2015 EQUINE PRODUCTS AND SERVICES

U.S. EQUINE

zoetis

ZOETIS EQUINE PRODUCTS

ANTI-INFLAMMATORIES

ANTI-INFECTIVES

ANTISEPTICS

VACCINES

zoetis™

ZOETIS EQUINE PRODUCTS

VACCINES CONTINUED

PARASITICIDES & INSECTICIDES

SEDATIVES, ANESTHETICS & ANALGESICS

zoetis™

ZOETIS EQUINE PRODUCTS

SUPPLEMENTS

REPRODUCTIVE

OTHER

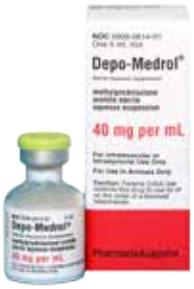
SERVICES

PRESCRIBING INFORMATION

zoetis™

DEPO-MEDROL® Injectable
(methylprednisolone acetate)

USES:
For the treatment of pain and lameness associated with acute localized arthritic conditions and generalized arthritic conditions.



SUPPLIED:
- 20 mg/mL (20 mL vial)
- 40 mg/mL (5 mL vial)

KEY FACTS:
- Produces a more prolonged anti-inflammatory effect than equimolar hydrocortisone acetate.
- Provides relief from pain within 12-24 hrs of intrasynovial injection.
- Duration of pain relief averages 3-4 weeks, in some cases longer.
- The usual intramuscular dose for horses is 200 mg repeated as necessary.
- The usual intrasynovial dose for horses is between 40mg and 240 mg with a total body target dose of 100 mg for performance horses.
- Research updates on withdrawal time at: http://www.rmtcnet.com/withdrawal_agree.asp

IMPORTANT SAFETY INFORMATION:
Do not use DEPO-MEDROL in animals with tuberculosis, peptic ulcer and Cushing's syndrome. Use with extreme caution in pregnant animals, Watch for evidence of concurrent infection. See full Prescribing Information, attached.

DOMOSO® Solution
(*dimethyl sulfoxide*)

USES:
Administer topically to reduce acute swelling due to trauma. For the treatment of pain relief and inflammation in critical conditions.

SUPPLIED:
- 1 pint bottle
- 1 gallon bottle

KEY FACTS:
- Medical grade Dimethyl Sulfoxide.
- Provides relief of pain and inflammation.
- Apply liberally 3-4 times per day but do not exceed 100 mL.
- It may mask certain disease signs such as are seen in fractures, it should not be used directly prior to racing or other physical stress.

IMPORTANT SAFETY INFORMATION:
Avoid contact of DOMOSO SOLUTION with skin and eyes. Use gloves and apply in a well ventilated area. For topical use only. Do not use in conditions of physical stress or activity where this product could mask existing pathology. Use caution when applying other topical drugs, and in conjunction with other pharmaceutical preparations, especially those affecting the cardiovascular and central nervous system. See full Prescribing Information, attached.

HYLARTIN® V Injection
(sodium hyaluronate)

USES:
Treatment of joint dysfunction due to non-infectious synovitis associated with equine osteoarthritis. For small to medium sized joints (carpal, fetlock) dosage of 2mL is administered. For the treatment of larger joints (hock) dosage is 4 mL.

SUPPLIED:

- 2 mL vials containing 20mg of active ingredient

KEY FACTS:

- Lubricates the soft tissues of the joint – reducing friction and improving joint activity by replacing natural hyaluronate.
- The highest molecular weight HA approved for equine (up to 6X the weight of low molecular weight competitor Hylovet®).[1]
- Superior viscosity contributes to the maximum possible period of soundness, at least 16 weeks.[2]
- May be repeated at weekly intervals for a total of three treatments.
- Horses should be given two days stall rest before gradually resuming normal activity.

IMPORTANT SAFETY INFORMATION:
Do not administer HYLARTIN V intravascularly. Occasional mild side effects may include heat, transient edema and pain around the treated joint. Do not use in horses intended for human consumption. See full Prescribing Information, attached.

[1] Car on JP. Intra-articular injections for joint disease in horses. Vet Clin North Am Equine Pract 2005; 21: 559-573.

[2] White, Gary W, et. al. Evaluation of the efficacy of various preparations of sodium hyaluronate in an induced equine carpitis model. Journal of Equine Veterinary Science 1999; Vol 19, No. 5: 331-337.

PREDEF® 2X Sterile Aqueous Suspension
(isoflupredone acetate)

USES:
Administered by deep intramuscular injection for systematic effect, or into joint cavity, tendon sheath, or bursa for local effect.

SUPPLIED:

- 100 mL vial

KEY FACTS:

- Treatment was found useful in alleviating the pain and lameness associated with generalized and local arthritic conditions.
- Dosage is 5 to 20 mg repeated as necessary depending on the size of the cavity to be injected.

IMPORTANT SAFETY INFORMATION:
Do not use in horses intended for human consumption. When administered during the last trimester of pregnancy, use of oral or injectable corticosteroids may induce parturition and may be associated with birth related complications and birth defects. See full Prescribing Information, attached.

AMIGLYDE®-V
(*amikacin sulfate*)

USES:
Treatment of uterine infections (endometritis, metritis and pyometra) caused by *Escherichia coli, Pseudomonas spp.*, and *Klebsiella spp.*

SUPPLIED:
- 48 mL vial

KEY FACTS:
- Amikacin has been shown to be effective against many aminoglycoside-resistant strains due to its ability to resist degradation by certain aminoglycoside inactivating enzymes.

IMPORTANT SAFETY INFORMATION:
Concurrent use of other aminoglycosides should be avoided because of the potential for additive effects. Do not use AMIGLYDE V in horses intended for human consumption. See full Prescribing Information, attached.

EXCEDE® Sterile Suspension
(*ceftiofur crystalline free acid*)

USES:
A sustained-release antibiotic used in the treatment of lower respiratory tract infections in horses caused by susceptible strains of *Streptococcus equi subspecies zooepidemicus (S. zooepidemicus).*

SUPPLIED:
- 100 mL vial
- 250 mL vial

KEY FACTS:
- First and only licensed antibiotic that offers a full 10-day course of therapy in just 2 treatments.
- One single sustained dose provides therapeutic care for 96 hours.
- The sustained-release nature of the product means less systemic exposure to the antibiotic with comparable efficacy.
- 100% effective against target pathogens.
- FDA Approved for horses.
- Dosage of two intramuscular injections, 96 hours apart, at a dosage of 1.5 mL/100 lb body weight provides 10 days of therapy for optimized compliance.
- A maximum of 20 mL per injection site may be administered.
- Contents should be used within 12 weeks after the first dose is removed.

IMPORTANT SAFETY INFORMATION:
People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to EXCEDE. EXCEDE is contraindicated in animals with known allergy to ceftiofur or to the β-lactam group (penicillin and cephalosporins) of antimicrobials. Do not use in horses intended for human consumption. The administration of antimicrobials in horses under conditions of stress may be associated with diarrhea, which may require appropriate veterinary therapy. See full Prescribing Information, attached.

NAXCEL® Sterile Powder
(ceftiofur sodium)

USES:
The treatment of respiratory infections associated with *Streptococcus equi subspecies (S. zooepidemicus)*.

SUPPLIED:
- 1 gram vial
- 4 gram vial

KEY FACTS:
- Administer by intramuscular injection at the dosage of 1 to 2 mg ceftiofur per pound of body weight, with a maximum of 10 mL per injection site.
- Treatment should be repeated at 24 hour intervals, and continued for 48 hours after clinical signs have disappeared but should not exceed 10 days.

IMPORTANT SAFETY INFORMATION:
People with known hypersensitivity to penicillin or cephalosporins should avoid exposure to NAXCEL. Do not use in horses intended for human consumption. Do not use in animals found to be hypersensitive to the product. The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that could be fatal. See full Prescribing Information, attached.

Sterile Water

USES:
For usage in diluting Naxcel Sterile Powder.

SUPPLIED:
- 80 mL (for 4g Naxcel)

TUCOPRIM®
(*trimethoprim and sulfadiazine powder*)

USES:
Indicated in horses where potent systemic antibacterial action against sensitive organisms is required. Trimethoprim/ sulfadiazine is indicated where the control of bacterial infections is required during the treatment of: acute strangles, acute urogenital infections, respiratory tract infections, and wound infections or abscesses.

SUPPLIED:
- 400 gram pail
- 2000 gram pail

KEY FACTS:
- The recommended dose is 3.75 grams TUCOPRIM Powder per 50 kg (110 lbs) body weight per day. Each level, loose-filled scoop contains approximately 15 grams which is sufficient to treat 200 kg (440 lbs) of body weight.
- Administer orally in a small amount of palatable food.
- The usual course of treatment is a single, daily dose for five to seven days, continuing acute infection therapy for two to three days after clinical signs have subsided.
- Low toxicity.

IMPORTANT SAFETY INFORMATION:
TUCOPRIM should not be used in horses showing liver parenchymal damage, blood dyscrasias or in those with a history of sulfonamide sensitivity. Do not use in horses intended for human consumption. See full Prescribing Information, attached.

NOLVASAN® Solution
(chlorhexidine diacetate)

USES:
Powerful cleaner, disinfectant and deodorizer recommended for the disinfection of inanimate objects.

