EQUINE PRODUCTS

Reference Guide

MERCK
Animal Health

Vaccines

Prestige® V + WNV
with Havlogen®*
ENCEPHALOMYELITIS - RHINOPNEUMONITIS - INFLUENZA - WEST NILE VIRUS VACCINE

EASTERN & WESTERN, KILLED VIRUS, KILLED FLAVIVIRUS CHIMERA
TETANUS TOXOID

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of disease caused by Eastern and Western encephalomyelitis viruses and tetanus, as an aid in the control of respiratory disease caused by EIV, EHV-1 and EHV-4, as an aid in reduction of virus shedding of EIV, EHV-1 and EHV-4 and as an aid in reduction of disease, encephalitis and viremia caused by West Nile virus. Duration of immunity (DOI) has been shown to be at least 6 months for EIV.
1 x 10 mL, 10 x 1 mL

Prestige® V + VEE
with Havlogen®*
ENCEPHALOMYELITIS - RHINOPNEUMONITIS - INFLUENZA VACCINE

EASTERN, WESTERN, AND VENEZUELAN, KILLED VIRUS
TETANUS TOXOID

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of disease caused by Eastern, Western and Venezuelan encephalomyelitis viruses and tetanus, as an aid in the control of respiratory disease caused by EIV, EHV-1 and EHV-4 and as an aid in reduction of virus shedding of EIV and EHV-1. Duration of immunity (DOI) has been shown to be at least 6 months for EIV.
1 x 10 mL, 10 x 1 mL

Prestige® V
with Havlogen®*
ENCEPHALOMYELITIS - RHINOPNEUMONITIS - INFLUENZA VACCINE

EASTERN AND WESTERN, KILLED VIRUS
TETANUS TOXOID

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of disease caused by Eastern and Western encephalomyelitis viruses and tetanus, as an aid in the control of respiratory disease caused by EIV, EHV-1 and EHV-4 and as an aid in reduction of virus shedding of EIV and EHV-1. Duration of immunity (DOI) has been shown to be at least 6 months for EIV.
1 x 10 mL, 10 x 1 mL

Prestige® II
with Havlogen®*
EQUINE RHINOPNEUMONITIS - INFLUENZA VACCINE

KILLED VIRUS

For vaccination of healthy horses 6 months of age or older, as an aid in the control of respiratory disease caused by EIV, EHV-1 and EHV-4 and as an aid in reduction of virus shedding of EIV and EHV-1. Duration of immunity (DOI) has been shown to be at least 6 months for EIV.
1 x 10 mL, 10 x 1 mL

Encevac® TC-4 + VEE
with Havlogen®*
ENCEPHALOMYELITIS - INFLUENZA VACCINE

EASTERN, WESTERN, AND VENEZUELAN, KILLED VIRUS
TETANUS TOXOID

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of disease caused by Eastern, Western and Venezuelan encephalomyelitis viruses and tetanus and as an aid in the control of respiratory disease and as an aid in the reduction of virus shedding caused by EIV. Duration of immunity (DOI) has been shown to be at least 6 months for EIV.
1 x 10 mL

Encevac® TC-4
with Havlogen®*
ENCEPHALOMYELITIS - INFLUENZA VACCINE

EASTERN AND WESTERN, KILLED VIRUS
TETANUS TOXOID

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of disease caused by Eastern and Western encephalomyelitis viruses and tetanus and as an aid in the control of respiratory disease and as an aid in the reduction of virus shedding caused by EIV. Duration of immunity (DOI) has been shown to be at least 6 months for EIV.
1 x 10 mL, 10 x 1 mL

Encevac® T + WNV
with Havlogen®*
ENCEPHALOMYELITIS - WEST NILE VIRUS VACCINE

EASTERN & WESTERN, KILLED VIRUS, KILLED FLAVIVIRUS CHIMERA
TETANUS TOXOID

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of disease caused by Eastern and Western encephalomyelitis viruses and tetanus and as an aid in reduction of disease, encephalitis and viremia caused by West Nile virus.
1 x 10 mL, 10 x 1 mL

Encevac® T + VEE
with Havlogen®*
ENCEPHALOMYELITIS VACCINE

EASTERN, WESTERN AND VENEZUELAN, KILLED VIRUS
TETANUS TOXOID

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of disease caused by Eastern, Western and Venezuelan encephalomyelitis viruses and tetanus.
1 x 10 mL

Encevac® T
with Havlogen®*
ENCEPHALOMYELITIS VACCINE

EASTERN AND WESTERN, KILLED VIRUS
TETANUS TOXOID

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of disease caused by Eastern and Western encephalomyelitis viruses and tetanus.
1 x 10 mL, 10 x 1mL

Equi-Nile™
with Havlogen®*
WEST NILE VIRUS VACCINE

KILLED FLAVIVIRUS CHIMERA

For vaccination of healthy horses 6 months of age or older, as an aid in reduction of disease, encephalitis, and viremia caused by West Nile virus.

1 x 10 mL, 10 x 1 mL

Prodigy®
with Havlogen®*
EQUINE RHINOPNEUMONITIS VACCINE

KILLED VIRUS

For vaccination of healthy horses 6 months of age or older, as an aid in the prevention of abortion and respiratory disease caused by EHV-1 infection.

1 x 20 mL, 10 x 2 mL

Super-Tet®
with Havlogen®*
TETANUS TOXOID

Tetanus Toxoid for vaccination of healthy horses, cattle, swine and sheep, 6 months of age or older, as an aid in the prevention of disease caused by tetanus.

10 x 1 mL

Prestige®
with Havlogen®*
EQUINE RHINOPNEUMONITIS VACCINE

KILLED VIRUS

For vaccination of healthy horses 6 months of age or older, as an aid in the control of respiratory disease and as an aid in the reduction of virus shedding caused by EHV-1 and EHV-4.

1 x 10 mL

EquiRab®
with Havlogen®*
RABIES VACCINE

KILLED VIRUS

For vaccination of healthy horses 4 months of age or older, as an aid in the prevention of disease due to rabies virus up to 14 months following vaccination.

1 x 10 mL, 10 x 1 mL

Flu Avert® I.N.
EQUINE INFLUENZA VACCINE

MODIFIED LIVE VIRUS – FOR INTRANASAL USE ONLY

For the vaccination of healthy horses, 11 months of age or older, as an aid in the reduction of clinical disease and viral shedding caused by equine influenza viruses of both the American and Eurasian lineages.

10 x 1 mL

Vaccine Chart

Merck Vaccine	Tetanus	WNV	Rabies	EEE/WEE	VEE	Influenza	EHV-1/EHV-4	EHV-1/Abortion
Prestige® V + WNV	●	●		●		●	●	
Prestige® V + VEE	●			●	●	●	●	
Prestige® V	●			●		●	●	
Prestige®II						●	●	
Encevac® TC-4 + VEE	●			●	●	●		
Encevac® TC-4	●			●		●		
Encevac® T + WNV	●	●		●				
Encevac® T + VEE	●			●	●			
Encevac® T	●			●				
Equi-Nile™		●						
Super-Tet®	●							
EquiRab®			●					
Prodigy®								●
Prestige®							●	
Flu Avert® I.N.						●		

*Adjuvant – Merck's Proprietary Technology

Pharmaceuticals

Regu-Mate®
(altrenogest) Solution 0.22%

REGU-MATE® Solution 0.22% is indicated to suppress estrus in mares. Suppression of estrus allows for a predictable occurrence of estrus following drug withdrawal. This facilitates the attainment of regular cyclicity during the transition from winter anestrus to the physiological breeding season. Suppression of estrus will also facilitate management of prolonged estrus conditions. Suppression of estrus may be used to facilitate scheduled breeding during the physiological breeding season.

1,000 mL bottle

Dolorex®
(butorphanol tartrate)

DOLOREX® is indicated for the relief of pain associated with colic in adult horses and yearlings. Clinical studies in the horse have shown that butorphanol tartrate alleviates abdominal pain associated with torsion, impaction, intussusception, spasmodic and tympanic colic, and postpartum pain.

