGHTS:

1 Pound (lb.) = 0.454 kg = 454 grams = 16 ounces
1 kilogram (kg) = 2.2 pounds = 1000 grams
1 grain (gr.) = 64.8 mg (often rounded to 60 or 65 mg)
1 gram = 15.43 grains = 1000 mg
1 ounce = 28.4 grams
1 gram = 1000 mg
1 milligram (mg) = 1000 mcg (µg)
1 microgram (mcg or µg) = 1000 nanograms (ng)

LIQUID MEASURE:

1 gallon (gal.) = 4 qts. = 8 pts. = 128 fl. oz. = 3.785 liters = 3785 ml
1 quart (qt) = 2 pints = 32 fl. oz. = 946 ml
1 pint = 2 cups = 16 fl. oz. = 473 ml
1 cup = 8 fl. oz = 237 ml = 16 tablespoons
1 tablespoon = 15 ml = 3 teaspoons
1 teaspoon = 5 ml
4 liters = 1.057 gals.
1 liter = 1000 ml = 10 deciliters
1 deciliter (dl) = 100 ml
1 milliliter (ml) = 1 cubic centimeter (cc) = 1000 microliters (µl)

TEMPERATURE CONVERSION:

9 x ( °C) = (5 x °F) – 160
°C to °F = (°C x 1.8) + 32 = °F
°F to °C = (°F – 32) x .555 = °C

To Drug Monograph Index To Ophthalmic Product Index

# Simple Formula to Dilute Concentrated Solutions

Formula: C1V1=C2V2

C1 = % of the concentrated solution

V1 = the unknown volume of concentrate to use

C2 = the % of desired dilution

V2 = the amount of the solution you need

Example: How much 10% povidone iodine to add to 4 liters to make a dilution of 0.2% ?

C1 = 10 % povidone iodine
V1 = the unknown amount of the concentrated povidone iodine you need to add
C2 = 0.2% (the desired dilution)
V2 = the amount of solution you are making (4 liters)

C1V1 = C2V2

10 x V1 = .2% x 4000 ml
10 x V1 = 800
X = 80

Add 80 ml of 10% povidone iodine added to 4000 ml water to = 0.2% povidone iodine

To Drug Monograph Index To Ophthalmic Product Index

# Millequivalents – Molecular Weights

## Milliequivalents & Molecular Weights

Milliequivalents: The term milliequivalents (mEq) is usually used to express the quantities of electrolytes administered to patients. A mEq is 1/1000 of an equivalent (Eq). For pharmaceutical purposes an equivalent may be thought of as equal to the equivalent weight of a given substance. This, in practical terms, is the molecular weight of the substance divided by the valence or the radical. For example:

How many milligrams are equivalent to 1 mEq of potassium chloride (KCl)?

1. Determine the equivalent weight = gram atomic weight ÷ valence
   Molecular weight of KCl = 74.5
   Valence = 1 (K+; Cl-)
   Equivalent weight = 74.5 ÷ 1 = 74.5 grams

2. Determine the mEq weight
   Equivalent weight ÷ 1000
   74.5 ÷ 1000 = 74.5 mg = 1 mEq of KCl = 1 mEq of K+ & 1 mEq of Cl-

If the substance would have been CaCl2, the process would be identical using the gram molecular weight of CaCl2 (MW 111 if anhydrous; 147 if dihydrate) and a valence of 2.

Listed below are several commonly used electrolytes with their molecular weights and valences in parentheses:

| | |
|---|---|
| Sodium Chloride | 58.44 (1) |
| Sodium Bicarbonate | 84 (1) |
| Sodium Acetate | |
| anhydrous | 82 (1) |
| trihydrate | 136 (1) |
| Sodium Lactate | 112 (1) |
| Potassium Chloride | 74.55 (1) |
| Potassium Gluconate | 234.25(1) |
| Calcium Gluconate | 430.4 (2) |
| Calcium Lactate | |
| (anhydrous) | 218.22 (2) |
| Calcium Chloride | |
| anhydrous | 111 (2) |
| dihydrate | 147 (2) |
| Magnesium Sulfate | |
| heptahydrate | 246.5 (2) |
| anhydrous | 120.4 (2) |
| Magnesium Chloride | |
| anhydrous | 95.21 (2) |
| hexahydrate | 203.3 (2) |

To Drug Monograph Index  To Ophthalmic Product Index