SUPPLIED:
- 1 gallon

NOLVASAN® S
(chlorhexidine diacetate)

USES:
Disinfects inanimate objects to aid in the control of many viruses.

SUPPLIED:
- 16 oz.
- 1 gallon

NOLVASAN® Skin and Wound Cleanser
(chlorhexidine)

USES:
Powerful cleaner, disinfectant and deodorizer recommended for the disinfection of inanimate objects.

SUPPLIED:
- 4 oz

KEY FACTS:
- For wound cleansing rinse the area to be cleansed with clean water. A moistened gauze pad may be used to apply a small amount of Nolvasan Skin and Wound Cleanser to the affected area. Gently cleanse for 2-4 minutes. Additional water may be needed to obtain adequate sudsing.
- Repeat cleaning if necessary. Wipe away excess foam with a clean gauze pad
- After cleansing, an antiseptic ointment or suitable dressing may be applied.
- For general skin cleansing thoroughly rinse area to be cleansed with water, apply sufficient Nolvasan Skin and Wound Cleanser and wash gently. Rinse again thoroughly.

NOLVASAN® Surgical Scrub
(chlorhexidine)

USES:
Antimicrobial skin and wound cleanser.

SUPPLIED:
- 1 gallon

KEY FACTS:
- Rinse the area to be cleansed with clean water.
- Apply 1 to 5 mL of Nolvasan Surgical Scrub to the area and wash with a sponge or brush for 2 to 4 minutes.
- It may be necessary to apply additional water to obtain adequate sudsing. Wipe away excess foam with sterile sponge.

ARVAC®
Equine Arteritis Virus Vaccine

USES:
Equine Arteritis Virus (EAV) vaccine for the vaccination of healthy non-stressed adult horses as an aid in the prevention of viral abortion and respiratory infection due to equine arteritis virus.

SUPPLIED:
- 10 x 1 dose vial

KEY FACTS:
- ARVAC vaccine contains a modified-live equine arteritis virus.
- Administer one 1 mL dose intramuscularly.
- Vaccinate males and young animals at any time, but stallions should be vaccinated not less than 3 weeks prior to breeding.
- Vaccinate mares preferably as maidens or when open.
- Mares in foal should not be vaccinated until after foaling and then not less than 3 weeks prior to breeding.
- Maiden and barren mares may be vaccinated anytime but should be vaccinated not less than 3 weeks prior to breeding.
- Annual booster dose is recommended.
- Store in the dark at 2° to 7°C (35° to 45°F).
- Use entire contents within 60 minutes after rehydration
- Burn container and unused contents.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.
- The vaccinal virus has been modified to the extent that it may be irregularly infective when given by natural portals of entry.
- A high degree of safety has been demonstrated for horses of any age and pregnant mares. However, the vaccination of foals under six weeks of age is not recommended except in emergency situations when threatened by natural exposure.
- Pregnant mares SHOULD NOT be vaccinated during the last two months of gestation since a few instances of fetal invasion by vaccinal virus have been demonstrated during this period.

EQUILOID INNOVATOR®
Encephalomyelitis Vaccine-Tetanus Toxoid

USES:
For the vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to eastern and western viruses, and tetanus.

SUPPLIED:
- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:
- Inject one 1 mL dose intramuscularly using aseptic technique, administer a second 1 mL dose 3 to 4 weeks after first dose.
- A 1 mL booster dose should be given annually.
- Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not use within 21 days of slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

EQUIVAC INNOVATOR® EHV-1/4
Rhinopneumonitis Vaccine

USES:
For the vaccination of healthy horses as an aid in the prevention of equine rhinopneumonitis due to type 1 and 4 equine herpesviruses.

SUPPLIED:
- 10 dose vial

KEY FACTS:
- Inject one 1 mL dose intramuscularly using aseptic technique, administer a second 1 mL dose 3 to 4 weeks after first dose.
- A 1 mL booster dose should be given annually.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not use within 21 days of slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

FLUVAC INNOVATOR®
Equine Influenza Vaccine

USES:
FLUVAC INNOVATOR is for the vaccination of healthy horses as an aid in prevention of equine influenza due to type A_2 viruses.

SUPPLIED:
- 12 x 1 dose syringes
- 10 dose vial

KEY FACTS:
- The only vaccine with equine influenza virus (EIV) strain KY '97 that has demonstrated protection against heterologous challenge with EIV strain OH '03.[3]
- Since 2002, the vaccine strain in FLUVAC INNOVATOR has been demonstrated to be effective against six emergent strains of equine influenza including Richmond 07.[4]
- Only INNOVATOR vaccines are adjuvanted with METASTIM® for improved immune response.
- Inject 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose in unvaccinated or naïve horses.
- A 1 mL annual revaccination in previously vaccinated horses is recommended.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not use within 21 days of slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

FLUVAC INNOVATOR® EHV-4/1
Rhinopneumonitis-Equine Influenza Vaccine

USES:
For intramuscular vaccination of healthy horses as an aid in the prevention of equine rhinopneumonitis due to types 1 and 4 herpesviruses, and equine influenza due to the type A_2 viruses.

SUPPLIED:
- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:
- Helps deliver demonstrated protection against circulating contemporary equine influenza virus (EIV) strains.
- Since 2002, the vaccine strain in FLUVAC INNOVATOR has been demonstrated to be effective against six emergent strains of equine influenza including Richmond 07.[4]
- The only vaccines shown to help prevent clinical disease in 100% of vaccinated horses following EIV OH '03 challenge.[5]
- FLUVAC INNOVATOR vaccines contain the Kentucky/97 subtype of EIV and METASTIM, a proprietary oil emulsion adjuvant with immunostimulating properties.
- Inject 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- A 1 mL annual revaccination in previously vaccinated horses is recommended.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not use within 21 days of slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

[3] Data on file, Study Report No. B671-08-004R, Zoetis Inc.
[4] Data on file, Study Report No. 14OREQBIO-1, Zoetis Inc.
[5] Data on file, Study Report No. B671-08-004R, Zoetis Inc.

FLUVAC INNOVATOR® 4
Encephalomyelitis-Influenza Vaccine-Tetanus Toxoid

USES:

For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses, equine influenza due to type A_2 viruses, and tetanus.

SUPPLIED:

- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:

- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- Since 2002, the vaccine strain in FLUVAC INNOVATOR has been demonstrated to be effective against six emergent strains of equine influenza including Richmond 07.[6]
- A 1 mL booster dose should be given annually.
- Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

FLUVAC INNOVATOR® 6
Encephalomyelitis-Rhinopneumonitis-Influenza Vaccine-Tetanus Toxoid

USES:

For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern, Western and Venezuelan viruses, equine rhinopneumonitis due to type 1 and 4 herpesviruses, equine influenza due to type A_2 viruses, and tetanus.

SUPPLIED:

- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:

- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- Since 2002, the vaccine strain in FLUVAC INNOVATOR has been demonstrated to be effective against six emergent strains of equine influenza including Richmond 07.[6]
- A 1 mL booster dose should be given annually.
- Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

[6] Data on file, Study Report No. 14OREQBIO-1, Zoetis Inc.

FLUVAC INNOVATOR® 5
Encephalomyelitis-Rhinopneumonitis-Influenza Vaccine-Tetanus Toxoid

USES:

For vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses, equine rhinopneumonitis due to type 1 and 4 herpesviruses, equine influenza due to type A_2 viruses, and tetanus.

SUPPLIED:
- 12 x 1 dose syringes
- 10 dose vials

KEY FACTS:
- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- Since 2002, the vaccine strain in FLUVAC INNOVATOR has been demonstrated to be effective against six emergent strains of equine influenza including Richmond 07.[7]
- A 1 mL booster dose should be given annually.
- Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

FLUVAC INNOVATOR® Triple-E FT®
Encephalomyelitis-Influenza Vaccine-Tetanus Toxoid

USES:

For vaccination of healthy horses 10 months of age or older as an aid in the prevention of equine encephalomyelitis due to Eastern, Western and Venezuelan viruses, equine influenza due to type A_2 viruses, and tetanus.

SUPPLIED:
- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:
- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- Since 2002, the vaccine strain in FLUVAC INNOVATOR has been demonstrated to be effective against six emergent strains of equine influenza including Richmond 07.[7]
- A 1 mL booster dose should be given annually.
- Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

[7] Data on file, Study Report No. 14OREQBIO-1, Zoetis Inc.

PINNACLE® I.N.

USES:
For the vaccination of healthy horses as an aid in the prevention of disease caused by *Streptococcus equi*.

SUPPLIED:
- 10 x 1 dose vial

KEY FACTS:
- The only two-dose modified-live vaccine developed to help prevent strangles caused by *Streptococcus equi*.
- Intranasal administration helps provide a "more natural" immune response, stimulating innate and mucosal immunity at the site of natural infection.
- Pinnacle I.N. utilizes a specially designed cannula that helps deliver the vaccine to the pharyngeal (throat) area.
- Aseptically rehydrate with the entire contents of the accompanying sterile diluent. Instill the entire rehydrated vaccine into one nostril using a syringe with applicator tip. Administer a second dose 2 to 3 weeks later.
- Annual revaccination is recommended.
- For intranasal use only. Do not administer by any other route than intranasal.
- Use entire contents when first opened.
- After administration a small number of horses may experience non-contagious transitory upper respiratory signs including nasal discharge and lymphadenectasis. Purpura hemorrhagica may be seen in hypersensitive individuals following exposure to streptococcal proteins.
- Do not vaccinate within 30 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

PNEUMABORT-K® + 1b
Equine Rhinopneumonitis Vaccine

USES:
The only equine vaccine labeled for use in pregnant mares to aid in the prevention of abortion due to EHV-1 infections, as well as to help prevent respiratory infections caused by equine herpesvirus (EHV)-1p and EHV-1b.