10 mg/mL 50 mL vial

POWERPAC
Equine Dewormer

Paste 10% Equine
Dewormer

Panacur®
(fenbendazole)

PANACUR® Paste 10% is indicated for the control of large strongyles (*Strongylus edentatus, S. equinus, S.vulgaris*), encysted early third stage (hypobiotic), late third stage and fourth stage cyathostome larvae, small strongyles, pinworms (*Oxyuris equi*), ascarids (Parascaris equorum), and arteritis caused by fourth stage larvae of *Strongylus vulgaris* in horses.

5 x 57 g syringes (POWERPAC)
12 x 25 g syringes (Paste)

Banamine®
Paste/Injectable
(flunixin meglumine)

BANAMINE® Paste and BANAMINE® Injectable are recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. BANAMINE® Injectable is also recommended for the alleviation of visceral pain associated with colic in the horse.

100 mL vial, 250 mL vial
30 g syringe

Protazil®
(1.56% diclazuril)

PROTAZIL® Antiprotozoal Pellets are indicated for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses.

2.4 lb. pail

E-SE®
(selenium, vitamin E)

E-SE® Injection is recommended for the control of the following clinical signs when associated with myositis (Selenium-Tocopherol Deficiency) syndrome: rapid respiration, profuse sweating, muscle spasms and stiffness, elevated SGOT.

100 mL vial

Salix®
(furosemide)

SALIX® is an effective diuretic possessing a wide therapeutic range. Pharmacologically it promotes the rapid removal of abnormally retained extracellular fluids. The rationale for the efficacious use of diuretic therapy is determined by the clinical pathology producing the edema. SALIX® is indicated for the treatment of edema, (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema.

The continued use of heart stimulants, such as digitalis or its glycosides is indicated in cases of edema involving cardiac insufficiency.

50 mL vial

To learn more about Merck Animal Health equine products please contact your equine sales representative or call 1-800-521-5767

BANAMINE® PASTE

Intervet/Merck Animal Health
PRODUCT INFORMATION
(FLUNIXIN MEGLUMINE)
Paste - 1500 mg flunixin/syringe
Veterinary

For Oral Use in Horses Only

CAUTION Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION Each 30-gram syringe of BANAMINE Paste contains flunixin meglumine equivalent to 1500 mg flunixin.

INDICATIONS BANAMINE Paste is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse.

ACTIVITY Flunixin meglumine is a potent, nonnarcotic, nonsteroidal, analgesic agent with anti-inflammatory and antipyretic activity. It is significantly more potent than pentazocine, meperidine, and codeine as an analgesic in the rat yeast paw test. Oral studies in the horse show onset of flunixin activity occurs within 2 hours of administration. Peak response occurs between 12 and 16 hours and duration of activity is 24 to 36 hours.

CONTRAINDICATIONS There are no known contraindications to this drug when used as directed.

WARNING Not for use in horses intended for food.

PRECAUTIONS The effect of BANAMINE Paste on pregnancy has not been determined. Studies to date show there is no detrimental effect on stallion spermatogenesis with or following the recommended dose of BANAMINE Paste.

SIDE EFFECTS During field studies with BANAMINE Paste, no significant side effects were reported.

DOSAGE AND ADMINISTRATION The recommended dose of flunixin is 0.5 mg per lb of body weight once daily. The BANAMINE Paste syringe, calibrated in twelve 250-lb weight increments, delivers 125 mg of flunixin for each 250 lbs (see dosage table). One syringe will treat a 1000-lb horse once daily for 3 days, or three 1000-lb horses one time.

DOSAGE TABLE			
Syringe Mark*	Horse Weight (lbs)	Banamine Paste Delivered(g)	Mg Flunix Delivered
0	-	-	-
250	**250**	**2.5**	**125**
500	**500**	**5.0**	**250**
750	**750**	**7.5**	**375**
1000	**1000**	**10.0**	**500**

*Use dial edge nearest syringe barrel to mark dose.
The paste is orally administered by inserting the nozzle of the syringe through the interdental space, and depositing the required amount of paste on the back of the tongue by depressing the plunger.
Treatment may be given initially by intravenous or intramuscular injection of BANAMINE Solution, followed by BANAMINE Granules or BANAMINE Paste on Days 2 to 5. BANAMINE treatment should not exceed 5 consecutive days.

TOXICITY No toxic effects were observed in rats given oral flunixin 2 mg/kg per day for 42 days. Higher doses produced ulceration of the gastrointestinal tract. The emetic dose in dogs is between 150 and 250 mg/kg. Flunixin was well tolerated in monkeys dosed daily with 4 mg/kg for 56 days. No adverse effects occurred in horses dosed orally with 1.0 or 1.5 mg/lb for fifteen consecutive days.

HOW SUPPLIED BANAMINE Paste, 1500 mg is available in a single 30-g syringe.
Store below 25°C (77°F).
U.S. Patent Nos. 5,484,931
NADA #137-409, Approved by FDA.
Made in France.

Net Wt.	NDC	
30 g	**0061-0214-02**	**105039 R6**

NAC No.: 1047019.4

BANAMINE®

Intervet/Merck Animal Health

PRODUCT INFORMATION
NADA #101-479, Approved by FDA.
(FLUNIXIN MEGLUMINE)
Injectable Solution
50 mg/mL
Veterinary

Only for Intravenous Use in Beef and Dairy Cattle. Not for Use in Dry Dairy Cows and Veal Calves. For Intravenous or Intramuscular Use in Horses.

CAUTION Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION Each milliliter of BANAMINE Injectable Solution contains flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.5 mg sodium formaldehyde sulfoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol; 5.0 mg phenol as preservative, hydrochloric acid, water for injection qs.

PHARMACOLOGY Flunixin meglumine is a potent, non-narcotic, nonsteroidal, analgesic agent with anti-inflammatory and antipyretic activity. It is significantly more potent than pentazocine, meperidine, and codeine as an analgesic in the rat yeast paw test.
Horse: Flunixin is four times as potent on a mg-per-mg basis as phenylbutazone as measured by the reduction in lameness and swelling in the horse. Plasma half-life in horse serum is 1.6 hours following a single dose of 1.1 mg/kg. Measurable amounts are detectable in horse plasma at 8 hours postinjection.
Cattle: Flunixin meglumine is a weak acid (pKa=5.82)[1] which exhibits a high degree of plasma protein binding (approximately 99%).[2] However, free (unbound) drug appears to readily partition into body tissues (VSS predictions range from 297 to 782 mL/kg.[2-5] Total body water is approximately equal to 570 mL/kg).[6] In cattle, elimination occurs primarily through biliary excretion.[7] This may, at least in part, explain the presence of multiple peaks in the blood concentration/time profile following IV administration.[2]
In healthy cattle, total body clearance has been reported to range from 90 to 151 mL/kg/hr.[2-5] These studies also report a large discrepancy between the volume of distribution at steady state (V_{ss}) and the volume of distribution associated with the terminal elimination phase (V_{β}). This discrepancy appears to be attributable to extended drug elimination from a deep compartment.[8] The terminal half-life has been shown to vary from 3.14 to 8.12 hours.[2-5]
Flunixin persists in inflammatory tissues[9] and is associated with anti-inflammatory properties which extend well beyond the period associated with detectable plasma drug concentrations.[4,9] These observations account for the counterclockwise hysteresis associated with flunixin's pharmacokinetic/pharmacodynamic relationships.[10]
Therefore, prediction of drug concentrations based upon the estimated plasma terminal elimination half-life will likely underestimate both the duration of drug action and the concentration of drug remaining at the site of activity.

INDICATIONS *Horse:* BANAMINE Injectable Solution is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse.
Cattle: BANAMINE Injectable Solution is indicated for the control of pyrexia associated with bovine respiratory disease, endotoxemia and acute bovine mastitis. BANAMINE Injectable Solution is also indicated for the control of inflammation in endotoxemia.