SUPPLIED:
- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:
- Broad protection—the only equine vaccine labeled for use in pregnant mares as an aid in the prevention of abortion due to EHV-1 infections, as well as to help prevent respiratory infections caused by equine herpesvirus (EHV)-1p and EHV-1b.
- Prevalence—the 1b subgroup of EHV-1 continues to be an important group, as are abortions associated with EHV-1 infections.[8]
- PNEUMABORT-K +1b is uniquely adjuvanted for improved immune responses.
- Recommended for whole-herd management, including geldings, stallions and mares where there is evidence of EHV-1 in the herd population.
- For pregnant mares, aseptically administer one 2 mL dose intramuscularly during the 5th, 7th and 9th months of pregnancy. Revaccinate annually at the 5th, 7th and 9th months of pregnancy.
- For young horses, aseptically administer one 2 mL dose intramuscularly followed by a second 2 mL dose 3 to 4 weeks later. Revaccinate with a single 2 mL dose 6 months after the second primary dose and annually thereafter.
- To insure proper placement and retention of the vaccine, inject deep into the heavy muscles of the hindquarter.
- Mild exercise to promote absorption is recommended for one week after injection.
- Maiden and barren mares kept in barn- or pasture-contact with vaccinated pregnant mares should be vaccinated on the same schedule as the pregnant mares with which they are in contact. Mares more than five months pregnant at the time of arrival on a farm should be vaccinated upon arrival and at two-month intervals until foaling.
- Pregnant mares that are in contact with mares that have aborted equine herpesvirus 1 infected fetuses should be vaccinated. Such vaccination may provide immunity for those mares in the group which are not incubating an abortigenic infection at the time of vaccination.
- Do not vaccinate within 60 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

[8] Paillot R, Case R, Ross J, Newton R, Nugent J. Equine Herpes Virus - 1:Virus, Immunity and Vaccines, The open Veterinary Science Journal 2008:2,68-91.

EQUINE ROTAVIRUS VACCINE*
Conditional License

USES:
For the vaccination of pregnant mares to provide the passive transfer of antibodies to foals against equine rotavirus.

SUPPLIED:
• 10 dose vial

KEY FACTS:
• Pregnant mares, inject one 1 mL dose intramuscularly at the eighth month of pregnancy using aseptic technique.
• Administer a second 1 mL dose one month later (i.e., at the ninth month of pregnancy).
• A third 1 mL dose is then given one month later (i.e., at the tenth month of pregnancy).
• Each pregnancy requires vaccination with 3 doses.
• Use entire contents when first opened.
• Do not vaccinate within 21 days before slaughter.
• In case of anaphylactoid reaction, administer epinephrine.

** This product is conditionally licensed by the USDA while additional efficacy and potency data are being developed.*

TETANUS ANTITOXIN

USES:
For the use in domestic animals for the prevention and treatment of tetanus.

SUPPLIED:
• 10 x 1,500 IU vial

KEY FACTS:
• 1500 units, minimum, if injected within 24 hours of exposure.
• Administer subcutaneously, intravenously or intraperitoneally.
• Increase dose relative to the lapse of time following exposure to as much as 30,000 to 100,000 units in animals which are showing symptoms.
• It should always be remembered that good nursing and proper supportive treatment, in addition to the administration of antitoxin, will help improve the patient's chances for recovery.
• This product is prepared from the blood of horses repeatedly injected with large doses of the toxin from *Clostridium tetani*.
• It has been reported that biologicals of equine origin may in some manner be associated with the development of hepatitis (Theiler's disease) when injected into equine species. The incidence of Theiler's disease is rare and in affected animals may be manifested as hepatitis, icterus, anorexia, emaciation and death.
• Use entire contents when first opened.
• Do not vaccinate within 21 days before slaughter.
• In case of anaphylactoid reaction, administer epinephrine.

TETANUS TOXOID

USES:
For the vaccination of healthy horses as an aid in the prevention of tetanus.

SUPPLIED:
- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:
- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 4 to 8 weeks after the first dose. A 1 mL booster dose should be given annually.
- The MetaStim® adjuvant is added to enhance the immune response and to promote the proper rate of vaccine absorption following inoculation.
- Protective tetanus antibody titers usually occur two weeks after the second injection of the initial series. In the event of injury during the course of the initial vaccination program, or if annual boosters have not been given, a prophylactic dose of at least 1500 units of tetanus antitoxin should be given.
- Transitory local reactions at the injection site may occur
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

TRIPLE-E T INNOVATOR®
Encephalomyelitis Vaccine-Tetanus Toxoid

USES:
For intramuscular vaccination of healthy horses as an aid in the prevention of equine encephalomyelitis due to Eastern, Western and Venezuelan viruses, and tetanus.

SUPPLIED:
- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:
- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- Early revaccination may be advisable when horses are faced with an outbreak or other conditions which might make heavy exposure likely.
- A 1 mL booster dose should be given annually.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

WEST NILE-INNOVATOR®
West Nile Virus Vaccine

USES:
For intramuscular vaccination of healthy horses 10 months of age or older as an aid in the prevention of viremia caused by West Nile Virus (WNV).

SUPPLIED:
- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:
- Efficacy of 96.7% demonstrated in independent field study with almost 900 horses.[9]
- Antigen-specific Cell-mediated Immunity as early as 5 days after first vaccination in naïve horse.[10]
- Adjuvanted with Metastim dual-phase adjuvant for enhanced efficacy and safety.
- Supported by the Equine Immunization Support Guarantee for peace of mind.
- The veterinarian's #1 choice for mosquito-borne disease protection.[11]
- First West Nile Vaccine – WEST NILE INNOVATOR (2001).
- The vaccine credited for helping reduce the number of equine WNV cases by nearly 70 percent from 2002 to 2003.[12]
- Helps stimulate fast, antigen-specific, cell-mediated and humoral responses against WNV.[10]
- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 6 weeks after the first dose in unvaccinated or naïve horses.
- A 1 mL revaccination should be given annually in previously vaccinated horses.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

[9] Epp T, Waldner C, Townsend HG. A case control study of factors associated with the development of clinical disease due to West Nile virus, Saskatchewan 2003. Equine Vet J 2007;39:498-503.

[10] Davis EG, et al. Investigation of Antigen Specific Lymphocyte Responses in Healthy Horses Vaccinated with an Inactivated West Nile Virus Vaccine. Vet Immunol Immunopathol 2008; 126(3-4):293-301.

[11] Market Dynamics Inc., September 2013.

[12] 2003 Equine WNV Outlook for the United States. USDA APHIS Info Sheet, June 2003.

WEST NILE-INNOVATOR® + EW
Encephalomyelitis-West Nile Virus Vaccine

USES:
For vaccination of healthy horses as an aid in the prevention of viremia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses.

SUPPLIED:
- 10 dose vial

KEY FACTS:
- Efficacy of the West Nile fraction was demonstrated in horses that received two doses of the vaccine and were challenged one year post-vaccination with West Nile virus.
- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- A 1 mL booster dose should be given annually.
- Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

WEST NILE-INNOVATOR® + EWT

Encephalomyelitis-West Nile Virus Vaccine-Tetanus Toxoid

USES:

For vaccination of healthy horses as an aid in the prevention of viremia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis due to Eastern and Western viruses, and tetanus.

SUPPLIED:

- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:

- Efficacy of the West Nile fraction was demonstrated in horses that received two doses of the vaccine and were challenged one year post-vaccination with West Nile virus.
- Inject one 1 mL dose intramuscularly using aseptic technique. Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- A 1 mL booster dose should be given annually.
- Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

WEST NILE-INNOVATOR® + VEWT

Encephalomyelitis-West Nile Virus Vaccine-Tetanus Toxoid

USES:

For vaccination of healthy horses as an aid in the prevention of viremia caused by West Nile virus, and as an aid in the prevention of equine encephalomyelitis due to Eastern, Western and Venezuelan viruses, and tetanus.

SUPPLIED:

- 12 x 1 dose syringe
- 10 dose vial

KEY FACTS:

- Efficacy of the West Nile fraction was demonstrated in horses that received two doses of the vaccine and were challenged one year post-vaccination with West Nile virus.
- Inject one 1 mL dose intramuscularly using aseptic technique.
- Administer a second 1 mL dose 3 to 4 weeks after the first dose.
- A 1 mL booster dose should be given annually.
- Early revaccination may be advisable when horses are faced with an outbreak or with other conditions which might make heavy exposure likely.
- Use entire contents when first opened.
- In some instances, transient local reactions may occur at the injection site.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine.