DOSE AND ADMINISTRATION *Horse:* The recommended dose for musculoskeletal disorders is 0.5 mg per pound (1 mL/100 lbs) of body weight once daily. Treatment may be given by intravenous or intramuscular injection and repeated for up to 5 days. Studies show onset of activity is within 2 hours. Peak response occurs between 12 and 16 hours and duration of activity is 24-36 hours. The recommended dose for the alleviation of pain associated with equine colic is 0.5 mg per pound of body weight. Intravenous administration is recommended for prompt relief. Clinical studies show pain is alleviated in less than 15 minutes in many cases. Treatment may be repeated when signs of colic recur. During clinical studies approximately 10% of the horses required one or two additional treatments. The cause of colic should be determined and treated with concomitant therapy.
Cattle: The recommended dose for control of pyrexia associated with bovine respiratory disease and endotoxemia and control of inflammation in endotoxemia, is 1.1 to 2.2 mg/kg (0.5 to 1 mg/lb; 1 to 2 mL per 100 lbs) of body weight given by slow intravenous administration either once a day as a single dose or divided into two doses administered at 12-hour intervals for up to 3 days. The total daily dose should not exceed 2.2 mg/kg (1.0 mg/lb) of body weight. Avoid rapid intravenous administration of the drug. The recommended dose for acute bovine mastitis is 2.2 mg/kg (1 mg/lb; 2 mL per 100 lbs) of body weight given once by intravenous administration.

CONTRAINDICATIONS *Horse:* There are no known contraindications to this drug when used as directed. Intra-arterial injection should be avoided. Horses inadvertently injected intra-arterially can show adverse reactions. Signs can be ataxia, incoordination, hyperventilation, hysteria, and muscle weakness. Signs are transient and disappear without antidotal medication within a few minutes. Do not use in horses showing hypersensitivity to flunixin meglumine.
Cattle: NSAIDs inhibit production of prostaglandins which are important in signaling the initiation of parturition. The use of flunixin can delay parturition and prolong labor which may increase the risk of stillbirth. Do not use BANAMINE Injectable Solution within 48 hours of expected parturition. Do not use in animals showing hypersensitivity to flunixin meglumine. Use judiciously when renal impairment or gastric ulceration are suspected.

RESIDUE WARNING Cattle must not be slaughtered for human consumption within 4 days of the last treatment. Milk that has been taken during treatment and for 36 hours after the last treatment must not be used for food. Not for use in dry dairy cows. A withdrawal period has not been established for this product in preruminating calves. Do not use in calves to be processed for veal. Not for use in horses intended for food.
Approved only for intravenous administration in cattle. Intramuscular administration has resulted in violative residues in the edible tissues of cattle sent to slaughter.

PRECAUTIONS As a class, cyclo-oxygenase inhibitory NSAIDs may be associated with gastrointestinal and renal toxicity. Sensitivity to drug-associated adverse effects varies with the individual patient. Patients at greatest risk for renal toxicity are those that are dehydrated, on concomitant diuretic therapy, or those with renal, cardiovascular, and/or hepatic dysfunction. Since many NSAIDs possess the potential to induce gastrointestinal ulceration, concomitant use of BANAMINE Injectable Solution with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.
Horse: The effect of BANAMINE Injectable Solution on pregnancy has not been determined. Studies to determine activity of BANAMINE Injectable Solution when administered concomitantly with other drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring adjunctive therapy.
Cattle: Do not use in bulls intended for breeding, as reproductive effects of Banamine Injectable Solution in these classes of cattle have not been investigated. NSAIDs are known to have potential effects on both parturition (See Contraindications) and the estrous cycle. There may be a delay in the onset of estrus if flunixin is administered during the prostaglandin phase of the estrous cycle. NSAIDs are known to have the potential to delay parturition through a tocolytic effect. The use of NSAIDs in the immediate post-partum period may interfere with uterine involution and expulsion of fetal membranes. Cows should be monitored carefully for placental retention if Banamine Injectable Solution is used within 24 hours after parturition.

SAFETY *Horse:* A 3-fold intramuscular dose of 1.5 mg/lb of body weight daily for 10 consecutive days was safe. No changes were observed in hematology, serum chemistry, or urinalysis values. Intravenous dosages of 0.5 mg/lb daily for 15 days; 1.5 mg/lb daily for 10 days; and 2.5 mg/lb daily for 5 days produced no changes in blood or urine parameters. No injection site irritation was observed following intramuscular injection of the 0.5 mg/lb recommended dose. Some irritation was observed following a 3-fold dose administered intramuscularly.
Cattle: No flunixin-related changes (adverse reactions) were noted in cattle administered a 1X (2.2 mg/kg; 1.0 mg/lb) dose for 9 days (three times the maximum clinical duration). Minimal toxicity manifested itself at moderately elevated doses (3X and 5X) when flunixin was administered daily for 9 days, with occasional findings of blood in the feces and/or urine. Discontinue use if hematuria or fecal blood are observed.

ADVERSE REACTIONS In horses, isolated reports of local reactions following intramuscular injection, particularly in the neck, have been received. These include localized swelling, sweating, induration, and stiffness. In rare instances in horses, fatal or nonfatal clostridial infections or other infections have been reported in association with intramuscular use of BANAMINE Injectable Solution. In horses and cattle, rare instances of anaphylactic-like reactions, some of which have been fatal, have been reported, primarily following intravenous use.

HOW SUPPLIED BANAMINE Injectable Solution, 50 mg/mL, is available in 100-mL (NDC 0061-0851-03), and 250-mL (NDC 0061-0851-04) multi-dose vials.

Store between 2° and 30°C (36° and 86°F).

REFERENCES
1. Johansson M, Anler EL. Gas chromatographic analysis of flunixin in equine urine after extractive methylation. *J Chromatogr*. 1988;427:55-66.
2. Odensvik K, Johansson M. High-performance liquid chromatography method for determination of flunixin in bovine plasma and pharmacokinetics after single and repeated doses of the drug. *Am J Vet Res*. 1995;56:489-495.
3. Anderson KL, Neff-Davis CA, Davis LE, Bass VD. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. *Am J Vet Res*. 1990;51:1464-1467.
4. Odensvik K. Pharmacokinetics of flunixin and its effect on prostaglandin $F_{2\alpha}$ metabolite concentrations after oral and intravenous administration in heifers. *J Vet Pharmacol Ther*. 1995;18:254-259.
5. Hardee GE, Smith JA, Harris SJ. Pharmacokinetics of flunixin meglumine in the cow. *Res Vet Sci*. 1985;39:110-112.
6. Ruckebusch Y, Phaneuf LP, Dunlop R. Physiology of Small and Large Animals. Chapter 2: "Body Fluid Compartments," Philadelphia, Pa: B.C. Decker; 1991:8-18.
7. Kopcha M, Ahl AS. Experimental uses of flunixin meglumine and phenylbutazone in food-producing animals. *J Am Vet Med Assoc*. 1989;194:45-49.
8. Wagner JG. Significance of ratios of different volumes of distribution in pharmacokinetics. *Biopharm & Drug Dispos*. 1983;4:263-270.
9. Lees P, Higgins AJ. Flunixin inhibits prostaglandin E_2 production in equine inflammation. *Res Vet Sci*. 1984;37:347-349.
10. Landoni MF, Cunningham FM, Lees P. Determination of pharmacokinetics and pharmacodynamics of flunixin in calves by use of pharmacokinetic/pharmacodynamic modeling. *Am J Vet Res*. 1995;56:786-794.

April 2012

Made in Germany
124589 R3

NAC No.: 1047018.6

E-SE®

Intervet/Merck Animal Health
PRODUCT INFORMATION
(SELENIUM, VITAMIN E)
Injection

FOR VETERINARY USE ONLY
NADA #30-315, Approved by FDA.

CAUTION Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION E-SE Injection is an emulsion of selenium-tocopherol for the prevention and treatment of myositis (Selenium-Tocopherol Deficiency) syndrome in horses. **Each mL contains:** 5.48 mg sodium selenite (equivalent to 2.5 mg selenium), 50 mg (68 IU) vitamin E (as d-alpha tocopheryl acetate), 250 mg polyoxyethylated vegetable oil, 2% benzyl alcohol (preservative), water for injection q.s. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH.

PHARMACOLOGY It has been demonstrated that selenium and tocopherol exert physiological effects and that these effects are intertwined with sulfur metabolism. Additionally, tocopherol appears to have a significant role in the oxidation process, thus suggesting an interrelationship between selenium and tocopherol in overcoming sulfur-induced depletion and restoring normal metabolism. Although oral ingestion of adequate amounts of selenium and tocopherol would seemingly restore normal metabolism, it is apparent that the presence of sulfur and perhaps other factors interfere during the digestive process with proper utilization of selenium and tocopherol. When selenium and tocopherol are injected, they bypass the digestive process and exert their full metabolic effects promptly on cell metabolism. Anti-inflammatory action has been demonstrated by selenium-tocopherol in the Selye Pouch Technique and experimentally induced polyarthritis study in rats.

INDICATIONS E-SE Injection is recommended for the control of the following clinical signs when associated with myositis (Selenium-Tocopherol Deficiency) syndrome: rapid respiration, profuse sweating, muscle spasms and stiffness, elevated SGOT.

CAUTION Intravenous administration, if elected, should be by slow injection.
Emulsions injected intramuscularly into the horse may produce transitory local muscle soreness and can be prevented to some degree by injecting deeply (2 to 2 1/2 inches), in divided doses, in two or more sites. Do not continue therapy in horses demonstrating such sensitivity.
Selenium is toxic if administered in excess. A fixed dose schedule is therefore important (read the package insert for each selenium-tocopherol product carefully before using).

WARNINGS Anaphylactoid reactions, some of which have been fatal, have been reported in horses administered E-SE Injection. Signs include excitement, sweating, trembling, ataxia, respiratory distress, and cardiac dysfunction. These reactions have been reported in association with both intravenous and intramuscular injections. It is presently unknown whether the mode of application affects the frequency of such reactions. However, reactions associated with intramuscular injections have been reported to manifest more slowly and hence may give more time to institute treatment for anaphylaxis, such as epinephrine and/or corticosteroid injection. Medications which have been reported to cause major adverse reactions in horses should be avoided when E-SE is administered, unless the condition of the animal requires such use.
Not to be used in horses intended for food.

DOSAGE AND ADMINISTRATION *Administration*: Administer by slow intravenous injection (see **WARNINGS**) or deep intramuscular injections, in divided doses in two or more sites in the gluteal or cervical muscles. *Dosage:* 1 mL per 100 pounds of body weight. May be repeated at 5-10 day intervals.

PRECAUTIONS Selenium-Tocopherol Deficiency (STD) syndrome produces a variety and complexity of symptoms often interfering with a proper diagnosis. Even in selenium deficient areas there are other disease conditions which produce similar clinical signs. It is imperative that all these conditions be carefully considered prior to the treatment of STD syndrome. Serum selenium levels, elevated SGOT, and creatine serum levels may serve as aids in arriving at a diagnosis of STD, when associated with other indices. Important Use only the selenium-tocopherol product recommended for each species. Each formulation is designed for the species indicated to produce the maximum efficacy and safety.

HOW SUPPLIED 100 mL sterile, multiple dose glass vial, NDC 0061-0709-04.

STORAGE Store between 2° and 30°C (36° and 86°F). Protect from freezing.

October 1998

Made in Germany.
141817 R2
NAC No.: 1047048.3

SALIX®

Intervet/Merck Animal Health
(furosemide)

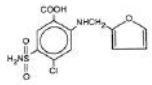
FOR VETERINARY USE ONLY

A diuretic-saluretic for prompt relief of edema

CAUTION Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
Salix® (furosemide) is a chemically distinct diuretic and saluretic pharmacodynamically characterized by the following:
1) A high degree of efficacy, low-inherent toxicity and a high therapeutic index.
2) A rapid onset of action and of comparatively short duration.[1,2]
3) A pharmacological action in the functional area of the nephron, i.e., proximal and distal tubules and the ascending limb of the loop of Henle.[2,3,4]
4) A dose-response relationship and a ratio of minimum to maximum effective dose range greater than tenfold.[1,2]
5) It may be administered orally or parenterally. It is readily absorbed from the intestinal tract and well tolerated.

The intravenous route produces the most rapid diuretic response.
The CAS Registry Number is 54-31-9.
Salix®, a diuretic, is an anthranilic acid derivative with the following structural formula:



Generic name: Furosemide (except in United Kingdom-furosemide). Chemical name: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

ACTIONS
The therapeutic efficacy of Salix® is from the activity of the intact and unaltered molecule throughout the nephron, inhibiting the reabsorption of sodium not only in the proximal and distal tubule but also in the ascending limb of the loop of Henle. The prompt onset of action is a result of the drug's rapid absorption and a poor lipid solubility. The low lipid solubility and a rapid renal excretion minimize the possibility of its accumulation in tissues and organs or crystalluria. Salix® has no inhibitory effect on carbonic anhydrase or aldosterone activity in the distal tubule. The drug possesses diuretic activity either in presence of acidosis or alkalosis.[1,2,3,4,5,6,7]

INDICATIONS
Dogs, Cats & Horses:
Salix® is an effective diuretic possessing a wide therapeutic range. Pharmacologically it promotes the rapid removal of abnormally retained extracellular fluids. The rationale for the efficacious use of diuretic therapy is determined by the clinical pathology producing the edema. Salix® is indicated for the treatment of edema, (pulmonary congestion, ascites) associated with cardiac insufficiency and acute noninflammatory tissue edema.The continued use of heart stimulants, such as digitalis or its glycosides is indicated in cases of edema involving cardiac insufficiency.
Cattle:
Salix® is indicated for the treatment of physiological parturient edema of the mammary gland and associated structures.

CONTRAINDICATIONS-PRECAUTIONS
Salix® is a highly effective diuretic-saluretic which if given in excessive amounts may result in dehydration and electrolyte imbalance. Therefore, the dosage and schedule may have to be adjusted to the patient's needs. The animal should be observed for early signs of electrolyte imbalance, and corrective measures administered. Early signs of electrolyte imbalance are: increased thirst, lethargy, drowsiness or restlessness, fatigue, oliguria, gastro-intestinal disturbances and tachycardia. Special attention should be given to potassium levels. Salix® may lower serum calcium levels and cause tetany in rare cases of animals having an existing hypocalcemic tendency.[10,11,12,13,14]
Although diabetes mellitus is a rarely reported disease in animals, active or latent diabetes mellitus may on rare occasions be exacerbated by Salix®. While it has not been reported in animals the use of high doses of salicylates, as in rheumatic diseases, in conjunction with Salix® may result in salicylate toxicity because of competition for renal excretory sites.
Transient loss of auditory capacity has been experimentally produced in cats following intravenous injection of excessive doses of Salix® at a very rapid rate.[15,16,17]
Electrolyte balance should be monitored prior to surgery in patients receiving Salix®. Imbalances must be corrected by administration of suitable fluid therapy. Salix® is contraindicated in anuria. Therapy should be discontinued in cases of progressive renal disease if increasing azotemia and oliguria occur during the treatment. Sudden alterations of fluid and electrolyte imbalance in an animal with cirrhosis may precipitate hepatic coma, therefore observation during period of therapy is necessary. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved or corrected. Potassium supplementation may be necessary in cases routinely treated with potassium-depleting steroids.