ZYLEXIS®
Parapox Ovis Virus Immunomodulator

USES:

Zylexis is an inactivated (killed) Parapox Ovis Virus Immunomodulator that has demonstrated efficacy and safety in stimulating the horse's immune response to aid in the reduction of equine upper respiratory disease associated with equine herpesvirus (EHV) types 1 and 4 infections.

SUPPLIED:
- 5 x 1 dose vial

KEY FACTS:
- One 2 mL injection on days 0, 2 & 9 by intramuscular route.
- Aids in the reduction of upper respiratory disease associated with equine herpesvirus types 1 and 4.
- ZYLEXIS treated horses showed significantly lower purulent nasal discharge ($p<0.01$) and clinical signs ($p<0.01$) than non-treated control horses.[13]
- Less days of mucopurulent nasal discharge were seen in ZYLEXIS treated horses vs. the control group.[13]
- Retreatment is recommended during subsequent disease episodes or prior to stress-inducing situations.
- EHV 1 & 4 infections can be easily triggered by common stressors to horses including trailering, competition, breeding and environmental changes.
- Use entire contents when first opened.
- Do not vaccinate within 21 days before slaughter.
- In case of anaphylactoid reaction, administer epinephrine or equivalent.

[13] Data on File, Study Report No. Equine 1-98, Zoetis Inc.

Equine Immunization Support Guarantee (ISG)

Zoetis will support reasonable diagnostic and treatment costs up to $5,000 if a horse properly vaccinated with one of our vaccine antigens contracts the corresponding equine disease.

EQUINE VETERINARIAN BENEFITS:
- Encourages horse owners to seek veterinary expertise and advice.
- Helps extend protection afforded by our INNOVATOR® line of quality vaccines.
- Reimburses clients up to $5,000 in the event of a vaccine break.
- Benefits applicable if the animal is properly vaccinated by a licensed veterinarian.

EQUINE HORSE OWNER BENEFITS:
- Offers peace of mind by helping to protect your horse against infectious diseases — an important responsibility.
- Builds partnership with your veterinarian when caring for your horse.
- Available at no extra cost to you.
- Reimburses you up to $5,000 for treatment and diagnostic costs.
- Provides an ongoing record of vaccinations.

DISEASES COVERED BY THE EQUINE ISG:
All products under the Zoetis WEST NILE-INNOVATOR® and FLUVAC INNOVATOR® line of vaccines are eligible for the Equine ISG. This includes vaccines against the following diseases:

- West Nile
- Equine Influenza
- Tetanus
- Eastern Equine Encephalomyelitis (EEE)
- Equine Herpesvirus 1 and 4 (respiratory)
- Western Equine Encephalomyelitis (WEE)
- Venezuelan Equine Encephalomyelitis (VEE)

Please contact your local Zoetis representative to find out more about the Equine Immunization Support Guarantee.

ZOETIS
EQUINE IMMUNIZATION SUPPORT GUARANTEE

Zoetis is proud to partner with veterinarians to assure horse owners that their horses are receiving the best possible health care and disease protection.

Zoetis will support reasonable diagnostic and treatment costs up to $5,000 if a horse properly vaccinated with one of our antigens contracts the corresponding equine disease:

- **West Nile**
- **Tetanus**
- **Western Equine Encephalitis**
- **Equine Influenza**
- **Eastern Equine Encephalitis**
- **Venezuelan Equine Encephalitis**
- **Equine Herpesvirus 1 and 4 (respiratory)**

- Program offers direct financial support specific to lack of vaccine efficacy for any properly vaccinated horse, pony or mule. Does not include any other adverse events associated with vaccine administration.
- Horse must be vaccinated by a licensed veterinarian with an established client-patient relationship.
- Veterinarian or clinic must be the primary point of contact for this support program to be valid. Zoetis will direct all requests from horse owners, breeders, etc., to the vaccinating veterinarian, who in turn will need to file the support request on their behalf.
- At the time of the support request, veterinarians must collaborate with Zoetis Veterinary Medical Information and Product Support (VMIPS) in designing an appropriate diagnostic and treatment regimen. A diagnosis must be made using criteria predetermined by VMIPS. To contact VMIPS, call 888-ZOETIS1 (888-963-8471).
- Veterinarians must submit a copy of medical records pertinent to the case, including vaccine brand, serial number and date of vaccination.
- Support requests involving foals less than 6 months of age, or involving onset of disease within three weeks of completing the initial immunization series, are not covered.
- Horse must have received an age-appropriate, initial vaccination series per the vaccine label. A Zoetis vaccine must be the most recent vaccine used in the series.
- All payments made under the immunization support program may require a signed consent form from the veterinarian and/or horse owner.

ZOETIS RESERVES THE RIGHT TO MODIFY THIS PROGRAM AT ANY TIME AND FOR ANY REASON.

Horse Name	Veterinarian Name	Date

zoetis™


FLUVAC INNOVATOR®
FLUVAC INNOVATOR® 4
FLUVAC INNOVATOR® 5
FLUVAC INNOVATOR® 6
FLUVAC INNOVATOR® EHV- 4/1
TRIPLE-ET INNOVATOR®
FLUVAC INNOVATOR® TRIPLE-E FT®
EQUILOID INNOVATOR®
EQUIVAC™ INNOVATOR® EHV- 1/4
PNEUMABORT-K®+1b
WEST NILE-INNOVATOR®
WEST NILE-INNOVATOR® + EW
WEST NILE-INNOVATOR® + EWT
WEST NILE-INNOVATOR® + VEWT
EQUINE ROTAVIRUS
TETANUS ANTITOXIN
TETANUS TOXOID
PINNACLE® I.N.
ARVAC®

A BROAD LINE OF VACCINES:	West Nile	Rhinopneumonitis (EHV-4/EHV-1)	Rhinopneumonitis (EHV-1b/1p)	Equine Influenza	Eastern/Western Encephalomyelitis	Venezuelan Encephalomyelitis	Tetanus Toxoid	Tetanus Antitoxin	Strangles (*S. equi*)	Equine viral arteritis	Rotavirus
WEST NILE-INNOVATOR®	●										
WEST NILE-INNOVATOR® + EW	●				●						
WEST NILE-INNOVATOR® + EWT	●				●		●				
WEST NILE-INNOVATOR® + VEWT	●				●	●	●				
FLUVAC INNOVATOR® EHV- 4/1		●		●							
FLUVAC INNOVATOR® 4				●	●		●				
FLUVAC INNOVATOR® 5		●		●	●		●				
FLUVAC INNOVATOR® 6		●		●	●	●	●				
FLUVAC INNOVATOR®				●							
FLUVAC INNOVATOR® Triple-E FT®				●	●	●	●				
EQUILOID INNOVATOR®					●		●				
TRIPLE-E T INNOVATOR®					●	●	●				
PINNACLE® I.N.*									●		
PNEUMABORT-K® + 1b			●								
EQUIVAC INNOVATOR® EHV-1/4		●									
TETANUS ANTITOXIN								●			
TETANUS TOXOID							●				
ARVAC®										●	
EQUINE ROTAVIRUS*,**											●

* Available only through a veterinarian

** This product license is conditional. Efficacy and potency test studies are in progress. Please consult your veterinarian.

PARASITICIDES & INSECTICIDES

ANTHELCIDE® EQ Paste
(oxibendazole)

USES:
Broad-spectrum equine dewormer containing the active ingredient oxibendazole.

SUPPLIED:
- 24 gram syringe

KEY FACTS:
- Paste is approved for the removal and control of large strongyles (*Strongylus edentatus, S. equinus, S. vulgaris*); small strongyles (species of the genera *Cylicostephanus, Cylicocyclus, Cyathostomum, Triodontophorus, Cylicodontophorus*, and *Gyalocephalus*); large roundworms (*Parascaris equorum*); pinworms (*Oxyuris equi*), including various larval stages and threadworms (*Strongyloides westeri*)
- One syringe doses up to 1,200-lb body weight.
- Shows efficacy against benzimidazole-resistant strongyles and has a known wide margin of safety.[14,15]

[14] Wood, C. Ascarids in Horses. University of Kentucky and UW Extension. Available at: http://www.extension.org/pages/10307/ascarids-in-horses Accessed August 21, 2012.

[15] Kivipelto J., Asquith, R.L., Efficacy of pyrantel pamoate against small strongyle populations. Equine Practice. 1997; 19(2): 14-18.

QUEST® Gel
(moxidectin)

USES:
Protect against large and small strongyles, roundworms, pinworms, hairworms, stomach worms, bots, and encysted small strongyles.

SUPPLIED:
- 11.3 g syringe

KEY FACTS:
- QUEST/QUEST Plus are the only FDA-approved broad-spectrum equine dewormers labeled to suppress production of small strongyle eggs for 84 days.
- One tube of QUEST covers more parasitic groups than five double-dose tubes of fenbendazole.[16]
- Approved for use in breeding mares and stallions, and foals six months of age and older.
- Clear gel dissolves instantly for an easier deworming process.
- Comes in ready to use syringes, for up to 1150-lb body weight, at 50 lb increments.

IMPORTANT SAFETY INFORMATION:
Do not use QUEST Gel or QUEST PLUS Gel in foals less than 6 months of age or in sick, debilitated and underweight horses. Do not use in other animal species, as severe adverse reactions, including fatalities in dogs, may result.