WARNINGS
Salix® is a highly effective diuretic and if given in excessive amounts as with any diuretic may lead to excessive diuresis which could result in electrolyte imbalance, dehydration and reduction of plasma volume enhancing the risk of circulatory collapse, thrombosis, and embolism. Therefore, the animal should be observed for early signs of fluid depletion with electrolyte imbalance, and corrective measures administered. Excessive loss of potassium in patients receiving digitalis or its glycosides may precipitate digitalis toxicity. Caution should be exercised in animals administered potassium-depleting steroids.
It is important to correct potassium deficiency with dietary supplementation. Caution should be exercised in prescribing enteric-coated potassium tablets.
There have been several reports in human literature, published and unpublished, concerning non-specific small-bowel lesions consisting of stenosis, with or without ulceration, associated with the administration of enteric-coated thiazides with potassium salts. These lesions may occur with enteric-coated potassium tablets alone or when they are used with nonenteric-coated thiazides, or certain other oral diuretics. These small-bowel lesions may have caused obstruction, hemorrhage, and perforation. Surgery was frequently required, and deaths have occurred. Available information tends to implicate enteric-coated potassium salts, although lesions of this type also occur spontaneously. Therefore, coated potassium-containing formulations should be administered only when indicated and should be discontinued immediately if abdominal pain, distention, nausea, vomiting, or gastro-intestinal bleeding occurs.
Human patients with known sulfonamide sensitivity may show allergic reactions to Salix®; however, these reactions have not been reported in animals.
Sulfonamide diuretics have been reported to decrease arterial responsiveness to pressor amines and to enhance the effect of tubocurarine. Caution should be exercised in administering curare or its derivatives to patients undergoing therapy with Salix® and it is advisable to discontinue Salix® for one day prior to any elective surgery.

WARNING
CATTLE: Milk taken from animals during treatment and for 48 hours (four milkings) after the last treatment must not be used for food. Cattle must not be slaughtered for food within 48 hours following last treatment.
HORSES: Do not use in horses intended for human consumption.

DOSAGE AND ADMINISTRATION
The usual dosage of Salix® is 1 to 2 mg/lb. body weight (approximately 2.5 to 5 mg/kg). The lower dosage is suggested for cats. Administer once or twice daily at 6 to 8 hour intervals either orally, intravenously, or intramuscularly. A prompt diuresis usually ensues from the initial treatment. Diuresis may be initiated by the parenteral administration of Salix® Injection and then maintained by oral administration.
The dosage should be adjusted to the individual's response. In severe edematous or refractory cases, the dose may be doubled or increased by increments of 1 mg per pound body weight. The established effective dose should be administered once or twice daily. The daily schedule of administration can be timed to control the period of micturition for the convenience of the client or veterinarian. Mobilization of the edema may be most efficiently and safely accomplished by utilizing an intermittent daily dosage schedule, i.e., every other day or 2 to 4 consecutive days weekly. Diuretic therapy should be discontinued after reduction of the edema, or maintained after determining a carefully programmed dosage schedule to prevent recurrence of edema. For long-term treatment, the dose can generally be lowered after the edema has once been reduced. Re-examination and consultations with client will enhance the establishment of a satisfactorily programmed dosage schedule. Clinical examination and serum BUN, CO2 and electrolyte determinations should be performed during the early period of therapy and periodically thereafter, especially in refractory cases. Abnormalities should be corrected or the drug temporarily withdrawn.

DOSAGE
The solution is acceptable for use when clear, colorless to pale yellow to pale brown. Do not use this solution if it appears discolored. Do not puncture the stopper more than 32 times.
DOG AND CAT
Administer intramuscularly or intravenously 1/4 to 1/2 mL per 10 pounds body weight.
Administer once or twice daily, permitting a 6 to 8 hour interval between treatments. In refractory or severe edematous cases, the dosage may be doubled or increased by increments of 1 mg per pound body weight as recommended in preceding paragraphs, "Dosage and Administration".
HORSE
The individual dose is 250 mg to 500 mg (5 to 10 mL) administered intramuscularly or intravenously once or twice daily at 6 to 8 hour intervals until desired results are achieved. The veterinarian should evaluate the degree of edema present and adjust dosage schedule accordingly. **Do not use in horses intended for human consumption.**
CATTLE
The individual dose administered intramuscularly or intravenously is 500 mg (10 mL) once daily or 250 mg (5 mL) twice daily at 12 hour intervals. Treatment not to exceed 48 hours postparturition.
Milk taken from animals during treatment and for 48 hours (four milkings) after the last treatment must not be used for food. Cattle must not be slaughtered for food within 48 hours following last treatment.

HOW SUPPLIED/STORAGE AND HANDLING
Salix® (furosemide) Injection 5% Each mL contains: 50 mg furosemide as a diethanolamine salt preserved and stabilized with myristyl-gamma-picolinium chloride 0.02%, EDTA sodium 0.1%, sodium sulfite 0.1% with sodium chloride 0.2% in distilled water, pH adjusted with sodium hydroxide.
Available in 50 mL multidose vials.

Store Conditions
Store between 15° and 30°C (59° and 86°F). Protect from freezing. Protect from light. Use contents within 28 days of first vial puncture.

TOXICOLOGY
Acute Toxicity
The following table illustrates low acute toxicity of Salix® in three different species. (Two values indicate two different studies.)

LD_{50} of Salix® in mg/kg body weight

SPECIES	INTRAVENOUS
Mouse	**308**
Rat	**680**
Dog	**>300 and >464**

*NOTE: The lower value for the rat oral LD_{50} was obtained in a group of fasted animals; the higher figure is from a study performed in fed rats. Toxic doses lead to convulsions, ataxia, paralysis and collapse. Animals surviving toxic dosages may become dehydrated and depleted of electrolytes due to the massive diuresis and saluresis.

Chronic Toxicity
Chronic toxicity studies with Salix® were done in a one-year study in rats and dogs. In a one-year study in rats, renal tubular degeneration occurred with all doses higher than 50 mg/kg. A six-month study in dogs revealed calcification and scarring of the renal parenchyma at all doses above 10 mg/kg.
Reproductive Studies
Reproductive studies were conducted in mice, rats and rabbits. Only in rabbits administered high doses (equivalent to 10 to 25 times the recommended average dose of 2 mg/kg for dogs, cats, horses, and cattle) of furosemide during the second trimester period did unexplained maternal deaths and abortions occur. The administration of Salix® is not recommended during the second trimester of pregnancy.

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Distributed by: **Intervet Inc** (d/b/a Merck Animal Health), Madison, NJ 07940
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NADA # 34-478, Approved by FDA
www.merck-animal-health-usa.com
Rev. 2/15
142712 R2

NAC NO.: 1047329.2

REGU-MATE®

Intervet/Merck Animal Health
(altrenogest)

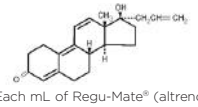
ORAL PROGESTIN
FOR USE IN ANIMALS ONLY
SOLUTION 0.22% (2.2 mg/mL)

For suppression of estrus in mares.
Suppression of estrus allows for a predictable occurrence of estrus following drug withdrawal in mares with ovarian follicles 20 mm or greater.
Suppression of estrus will facilitate:
- Attainment of regular cyclicity during the transition from winter anestrus to the physiological breeding season.
- Management of prolonged estrus conditions.
- Scheduled breeding during the physiological breeding season.

WARNING: DO NOT USE IN HORSES INTENDED FOR HUMAN CONSUMPTION.
Keep this and all medication out of the reach of children.

CAUTION
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
Regu-Mate® (altrenogest) Solution 0.22% contains the active synthetic progestin, altrenogest. The chemical name is 17α-allyl-17β-hydroxyestra-4,9,11-trien-3-one. The CAS Registry Number is 850-52-2. The chemical structure is:



Each mL of Regu-Mate® (altrenogest) Solution 0.22% contains 2.2 mg of altrenogest in an oil solution.

ACTIONS
Regu-Mate® (altrenogest) Solution 0.22% produces a progestational effect in mares.

INDICATIONS
Regu-Mate® (altrenogest) Solution 0.22% is indicated to suppress estrus in mares. Suppression of estrus allows for a predictable occurrence of estrus following drug withdrawal. This facilitates the attainment of regular cyclicity during the transition from winter anestrus to the physiological breeding season. Suppression of estrus will also facilitate management of prolonged estrus conditions. Suppression of estrus may be used to facilitate scheduled breeding during the physiological breeding season.

CONTRAINDICATIONS
Regu-Mate® (altrenogest) Solution 0.22% is contraindicated for use in mares having a previous or current history of uterine inflammation (i.e., acute, subacute, or chronic endometritis). Natural or synthetic gestagen therapy may exacerbate existing low-grade or "smoldering" uterine inflammation into a fulminating uterine infection in some instances.

PRECAUTIONS
Various synthetic progestins, including altrenogest, when administered to rats during the embryogenic stage of pregnancy at doses manyfold greater than the recommended equine dose caused fetal anomalies, specifically masculinization of the female genitalia.

DOSAGE AND ADMINISTRATION
While wearing protective gloves, remove shipping cap and seal; replace with enclosed plastic dispensing cap. Remove cover from bottle dispensing tip and connect luer lock syringe (without needle). Draw out appropriate volume of Regu-Mate® solution. (Note: Do not remove syringe while bottle is inverted as spillage may result.) Detach syringe and administer solution orally at the rate of 1 mL per 110 pounds body weight (0.044 mg/kg) once daily for 15 consecutive days. Administer solution directly on the base of the mare's tongue or on the mare's usual grain ration. Replace cover on bottle dispensing tip to prevent leakage. Excessive use of a syringe may cause the syringe to stick; therefore, replace syringe as necessary.

DOSAGE CHART

Approximate Weight in Pounds	Dose in mL
770	**7**
880	**8**
990	**9**
1100	**10**
1210	**11**
1320	**12**

WHICH MARES WILL RESPOND TO REGU-MATE® (altrenogest) SOLUTION 0.22%: Extensive clinical trials have demonstrated that estrus will be suppressed in approximately 95% of the mares within three days; however, the post-treatment response depended on the level of ovarian activity when treatment was initiated. Estrus in mares exhibiting regular estrus cycles during the breeding season will be suppressed during treatment; these mares return to estrus four to five days following treatment and continue to cycle normally. Mares in winter anestrus with small follicles continued in anestrus and failed to exhibit normal estrus following withdrawal.
Response in mares in the transition phase between winter anestrus and the summer breeding season depended on the degree of follicular activity. Mares with inactive ovaries and small follicles failed to respond with normal cycles post-treatment, whereas a higher proportion of mares with ovarian follicles 20 mm or greater in diameter exhibited normal estrus cycles post-treatment. Regu-Mate® (altrenogest) Solution 0.22% was very effective for suppressing the prolonged estrus behavior frequently observed in mares during the transition period (February, March and April). In addition, a high proportion of these mares responded with regular estrus cycles post-treatment

SPECIFIC USES FOR REGU-MATE® (altrenogest) SOLUTION 0.22%:
SUPPRESSION OF ESTRUS TO
1. Facilitate attainment of regular cycles during the transition period from winter anestrus to the physiological breeding season. To facilitate attainment of regular cycles during the transition phase, mares should be examined to determine the degree of ovarian activity. Estrus in mares with inactive ovaries (no follicles greater than 20 mm in diameter) will be suppressed but these mares may not begin regular cycles following treatment. However, mares with active ovaries (follicles greater than 20 mm in diameter) frequently respond with regular post-treatment estrus cycles.
2. Facilitate management of the mare exhibiting prolonged estrus during the transition period. Estrus will be suppressed in mares exhibiting prolonged behavioral estrus either early or late during the transition period. Again, the posttreatment response depends on the level of ovarian activity. The mares with greater ovarian activity initiate regular cycles and conceive sooner than the inactive mares. Regu-Mate® (altrenogest) Solution 0.22% may be administered early in the transition period to suppress estrus in mares with inactive ovaries to aid in the management of these mares or to mares later in the transition period with active ovaries to prepare and schedule the mare for breeding.
3. Permit scheduled breeding of mares during the physiological breeding season. To permit scheduled breeding, mares which are regularly cycling or which have active ovarian function should be given Regu-Mate® (altrenogest) Solution 0.22% daily for 15 consecutive days beginning 20 days before the date of the planned estrus. Ovulation will occur 5 to 7 days following the onset of estrus as expected for non-treated mares. Breeding should follow usual procedures for mares in estrus. Mares may be regulated and scheduled either individually or in groups.

ADDITIONAL INFORMATION
A 3-year well controlled reproductive safety study was

conducted in 27 pregnant mares, and compared with 24 untreated control mares. Treated mares received 2 mL Regu-Mate® (altrenogest) Solution 0.22% /110 lb body weight (2 x dosage recommended for estrus suppression) from day 20 to day 325 of gestation. This study provided the following data:
1. In filly offspring (all ages) of treated mares, clitoral size was increased.
2. Filly offspring from treated mares had shorter interval from Feb. 1 to first ovulation than fillies from their untreated mare counterparts.
3. There were no significant differences in reproductive performance between treated and untreated animals (mares & their respective offspring) measuring the following parameters:

- interval from Feb. 1 to first ovulation, in mares only
- mean interovulatory interval from first to second cycle and second to third cycle, mares only.
- follicle size, mares only.
- at 50 days gestation, pregnancy rate in treated mares was 81.8% (9/11) and untreated mares was 100% (4/4).
- after 3 cycles, 11/12 treated mares were pregnant (91.7%) and 4/4 untreated mares were pregnant (100%).
- colt offspring of treated and control mares reached puberty at approximately the same age (82 & 84 weeks respectively.)
- stallion offspring from treated and control mares showed no differences in seminal volume, spermatozoal concentration, spermatozoal motility, and total sperm per ejaculate.
- stallion offspring from treated and control mares showed no difference in sexual behavior.
- testicular characteristics (scrotal width, testis weight, parenchymal weight, epididymal weight and height, testicular height, width & length) were the same between stallion offspring of treated and control mares.

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WARNING For oral use in horses only. Keep this and all other medications out of the reach of children. Do not use in horses intended for human consumption.

HUMAN WARNINGS:
Skin contact must be avoided as Regu-Mate® (altrenogest) Solution 0.22% is readily absorbed through unbroken skin. Protective gloves must be worn by all persons handling this product. Pregnant women or women who suspect they are pregnant should not handle Regu-Mate® (altrenogest) Solution 0.22%. Women of child bearing age should exercise extreme caution when handling this product. Accidental absorption could lead to a disruption of the menstrual cycle or prolongation of pregnancy. Direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

INFORMATION FOR HANDLERS:
WARNING: Regu-Mate® (altrenogest) Solution 0.22% is readily absorbed by the skin. Skin contact must be avoided; protective gloves must be worn when handling this product.

Effects of Overexposure
There has been no human use of this specific product. The information contained in this section is extrapolated from data available on other products of the same pharmacological class that have been used in humans. Effects anticipated are due to the progestational activity of altrenogest.
Acute effects after a single exposure are possible; however, continued daily exposure has the potential for more untoward effects such as disruption of the menstrual cycle, uterine or abdominal cramping, increased or decreased uterine bleeding, prolongation of pregnancy and headaches. The oil base may also cause complications if swallowed.
In addition, the list of people who should not handle this product (see below) is based upon the known effects of progestins used in humans on a chronic basis.

PEOPLE WHO SHOULD NOT HANDLE THIS PRODUCT

1. Women who are or suspect they are pregnant.
2. Anyone with thrombophlebitis or thromboembolic disorders or with a history of these events.
3. Anyone with cerebral-vascular 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 tumors which developed during the use of oral contraceptives or other estrogen-containing products.
8. Anyone with liver dysfunction or disease.