[16] Betancourt A, Lyons E, Horohov D. The effect of anthelmintics on proinflammatory cytokine responses in treated horses, in Proceedings. 2010 Conference of Research Workers in Animal Diseases. Chicago, Ill. 2009.

QUEST® PLUS Gel
(moxidectin/praziquantel)

USES:
Protect against large and small strongyles, roundworms, pinworms, hairworms, stomach worms, bots, tapeworm and encysted small strongyles.

SUPPLIED:
- 11.6 g syringe

KEY FACTS:
- Effective in the treatment and control of tapeworm infections.
- QUEST/QUEST Plus are the only FDA-approved broad-spectrum equine dewormers labeled to suppress production of small strongyle eggs for 84 days.
- One tube of QUEST PLUS covers the same parasitic groups as six other tubes (five double-dose tubes of fenbendazole and one tube of ivermectin/praziquantel).[17]
- Approved for use horses and ponies six months of age and older.
- Clear gel dissolves instantly for an easier deworming process.
- Comes in ready to use syringes, for up to 1250-lb body weight, at 50 lb increments.

IMPORTANT SAFETY INFORMATION:
Do not use QUEST Gel or QUEST PLUS Gel in foals less than 6 months of age or in sick, debilitated and underweight horses. Do not use in other animal species, as severe adverse reactions, including fatalities in dogs, may result.

[17] Betancourt A, Lyons E, Horohov D. The effect of anthelmintics on proinflammatory cytokine responses in treated horses, in Proceedings. 2010 Conference of Research Workers in Animal Diseases. Chicago, Ill. 2009.

SOLITUDE® IGR Feed-Through Pellet
(2.12% cyromazine)

USES:
Insect growth regulator that inhibits development of the exoskeleton in immature house and stable flies, preventing them from becoming adults.

SUPPLIED:
- 6 lb pail (120 doses)
- 20 lb pail (640 doses)

KEY FACTS:
- SOLITUDE IGR can safely and dramatically reduce the number of flies around horse operations because it prevents immature flies from developing into adults.
- Feed through fly preventative which, when mixed 1/2 ounce into a horse's ration daily, will prevent house and stable flies in and around horses, horse barns, stables, paddocks and race tracks.
- 1/2 ounce scoop of SOLITUDE IGR per day top dressed onto grain or mixed with the horses total ration, no matter the size or weight of the horse.

STRONGID® Paste
(pyrantel pamoate)

USES:
Equine dewormer containing pyrantel, a compound from the tetrahydropyrimidine class. STRONGID Paste is approved for the removal and control of mature infections of large strongyles (*Strongylus vulgaris, S. edentatus, S. equinus*); pinworms (*Oxyuris equi*); large roundworms (*Parascaris equorum*); and small strongyles in horses and ponies.

SUPPLIED:
- 11.6 g syringe

KEY FACTS:
- Effective against mature infections of ascarids, large strongyles, small strongyles and pinworms.
- Demonstrated effective against benzimidazole resistant strongyles.[18]
- Safe for use in horses and ponies.
- Convenient disposable syringe treats up to 1,200-lb body weight.
- For maximum control of parasitism, it is recommended that foals (2 to 8 months of age) be dosed every four (4) weeks.
- To minimize the potential source of infection that the mare may pose to the foal, the mare should be treated one (1) month prior to the anticipated foaling date followed by retreatment 10 days to two (2) weeks after birth of foal. Horses and ponies over eight (8) months of age should be routinely dosed every six (6) weeks.

[18] Kivipelto J., Asquith, R.L., Efficacy of pyrantel pamoate against small strongyle populations. Equine Practice. 1997;19(2): 14-18.

STRONGID® C/C 2X Equine Anthelmintic
(pyrantel tartrate)

USES:
Equine anthelmintic designed to be fed on a daily basis to provide a continuous level of pyrantel in the intestinal tract. STRONGID C/C 2X are approved for the prevention of *Strongylus vulgaris* larval infestation in horses and for control of large strongyles–adults (*S. vulgaris, S. edentatus*); small strongyles–adults and 4th-stage larvae (*Cyathostomum spp., Cylicocyclus spp., Cylicostephanus spp., Cylicodontophorus spp., Poteriostomum spp., Triodontophorus spp.*); pinworms–adults and 4th-stage larvae (*Oxyuris equi*); ascarids–adults and 4th-stage larvae (*Parascaris equorum*).

SUPPLIED:
- Strongid C 25 lb pail (100 doses for a 1,000 lb horse)
- Strongid C 2X 10 lb pail (80 doses for a 1,000 lb horse)
- Strongid C 2X 50 lb bag (400 doses for a 1,000 lb horse)

KEY FACTS:
- Daily feeding of Strongid C/C 2X kills *S. vulgaris* larvae before they can damage vital organs or grow to adulthood and produce eggs that contaminate pastures.
- Strongid C 2X has concentrated double strength which is effective at lower volumes.
- Use of a daily dewormer help break the parasite life cycle, preventing reinfection and costly tissue damage.
- Daily use of Strongid C/C 2X in the last 30 days of gestation is a safe effective method of reducing foal exposure to parasites.
- Easy to top dress onto a daily grain ration.
- Helps prevent parasite build-up on a daily basis which may lead to better nutrition, health, appearance and performance.
- Particularly useful where stocking density is high, pasture rotation is impossible, or exposure is continuous.
- 1 oz of STRONGID C per 250 lb of body weight.
- 0.5 oz of STRONGID C 2X per 250 lb of body weight.

STRONGID® T Suspension

(pyrantel pamoate)

USES:
For the removal and control of mature infections of large strongyles (*Strongylus vulgaris, S. edentatus, S. equinus*); pinworms (*Oxyuris equi*); large roundworms (*Parascaris equorum*); and small strongyles in horses and ponies.

SUPPLIED:

- Quart containing 15 doses for a 1,000 lb horse

KEY FACTS:

- Effective against mature infections of ascarids, large strongyles, small strongyles and pinworms.
- Caramel flavored and easy to dose at 6ml per 100 pounds body weight.
- May be administered by means of a stomach tube, dose syringe or by mixing into the feed.
- For maximum control of parasitism, it is recommended that foals (2 to 8 months of age) be dosed every four (4) weeks.
- To minimize the potential source of infection that the mare may pose to the foal, the mare should be treated one (1) month prior to the anticipated foaling date followed by retreatment 10 days to two (2) weeks after birth of foal.
- Horses and ponies over eight (8) months of age should be routinely dosed every six (6) weeks.

IMPORTANT SAFETY INFORMATION:
STRONGID T is not recommended for use in severely debilitated animals. Not for use in horses intended for human consumption. See full Prescribing Information, attached.

PARASITICIDES COMPARISON CHART

Chemical Class	Trade Name	Active	# OF TUBES		LARGE STRONGYLES	SMALL STRONGYLES	ROUNDWORMS	PINWORMS	HAIRWORMS	STOMACH WORMS	BOTS	ENCYSTED SMALL STRONGYLES	TAPEWORMS
Combined Macrocyclic Lactones	Quest Plus®	*moxidectin/praziquantel*	*1*		•	•	•	•	•	•	•	•	•
	Equimax™	*ivermectin/praziquantel*	*1*		•	•	•	•	•	•	•		•
	Zimectrin® Gold	*ivermectin/praziquantel*	*1*		•	•	•	•	•	•	•		•
Macrocyclic Lactones	Quest®	*moxidectin*	*1*		•	•	•	•	•	•	•	•	
	Eqvalan®	*ivermectin*	*1*		•	•	•	•	•	•	•		
	Zimectrin®	*ivermectin*	*1*		•	•	•	•	•	•	•		
Benzimidazoles	Anthelicide® EQ	*oxibendazole*	*1*		•	•	•	•					
	Panacur®/Safe-Guard®	*fenbendazole*	*1*		•	•	•	•					
	Panacur®/Safe-Guard®	*fenbendazole*	*10*		•	•	•	•				•	
	Panacur® Power Pac	*fenbendazole*	*5*		•	•	•	•				•	
	Safe-Guard® Power-Dose	*fenbendazole*	*5*		•	•	•	•				•	
Tetrahydropyrimidines	Strongid® C	*pyrantel tartrate*	*daily*		•	•	•	•					
	Strongid® C2X	*pyrantel tartrate*	*daily*		•	•	•	•					
	Strongid® Paste	*pyrantel pamoate*	*1*		•	•	•	•					
	Strongid® T	*pyrantel pamoate*	*suspension*		•	•	•	•					

SEDATIVES, ANESTHETICS & ANALGESICS

CARBOCAINE®-V Sterile Aqueous Solution
(*mepivacaine hydrochloride*)

USES:
Recommended for infiltration, nerve block, intra-articular and epidural anesthesia. It has also been found useful for topical anesthesia of the laryngeal mucosa prior to ventriculectomy.

SUPPLIED:
- 50 mL multiple dose vial

KEY FACTS:
- Dosage varies considerably depending on anesthetic technique, body area to be desensitized and the surgical procedure.
- The drug produces complete and effective anesthesia at dosages that are no more than half those need when procaine is used.
- For nerve block 3 to 15 mL is recommended in the diagnosis of lameness, firing, pain relief in osteoarthritis, and navicular disease .
- For epidural anesthesia 5 to 20 mL is recommended.
- For intra-articular anesthesia 10 to 15 mL is recommended in the diagnosis of bone and bog spavin, removal of fractural chips, and arthritus.
- For anesthesia it may be administered topically, by infiltration or by a combination of the two.