Accidental Exposure
Altrenogest is readily absorbed from contact with the skin. In addition, this oil based product can penetrate porous gloves. Altrenogest should not penetrate intact rubber or impervious gloves; however, if there is leakage (i.e., pinhole, spillage, etc.), the contaminated area covered by such occlusive materials may have increased absorption. The following measures are recommended in case of accidental exposure.
Skin Exposure: Wash immediately with soap and water.
Eye Exposure: Immediately flush with plenty of water for 15 minutes. Get medical attention.
If Swallowed: Do not induce vomiting. Regu-Mate® (altrenogest) Solution 0.22% contains an oil. Call a physician. Vomiting should be supervised by a physician because of possible pulmonary damage via aspiration of the oil base. If possible, bring the container and labeling to the physician.

Store at or below 25°C (77°F).

HOW SUPPLIED
Regu-Mate® (altrenogest) Solution 0.22% (2.2 mg/mL). Each mL contains 2.2 mg altrenogest in an oil solution. Available in 1000mL plastic bottles.
Manufactured for: Intervet Inc (d/b/a Merck Animal Health), Summit, NJ 07901
Made in France
NADA # 131-310, Approved by FDA
01/07
141990 R1

NAC NO.: 1047378.2

PROTAZIL®

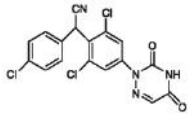
Intervet/Merck Animal Health
ANTIPROTOZOAL PELLETS
(1.56% DICLAZURIL)

FOR ORAL USE IN HORSES ONLY

CAUTION
Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

NADA #141-268, Approved by FDA

DESCRIPTION
Diclazuril, (±)-2,6-dichloro-α-(4-chlorophenyl)-4-(4,5-dihydro-3,5-dioxo-1,2,4-triazin-2(3H)-yl) benzeneacetonitrile, has a molecular formula of $C_{17}H_8Cl_3N_4O_2$, a molecular weight of 407.64, and a molecular structure as follows:



Diclazuril is an anticoccidial (antiprotozoal) compound with activity against several genera of the phylum Apicomplexa. PROTAZIL® (diclazuril) is supplied as oral pellets containing 1.56% diclazuril to be mixed as a top-dress in feed. Inert ingredients include dehydrated alfalfa meal, wheat middlings, cane molasses and propionic acid (preservative).

INDICATIONS
PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets are indicated for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona* in horses.

DOSAGE AND ADMINISTRATION
Dosage: PROTAZIL® (1.56% diclazuril) is administered as a top dress in the horse's daily grain ration at a rate of 1 mg diclazuril per kg (0.45 mg diclazuril/lb) of body weight for 28 days. The quantity of PROTAZIL® necessary to deliver this dose is 64 mg pellets per kg (29 mg pellets/lb) of body weight.
Administration: To achieve this dose, weigh the horse (or use a weigh tape). Scoop up PROTAZIL® to the level (cup mark) corresponding to the dose for the horse's body weight using the following chart:

Weight Range of Horses (lb)	mLs of Pellets
275-524	**20**
525-774	**30**
775-1024	**40**
1025-1274	**50**
1275-1524	**60**
1525-1774	**70**
1775-2074	**80**

One 2.4-lb bucket of PROTAZIL® will treat one 1274-lb horse for 28 days. One 10-lb bucket of PROTAZIL® will treat five 1100-lb horses for 28 days.

CONTRAINDICATIONS
Use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets is contraindicated in horses with known hypersensitivity to diclazuril.

WARNINGS
For use in horses only. Do not use in horses intended for human consumption. Not for human use. Keep out of reach of children.

PRECAUTIONS
The safe use of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets in horses used for breeding purposes, during pregnancy, or in lactating mares has not been evaluated. The safety of PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets with concomitant therapies in horses has not been evaluated.

ADVERSE REACTIONS
There were no adverse effects noted in the field study which could be ascribed to diclazuril. To report suspected adverse reactions, to obtain a MSDS, or for technical assistance call **1-800-224-5318**.

CLINICAL PHARMACOLOGY
The effectiveness of diclazuril in inhibiting merozoite production of Sarcocystis neurona and *S. falcatula* in bovine turbinate cell cultures was studied by Lindsay and Dubey (2000).[1] Diclazuril inhibited merozoite production by more than 80% in cultures of *S. neurona* or *S. falcatula* treated with 0.1 ng/mL diclazuril and greater than 95% inhibition of merozoite production (IC_{95}) was observed when infected cultures were treated with 1.0 ng/mL diclazuril. The clinical relevance of the *in vitro* cell culture data has not been determined.

PHARMACOKINETICS IN THE HORSE
The oral bioavailability of diclazuril from the PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets at a 5 mg/kg dose rate is approximately 5%. Related diclazuril concentrations in the cerebrospinal fluid (CSF) range between 1% and 5% of the concentrations observed in the plasma. Nevertheless, based upon equine pilot study data, CSF *concentrations* are expected to substantially exceed the *in vitro* IC_{95} estimates for merozoite production (*Dirikolu et al.*, 1999)[2]. Due to its long terminal elimination half-life in horses (approximately 43-65 hours), diclazuril accumulation occurs with once-daily dosing. Corresponding steady state blood levels are achieved by approximately Day 10 of administration.

EFFECTIVENESS
Two hundred and fourteen mares, stallions, and geldings of various breeds, ranging in age from 9.6 months to 30 years, were enrolled in a multi-center field study. All horses were confirmed EPM-positive based on the results of clinical examinations and laboratory testing, including CSF Western Blot analyses. Horses were administered PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets at doses of 1, 5, or 10 mg diclazuril/kg body weight as a top-dress on their daily grain ration for 28 days. The horses were then evaluated for clinical changes via a modified Mayhew neurological scale on Day 48 as follows:
0. Normal, neurological deficits not detected.
1. Neurological deficits may be detectable at normal gaits; signs exacerbated with manipulative procedures (e.g., backing, turning in tight circles, walking with head elevation, truncal swaying, etc.).
2. Neurological deficit obvious at normal gaits or posture; signs exacerbated with manipulative procedures.
3. Neurological deficit very prominent at normal gaits: horses give the impression they may fall (but do not) and buckle or fall with manipulative procedures.
4. Neurological deficit is profound at normal gait: horse frequently stumbles or trips and may fall at normal gaits or when manipulative procedures were utilized.
5. Horse is recumbent, unable to rise.
Each horse's response to treatment was compared to its pre-treatment values. Successful response to treatment was defined as clinical improvement of at least one grade by Day 48 3 conversion of CSF to Western Blot-negative status for *S. neurona* or achievement of Western Blot-negative CSF status without improvement of 1 ataxia grade.
Forty-two horses were initially evaluated for effectiveness and 214 horses were evaluated for safety. Clinical condition was evaluated by the clinical investigator's subjective scoring and then corroborated by evaluation of the neurological examination videotapes by a masked panel of three equine veterinarians. Although 42 horses were evaluated for clinical effectiveness, corroboration of clinical effectiveness via videotape evaluation was not possible for one horse due to missing neurologic examination videotapes. Therefore, this horse was not included in the success rate calculation.
Based on the numbers of horses that seroconverted to negative Western Blot status, and the numbers of horses classified as successes by the clinical investigators, 28 of 42 horses (67%) at 1 mg/kg were considered successes. With regard to independent expert masked videotape assessments, 10 of 24 horses (42%) at 1 mg/kg were considered successes. There was no clinical difference in effectiveness among the 1, 5, and 10 mg/kg treatment group results.
Adverse events were reported for two of the 214 horses evaluated for safety. In the first case, a horse was enrolled showing severe neurologic signs. Within 24 hours of dosing, the horse was recumbent, biting, and exhibiting signs of dementia. The horse died, and no cause of death was determined. In the second case, the horse began walking stiffly approximately 13 days after the start of dosing. The referring veterinarian reported that the horse had been fed grass clippings and possibly had laminitis.