IMPORTANT SAFETY INFORMATION:
Do not use CARBOCAINE V in horses intended for human consumption. Avoid intravenous administration. See full Prescribing Information, attached.

DORMOSEDAN®
(*detomidine hydrochloride*)

USES:
Long lasting sedative for standing procedures such as minor surgeries, diagnostic procedures, wound treatment, transportation, management of colic, general examinations, etc.

SUPPLIED:
- 5 mL
- 20 mL

KEY FACTS:
- Effective standing sedative and analgesic in a single, non-narcotic dose.
- Dormosedan has a graded dose response relationship; higher dosing increases duration of sedation and analgesic effects but does not increase the depth of sedation.
- Can be administered intravenously (IV) or intramuscularly.
- Predictable and effective because of Alpha 2 selectivity; for veterinarians this means no mixing of product and guesswork dosing.
- Dormosedan additional dosing prolongs not deepens sedation.
- Offers a wide margin of safety.
- Proper label use is proven to reduce the cost of re-sedation, compared to other sedation processes.

IMPORTANT SAFETY INFORMATION:
Do not use DORMOSEDAN Sterile Solution in horses with pre-existing atrioventricular (AV) or sinoatrial (SA) block, with severe coronary insufficiency, cerebrovascular disease, respiratory disease, or chronic renal failure. Do not use in anesthetized or sedated horses, or in conditions of shock, severe debilitation or stress due to extreme heat, cold, fatigue or high altitude. Do not use in horses intended for human consumption. Handle dosing syringes with caution to avoid direct exposure to skin, eyes or mouth. See full Prescribing Information, attached.

DORMOSEDAN® Gel
(*detomidine hydrochloride*)

USES:

A convenient solution when horse owners need a mild, standing sedative prior to certain stressful situations or minor, (nonpainful) husbandry procedures..

SUPPLIED:
- Syringe

KEY FACTS:
- Convenient and safe for a wide variety of procedures.
- Prescribed by the veterinarian, administered by the horse owner.
- FDA approved for mild sedation and restraint of horses at least one year of age.
- Administered sublingually.
- The only standing sedative of its kind.
- Single-dose syringe and is easy for horse owners to administer themselves.
- The duration and level of sedation are dose dependent. At the recommended 40 mcg/kg dose, the onset of sedation was observed at approximately 40 minutes with a duration of sedation lasting between 90 to 180 minutes.

IMPORTANT SAFETY INFORMATION:
Do not use DORMOSEDAN Gel in horses with pre-existing atrioventricular (AV) or sinoatrial (SA) block, with severe coronary insufficiency, cerebrovascular disease, respiratory disease, or chronic renal failure. Do not use in anesthetized or sedated horses, or in conditions of shock, severe debilitation or stress due to extreme heat, cold, fatigue or high altitude. Do not use in horses intended for human consumption. Handle dosing syringes with caution to avoid direct exposure to skin, eyes or mouth. See full Prescribing Information, attached.

FLUNIXAMINE® Injectable Solution
(*flunixin meglumine*)

USES:

For the alleviation of inflammation and pain associated with musculoskeletal disorders. Also recommended for the alleviation of visceral pain associated with colic.

SUPPLIED:
- 100 mL
- 250 mL vial

KEY FACTS:
- Administer 0.5 mg per pound of body weight once daily for alleviation of pain associated with lameness.
- Treatment may be given by intravenous or intramuscular injection and repeated for up to 5 days.
- Onset of activity is within 2 hours. Peak response occurs between 12 and 16 hours, and duration of activity is 24-36 hours.

IMPORTANT SAFETY INFORMATION:
Do not use FLUNIXAMINE in horses intended for human consumption. NSAIDS are known to have potential effects on both parturition and estrus cycle. Drug compatibility should be monitored closely in patients requiring adjunctive therapy. See full Prescribing Information, attached.

KETOFEN® Sterile Solution
(*ketoprofen*)

USES:
Non-narcotic, non-steroidal anti-inflammatory agent recommended for the alleviation of inflammation and pain associated with muscoskeletal disorders in horses.

SUPPLIED:
- 50 mL
- 100 mL

KEY FACTS:
- Recommended dosage is 1 mg/lb of body weight repeated once daily, treatment is administered by intravenous injection and may be repeated for up to five days.

IMPORTANT SAFETY INFORMATION:
KETOFEN should not be used in breeding horses. Do not use in horses intended for human consumption. See full Prescribing Information, attached.

TORBUGESIC®
Veterinary Injection 10 mg/mL
(*butorphanol tartrate*)

USES:
For the relief of pain associated with colic in adult horses and yearlings. Clinical studies have shown that TORBUGESIC alleviates abdominal pain associated with torsion, impaction, intussusception, spasmodic and tympanic colic and postpartum pain.

SUPPLIED:
- 10 mL
- 50 mL

KEY FACTS:
- Recommended dosage in horses is .1 mg of butorphanol per kg of body weight by intravenous injection, this is equivalent to 5 mL of TORBUGESIC for each 1,000 lbs of body weight.
- Common side effects in clinical trials was slight ataxia which lasted 3 to 10 minutes.

IMPORTANT SAFETY INFORMATION:
Use TORBUGESIC with caution with other sedative or analgesic drugs as these are likely to produce additive effects. Do not use in breeding horses, weanlings, or foals. Do not use in horses intended for human consumption. See full Prescribing Information, attached.

CLOVITE® Conditioner

USES:
Vitamin supplement containing vitamin A, vitamin D and vitamin B12.

SUPPLIED:
- 5 lb pail
- 25 lb pail

KEY FACTS:
- Suggested dosage for young foals and weanlings is 1 to 2 tablespoons daily; for broodmares 2 tbsp daily; for ponies 1 tbsp daily; for colts, stallions and horses in training dosage is 1 tbsp per 400 lbs of body weight.

LIXOTINIC® LIQUID

USES:
Vitamin-iron and mineral supplement.

SUPPLIED:
- Gallon

KEY FACTS:
- Recommended daily dosage for horses is 1-2 oz.

LUTALYSE® Injection
(*dinoprost injection*)

USES:
Indicated for the control of the timing of estrus in estrous cycling mares and clinically anestrous mares that have a corpus luteum.

SUPPLIED:
- 30 mL
- 100 mL

KEY FACTS:
- Mares treated with LUTALYSE during diestrus will return to estrus within 2 to 4 days in most cases and ovulate 8 to 12 days after treatment.
- In anestrus mares treatment usually results in regression of the corpus luteum followed by estrus/ovulation.
- In one study with mares in clinical anestrus for an average of 58 days and treated during the breeding season, behavioral estrus was detected in 81 percent at an average time of 3.7 days after injection with 5 mg LUTALYSE; ovulation occurred an average of 7.0 days after treatment.

IMPORTANT SAFETY INFORMATION:

Women of childbearing age and persons with respiratory problems should exercise extreme caution when handling LUTALYSE. LUTALYSE is readily absorbed through the skin and may cause abortion and/or bronchiospasms, therefore spillage on the skin should be washed off immediately with soap and water. Pregnancy status should be determined prior to treatment, as abortion and parturition have been reported. Aseptic technique should be used to reduce the possibility of post-injection clostridial infections. Do not use in horses intended for human consumption. See full Prescribing Information, attached.

KOPERTOX®

USES:
Aid in the treatment of thrush in horses and ponies due to organisms susceptible to copper naphthenate.

SUPPLIED:
- 8 oz
- 16 oz

KEY FACTS:
- Apply daily to affected hoofs with a narrow paint brush until fully healed.

IMPORTANT SAFETY INFORMATION:
Do not use KOPERTOX in horses intended for human consumption.

PEOPLEFIRST™

Human Capital Solutions

The industry's first comprehensive human capital and business management solutions service

Since 2009, PeopleFirst™ Human Capital Solutions has provided owners, managers, supervisors and employees of agricultural operations, veterinary clinics and ranch and farm retail with comprehensive and strategic services to address leadership development, employee training and business objectives and strategies. Find more information on helping build a more productive and profitable business and operation at GrowPeopleFirst.com.

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- **Strategic Planning** — Custom and standard consulting help create a strategic plan for your business by identifying your three-year objectives, aligning your team around your strategic intent and creating an action plan to accomplish your goals.
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- **Marketing Planning** — We'll work with your staff to develop plans to help your business grow.
- **Customized services** — An array of consultative services can be customized to meet your business needs, client surveys, scenario planning, action planning.

[1] ProfitSolver is the registered trademark of Fee Technology, Inc.