ANIMAL SAFETY
PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets were administered to 30 horses (15 males and 15 females, ranging from 5 to 9 months of age) in a target animal safety study. Five groups of 6 horses each (3 males and 3 females) received 0, 5 (5X), 15 (15X), 25 (25X) or 50 (50X) mg diclazuril/kg (2.27mg/lb) body weight/day for 42 consecutive days as a topdress on the grain ration of the horse. The variables measured during the study included: clinical and physical observations, body weights, food and water consumption, hematology, serum chemistry, urinalysis, fecal analysis, necropsy, organ weights, gross and histopathologic examinations. The safety of diclazuril top-dress administered to horses at 1 mg/kg once daily cannot be determined based solely on this study because of the lack of an adequate control group (control horses tested positive for the test drug in plasma and CSF). However, possible findings associated with the drug were limited to elevations in BUN, creatinine, and SDH and less than anticipated weight gain. Definitive test article-related effects were decreased grain/top-dress consumption in horses in the 50 mg/kg group.
In a second target animal safety study, PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets were administered to 24 horses (12 males and 12 females, ranging from 2 to 8 years of age). Three groups of 4 horses/sex/group received 0, 1, or 5 mg diclazuril/kg body weight/day for 42 days as a top-dress on the grain ration of the horse. The variables measured during the study included physical examinations, body weights, food and water consumption, hematology, and serum chemistry. There were no test article-related findings seen during the study.

STORAGE INFORMATION
Store between 15°C to 30°C (59°F to 86°F).

HOW SUPPLIED
PROTAZIL® (1.56% diclazuril) Antiprotozoal Pellets are supplied in 2.4-lb (1.1 kg) and 10-lb (4.5 kg) buckets.

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Intervet Inc d/b/a Merck Animal Health, 556 Morris Avenue, Summit, NJ 07901

2.4 lbs (1.1 kg)	**07-2014**
10 lbs (4.5 kg)	**09-2011**

NAC NO.: 1047490.1

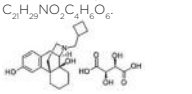
DOLOREX®

Intervet/Merck Animal Health
(BUTORPHANOL TARTRATE)

ANADA 200-239; APPROVED BY FDA

CAUTION
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

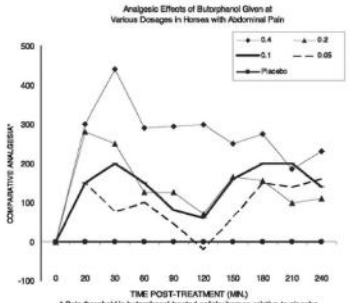
DESCRIPTION
DOLOREX (butorphanol tartrate) is a totally synthetic, centrally acting, narcotic agonist-antagonist analgesic with potent antitussive activity. It is a member of the phenanthrene series. The chemical name is Morphinan-3, 14-diol, 17-(cyclobutylmethyl)-, (-)-, (S-(R*, R*))- 2, 3-dihydroxybutanedioate (1:1) (salt). It is a white crystalline, water soluble substance having a molecular weight of 477.55; its molecular formula is $C_{21}H_{29}NO_2C_4H_6O_6$.



Each mL of DOLOREX contains 10 mg butorphanol base (as butorphanol tartrate, USP), 3.3 mg citric acid, Ph.Eur., 6.4 mg sodium citrate, Ph.Eur., 4.7 mg sodium chloride, Ph.Eur., and 0.1 mg benzethonium chloride, Ph.Eur., q.s. with water for injection, Ph.Eur.

COMPARATIVE PHARMACOLOGY
In animals, butorphanol has been demonstrated to be 4 to 30 times more potent than morphine and pentazocine (Talwin®-V) respectively.[1] In humans, butorphanol has been shown to have 5 to 7 times the analgesic activity of morphine and 20 times that of pentazocine.[2,3] Butorphanol has 15 to 20 times the oral antitussive activity of codeine or dextromethorphan in dogs and guinea pigs.[4]
As an antagonist, butorphanol is approximately equivalent to nalorphine and 30 times more potent than pentazocine.[1]
Cardiopulmonary depressant effects are minimal after treatment with butorphanol as demonstrated in dogs[5], humans[6,7] and horses.[8] Unlike classical narcotic agonist analgesics which are associated with decreases in blood pressure, reduction in heart rate, and concomitant release of histamine, butorphanol does not cause histamine release.[1] Furthermore, the cardiopulmonary effects of butorphanol are not distinctly dosage related but rather reach a ceiling effect beyond which further dosage increases result in relatively lesser effects.
Reproduction studies performed in mice and rabbits revealed no evidence of impaired fertility or harm to the fetus due to butorphanol tartrate. In the female rat, parenteral administration was associated with increased nervousness and decreased care for newborn, resulting in a decreased survival rate of the new born. This nervousness was seen only in the rat species.

EQUINE PHARMACOLOGY
Following intravenous injection in horses, butorphanol is largely eliminated from the blood within 3 to 4 hours. The drug is extensively metabolized in the liver and excreted in the urine.
In ponies, butorphanol given intramuscularly at a dosage of 0.22 mg/kg was shown to alleviate experimentally induced visceral pain for about 4 hours.[9]
In horses, intravenous dosages of butorphanol ranging from 0.05 to 0.4 mg/kg were shown to be effective in alleviating visceral and superficial pain for at least 4 hours.



A definite dosage-response relationship was detected in that butorphanol dosage of 0.1 mg/kg was more effective than 0.05 mg/kg, but not different from 0.2 mg/kg, in alleviating deep abdominal pain.

ACUTE EQUINE STUDIES
Rapid intravenous administration of butorphanol at a dosage of 2.0 mg/kg (20 times the recommended dosage) to a previously unmedicated horse resulted in a brief episode of inability to stand, muscle fasciculation, a convulsive seizure of 6 seconds duration, and recovery within 3 minutes. The same dosage administered after 10 successive daily 1.0 mg/kg dosages of butorphanol resulted only in transient sedative effects. During the 10 day course of administration at 1.0 mg/kg (10 times the recommended use level) in 2 horses, the only detectable drug effects were transient behavioral changes typical of narcotic agonist activity. These included muscle fasciculation about the head and

neck, dysphoria, lateral nystagmus, ataxia, and salivation. Repeated administration of butorphanol at 1.0 mg/kg (10 times the recommended dosage) every 4 hours for 48 hours caused constipation in one of two horses.

SUBACUTE EQUINE STUDIES
Horses were found to tolerate butorphanol given intravenously at dosages of 0.1, 0.3, and 0.5 mg/kg every 4 hours for 48 hours followed by once daily injections for a total of 21 days. The only detectable drug effects were slight transient ataxia observed occasionally in the high dosage group. No clinical, laboratory, or gross or histopathologic evidence of any butorphanol-related toxicity was encountered in the horses.

INDICATIONS
DOLOREX (butorphanol tartrate) is indicated for the relief of pain associated with colic in adult horses and yearlings. Clinical studies in the horse have shown that butorphanol tartrate alleviates abdominal pain associated with torsion, impaction, intussusception, spasmodic and tympanic colic, and postpartum pain.

WARNING
FOR USE IN HORSES ONLY. NOT FOR USE IN HORSES INTENDED FOR FOOD.

CAUTION
DOLOREX, a potent analgesic, should be used with caution with other sedative or analgesic drugs as these are likely to produce additive effects. There are no well controlled studies using butorphanol in breeding horses, weanlings, and foals. Therefore the drug should not be used in these groups.

ADVERSE REACTIONS
In clinical trials in horses, the most commonly observed side effect was slight ataxia which lasted 3 to 10 minutes. Marked ataxia was reported in 1.5% of the 327 horses treated. Mild sedation was reported in 9% of the horses.

DOSAGE
The recommended dosage in the horse is 0.1 mg butorphanol per kilogram of body weight (0.05 mg/lb) by intravenous injection. This is equivalent to 5 mL DOLOREX for each 1,000 Lb body weight. The dose may be repeated within 3 to 4 hours but treatment should not exceed 48 hours. Preclinical model studies and clinical field trials in horses demonstrate that the analgesic effects of butorphanol are seen within 15 minutes following injection and persist for about 4 hours.

HOW SUPPLIED
DOLOREX is supplied in 50 mL vials (Order Code No. 017070).
Store at or below 25°C (77°F).

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