PRESCRIBING INFORMATION

NADA 127-892, Approved by FDA

FORT DODGE®

Amiglyde-V®

AMIKACIN SULFATE

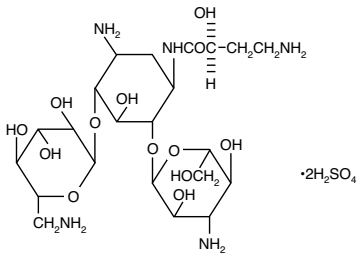
Veterinary Solution
Equivalent to 250 mg amikacin per mL

CAUTION

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

DESCRIPTION

Amikacin sulfate is a semi-synthetic aminoglycoside antibiotic derived from kanamycin. It is $C_{22}H_{43}N_5O_{13}•2H_2SO_4$, D-streptamine, 0-3-amino-3-deoxy-α-D-glucopyranosyl-(1→6)-0-[6-amino-6-deoxy-α-D-glucopyranosyl-(1→4)]-N[1]-(4-amino-2-hydroxy-1-oxobutyl)-2-deoxy-, (S)-, sulfate (1:2) (salt).



The dosage form supplied is a sterile, colorless to light straw-colored solution. The solution contains, in addition to amikacin sulfate, USP, 2.5% sodium citrate, USP with pH adjusted to 4.5 with sulfuric acid and 0.66% sodium bisulfite added. The multi-dose 12 gram–48 mL vial contains 0.01% benzethonium chloride, USP as a preservative.

ACTION

Antibacterial Activity

The effectiveness of AMIGLYDE-V (amikacin sulfate) in infections caused by *Escherichia coli, Pseudomonas* sp and *Klebsiella* sp has been demonstrated clinically in the horse. In addition, the following microorganisms have been shown to be susceptible to amikacin *in vitro*[1], although the clinical significance of this action has not been demonstrated in animals:

- *Enterobacter* sp
- *Proteus mirabilis*
- *Proteus* sp (indole positive)
- *Serratia marcescens*
- *Salmonella* sp
- *Shigella* sp
- *Providencia* sp
- *Citrobacter freundii*
- *Listeria monocytogenes*
- *Staphylococcus aureus* (both penicillin-resistant and penicillin-sensitive)

The aminoglycoside antibiotics in general have limited activity against gram-positive pathogens, although *Staphylococcus aureus* and *Listeria monocytogenes* are susceptible to amikacin as noted above.

Amikacin has been shown to be effective against many aminoglycoside-resistant strains due to its ability to resist degradation by aminoglycoside inactivating enzymes known to affect gentamicin, tobramycin and kanamycin[2].

CLINICAL PHARMACOLOGY

Endometrial Tissue Concentrations

Comparisons of amikacin activity in endometrial biopsy tissue following intrauterine infusion with that following intramuscular injection of AMIGLYDE-V in mares demonstrate superior endometrial tissue concentrations when the drug is administered by the intrauterine route.

Intrauterine infusion of 2 grams AMIGLYDE-V daily for three consecutive days in mares results in peak concentrations typically exceeding 40 mcg/g of endometrial biopsy tissue within one hour after infusion. Twenty-four hours after each treatment amikacin activity is still detectable at concentrations averaging 2 to 4 mcg/g. However, the drug is not appreciably absorbed systemically following intrauterine infusion. Endometrial tissue concentrations following intramuscular injection are roughly parallel, but are typically somewhat lower than corresponding serum concentrations of amikacin.

Safety

AMIGLYDE-V is non-irritating to equine endometrial tissue when infused into the uterus as directed (see ADMINISTRATION AND DOSAGE). In laboratory animals as well as equine studies, the drug was generally found not to be irritating when injected intravenously, subcutaneously or intramuscularly.

Although amikacin, like other aminoglycosides, is potentially nephrotoxic, ototoxic and neurotoxic, parenteral (intravenous) administration of AMIGLYDE-V (amikacin sulfate) twice daily at dosages of up to 10 mg/lb for 15 consecutive days in horses resulted in no clinical, laboratory or histopathologic evidence of toxicity.

Intrauterine infusion of 2 grams of AMIGLYDE-V 8 hours prior to breeding by natural service did not impair fertility in mares. Therefore, mares should not be bred for at least 8 hours following uterine infusion.

INDICATIONS

AMIGLYDE-V is indicated for the treatment of uterine infections (endometritis, metritis and pyometra) in mares, when caused by susceptible organisms including *Escherichia coli, Pseudomonas* sp and *Klebsiella* sp. The use of AMIGLYDE-V in eliminating infections caused by the above organisms has been shown clinically to improve fertility in infected mares.

While nearly all strains of *Escherichia coli, Pseudomonas* sp and *Klebsiella* sp, including those that are resistant to gentamicin, kanamycin or other aminoglycosides, are susceptible to amikacin at levels achieved following treatment, it is recommended that the invading organism be cultured and its susceptibility demonstrated as a guide to therapy. Amikacin susceptibility discs, 30 mcg, should be used for determining *in vitro* susceptibility.

ADMINISTRATION AND DOSAGE

For treatment of uterine infections in mares, 2 grams (8 mL) of AMIGLYDE-V, mixed with 200 mL 0.9% Sodium chloride injection, USP and aseptically infused into the uterus daily for three consecutive days, has been found to be the most efficacious dosage.

CONTRAINDICATIONS

There are no known contraindications for the use of AMIGLYDE-V in horses other than a history of hypersensitivity to amikacin.

PRECAUTIONS

Although AMIGLYDE-V is not absorbed to an appreciable extent following intrauterine infusion, concurrent use of other aminoglycosides should be avoided because of the potential for additive effects.

ADVERSE REACTIONS

No adverse reactions or other side effects have been reported.

WARNING

Do not use in horses intended for human consumption.

In vitro studies have demonstrated that when sperm are exposed to the preservative which is present in the 48 mL vials (250 mg/mL) sperm viability is impaired.

SUPPLY

AMIGLYDE-V (amikacin sulfate) Veterinary Solution is supplied as a colorless solution which is stable when stored at or below 25°C (77°F). At times the solution may become pale yellow in color. This does not indicate a decrease in potency.

NDC 0856-2332-20 – 48 mL vial, 250 mg/mL

Store at or below 25°C (77°F).

REFERENCES

1. Price, K.E., *et al*: Microbiological Evaluation of BB-K8, a New Semisynthetic Aminoglycoside. *J Antibiot* 25: 709–731, 1972.
2. Davies, J., Courvalin, P.: Mechanisms of Resistance to Aminoglycosides. *Am J Med* 62: 868–872, 1977.

Fort Dodge Animal Health
Fort Dodge, Iowa 50501

11800 Revised June 2010 4120JA&P
GEQ14004

Carbocaine®-V

(2% mepivacaine hydrochloride, USP)
Sterile Aqueous Solution

Local Anesthetic with Rapid and Prolonged Effect for Use in Horses

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
Mepivacaine hydrochloride, 1-methyl-2', 6'-pipecoloxylidide monohydrochloride, is a white, crystalline, odorless powder, readily soluble in water, and very stable in aqueous solution. It is available as a 2% sterile aqueous solution containing sodium chloride (for isotonicity) and 0.1% methylparaben (as preservative). The pH is adjusted with sodium hydroxide or hydrochloric acid.

CLINICAL PHARMACOLOGY
Mepivacaine hydrochloride is a potent local anesthetic whose effectiveness and safety have been well established in human medicine and dentistry. Laboratory and clinical studies in animals have confirmed its value in veterinary medicine. Its anesthetic activity is two to two and one half times that of procaine, and it is equal to or better than that of lidocaine. The compound has shown excellent tissue compatibility in laboratory animals and in horses. Moderate transient edema at the site of injection may occur in rare instances.

CARBOCAINE-V Sterile Aqueous Solution produces rapid and marked local anesthesia lasting for several hours. This enables the veterinarian to proceed with intended manipulations without delay and to complete the work under desensitization which is adequate even for prolonged operations. The innate vasoconstrictive activity of CARBOCAINE-V Sterile Aqueous Solution may be enhanced by the addition of epinephrine at 1:100,000. The addition should be carried out aseptically for current use and any unused portion should be discarded.

INDICATIONS
CARBOCAINE-V Sterile Aqueous Solution is recommended for infiltration, nerve block, intra-articular and epidural anesthesia for horses. It has also been found useful for topical anesthesia of the laryngeal mucosa prior to ventriculectomy. As with other anesthetics, the dosage varies considerably depending on the anesthetic technique, body area to be desensitized and the surgical procedure.

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

PRECAUTIONS
When administered by a skilled person, CARBOCAINE-V Sterile Aqueous Solution may be employed safely for local infiltration, for common nerve blocking procedures, and for intra-articular and epidural anesthesia.

The following precautions, which are observed with respect to all local anesthetics, also apply to this anesthetic. (1) Injections should always be made aseptically and with frequent aspirations. If blood is aspirated, the needle should be relocated and the injections continued cautiously. (2) When used for epidural anesthesia, care should be taken to avoid injection into the subarachnoid space. The skin should be shaved and sterilized, and the needles used must be sharp and of the proper length. (3) The depth of anesthesia should be checked by pricking the area before manipulations are begun.

DOSAGE AND ADMINISTRATION
Pharmacological studies in various species of animals, including horses, have shown that the drug produces complete and effective anesthesia at dosages that are no more than half those needed when procaine is used.

The following dosages have generally proved satisfactory in the horse and are therefore suggested as a guide:

For nerve block
(diagnosis of lameness, firing, pain relief in osteoarthritis, navicular disease)—3 to 15 mL

For epidural anesthesia
(animal standing)—5 to 20 mL

For intra-articular anesthesia
(removal of fracture chips, bone and bog spavin, arthritis)—10 to 15 mL

For infiltration
(alone or in combination with nerve block or intra-articular anesthesia) —as required

For anesthesia of the laryngeal mucosa prior to ventriculectomy
CARBOCAINE-V Sterile Aqueous Solution may be administered topically or by infiltration or by a combination of the two. For topical application, a total of 25 to 40 mL applied by spray (3 mL/application) is usually adequate. For infiltration, 20 to 50 mL will suffice.

HOW SUPPLIED
CARBOCAINE-V is available as 50 mL Multiple-Dose Vials.

Each mL contains 20 mg mepivacaine hydrochloride, 1 mg methylparaben as preservative, and sodium chloride for isotonicity. The pH was adjusted with sodium hydroxide or hydrochloric acid.

Store at controlled room temperature 20° to 25° C (68° to 77° F). Contents should be used within 90 days after the first dose is removed.

NADA #100-703, Approved by FDA

zoetis Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Made in Brazil

Revised: January 2013

054614ZOA&P
GEQ14005

Depo-Medrol®

methylprednisolone acetate sterile aqueous suspension

20 mg per mL and 40 mg per mL

For Use in Animals Only

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

These preparations are recommended for intramuscular and intrasynovial injection in horses and dogs, and intramuscular injection in cats. DEPO-MEDROL Sterile Aqueous Suspension is available in two concentrations, 20 mg per mL and 40 mg per mL. Each mL of these preparations contains:

	20 mg	40 mg
Methylprednisolone acetate	20 mg	40 mg
Polyethylene glycol 3350	29.6 mg	29 mg
Sodium chloride	8.9 mg	8.7 mg
Myristyl-gamma-picolinium chloride added as preservative	0.198 mg	0.195 mg

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid.

CLINICAL PHARMACOLOGY

Metabolic and Hormonal Effects

Methylprednisolone, an anti-inflammatory steroid synthesized and developed in the Research Laboratories of The Upjohn Company, is the 6-methyl derivative of prednisolone. Exceeding prednisolone in anti-inflammatory potency and having even less tendency than prednisolone to induce sodium and water retention, methylprednisolone offers the advantage over older corticosteroids of affording equally satisfactory anti-inflammatory effect with the use of lower doses and with an enhanced split between anti-inflammatory and mineralocorticoid activities. Estimates of the relative potencies of methylprednisolone and prednisolone range from 1.13 to 2.1, with an average of 1.5. In anti-inflammatory activity, as measured by the granuloma pouch assay, methylprednisolone is twice as active as prednisolone. In mineralocorticoid activity (ie, the capacity to induce retention of sodium and water in the adrenalectomized rat) methylprednisolone is slightly less active than prednisolone. The duration of plasma steroid levels following rapid intravenous injection in intact dogs is appreciably longer for methylprednisolone than for prednisolone, the respective "half-life" value for the two steroids being 80.9 ± 7.5 minutes for methylprednisolone and 71.3 ±1.7 minutes for prednisolone.

While the effect of parenterally administered DEPO-MEDROL is prolonged, it has the same metabolic and anti-inflammatory actions as orally administered methylprednisolone acetate.

INDICATIONS AND USAGE

Musculoskeletal Conditions. As with other adrenal steroids, DEPO-MEDROL Sterile Aqueous Suspension has been found useful in alleviating the pain and lameness associated with acute localized arthritic conditions and generalized arthritic conditions. It has been used successfully to treat rheumatoid arthritis, traumatic arthritis, osteoarthritis, periostitis, tendinitis, synovitis, tenosynovitis, bursitis, and myositis of horses; traumatic arthritis, osteoarthritis, and generalized arthritic conditions of dogs. Remission of musculoskeletal conditions may be permanent, or symptoms may recur, depending on the cause and extent of structural degeneration.

Allergic Conditions. This preparation is especially beneficial in relieving pruritus and inflammation of allergic dermatitis, acute moist dermatitis, dry eczema, urticaria, bronchial asthma, pollen sensitivities and otitis externa in dogs; allergic dermatitis and moist and dry eczema in cats. Onset of relief may begin within a few hours to a few days following injection and may persist for a few days to six weeks. Symptoms may be expected to recur if the cause of the allergic reaction is still present, in which case retreatment may be indicated. In treating acute hypersensitivity reactions, such as anaphylactic shock, intravenous SOLU-DELTA-CORTEF® Sterile Powder containing prednisolone sodium succinate, as well as other appropriate treatments, should be used.

Overwhelming Infections with Severe Toxicity. In dogs and cats moribund from overwhelmingly severe infections for which antibacterial therapy is available (eg, critical pneumonia, pyometritis), DEPO-MEDROL may be lifesaving, acting to inhibit the inflammatory reaction, which itself may be lethal; preventing vascular collapse and preserving the integrity of the blood vessels; modifying the patient's reaction to drugs; and preventing or reducing the exudative reaction which often complicates certain infections. As supportive therapy, it improves the general attitude of the animal being treated. All necessary procedures for the establishment of a bacterial diagnosis should be carried out whenever possible before institution of therapy. Corticosteroid therapy in the presence of infection should be administered for the shortest possible time compatible with maintenance of an adequate response, and antibacterial therapy should be continued for at least three days after the hormone has been withdrawn. Combined hormone and antibacterial therapy does not obviate the need for indicated surgical treatment.

Other Conditions. In certain conditions where it is desired to reduce inflammation, vascularization, fibroblastic infiltration, and scar tissue, the use of DEPO-MEDROL should be considered. Snakebite of dogs also is an indication for the use of this suspension because of its anti-toxemic, anti-shock, and anti-inflammatory activity. It is particularly effective in reducing swelling and preventing sloughing. Its employment in the treatment of such conditions is recommended as a supportive measure to standard procedures and time-honored treatments and will give comfort to the animal and hasten complete recovery.

CONTRAINDICATIONS

Systemic therapy with methylprednisolone acetate, as with other corticoids, is contraindicated in animals with arrested tuberculosis, peptic ulcer, and Cushing's syndrome. The presence of active tuberculosis, diabetes mellitus, osteoporosis, renal insufficiency, predisposition to thrombophlebitis, hypertension, or congestive heart failure necessitates carefully controlled use of corticosteroids. Intrasynovial, intratendinous, or other injections of corticosteroids for local effect are contraindicated in the presence of acute infectious conditions. Exacerbation of pain, further loss of joint motion, with fever and malaise following injection may indicate that the condition has become septic. Appropriate antibacterial therapy should be instituted immediately.

WARNING

Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta and metritis.

Additionally, corticosteroids administered to dogs, rabbits, and rodents during pregnancy have resulted in cleft palate in offspring. Corticosteroids administered to dogs during pregnancy have also resulted in other congenital anomalies, including deformed forelegs, phocomelia, and anasarca.

Not for human use. Do not use in horses intended for human consumption.

PRECAUTIONS

DEPO-MEDROL Sterile Aqueous Suspension exerts an inhibitory influence on the mechanisms and the tissue changes associated with inflammation. Vascular permeability is decreased, exudation diminished, and migration of the inflammatory cells markedly inhibited. In addition, systemic manifestations such as fever and signs of toxemia may also be suppressed. While certain aspects of this alteration of the inflammatory reaction may be beneficial, the suppression of inflammation may mask the signs of infection and tend to facilitate spread of microorganisms. Hence, all patients receiving this drug should be watched for evidence of intercurrent infection. Should infection occur, it must be brought under control by the use of appropriate antibacterial measures, or administration of this preparation should be discontinued. However, in infections characterized by overwhelming toxicity, methylprednisolone acetate therapy in conjunction with appropriate antibacterial therapy is effective in reducing mortality and morbidity. Without conjoint use of an antibiotic to which the invader-organism is sensitive, injudicious use of the adrenal hormones in animals with infections can be hazardous. As with other corticoids, continued or prolonged use is discouraged.

While no sodium retention or potassium depletion has been observed at the doses recommended, animals receiving methylprednisolone acetate, as with all corticoids, should be under close observation for possible untoward effects. If symptoms of hypopotassemia (hypokalemia) should occur, corticoid therapy should be discontinued and potassium chloride administered by continuous intravenous drip.

Since this drug lacks significant mineralocorticoid activity in usual therapeutic doses, it is not likely to afford adequate support in states of acute adrenocortical insufficiency. For treatment of the latter, the parent adrenocortical steroids, hydrocortisone or cortisone, should be used.

DOSAGE AND ADMINISTRATION

INTRAMUSCULAR

Following intramuscular injection of methylprednisolone acetate, a prolonged systemic effect results. The dose varies with the size of the animal patient, the severity of the condition under treatment, and the animal's response to therapy.

Dogs and Cats. The average intramuscular dose for dogs is 20 mg. In accordance with the size of the dog and severity of the condition under treatment, the dose may range from 2 mg in miniature breeds to 40 mg in medium breeds, and even as high as 120 mg in extremely large breeds or dogs with severe involvement.

The average intramuscular dose for cats is 10 mg with a range up to 20 mg.

Injections may be made at weekly intervals or in accordance with the severity of the condition and clinical response.

Horses. The usual intramuscular dose for horses is 200 mg repeated as necessary.

For maintenance therapy in chronic conditions, initial doses should be reduced gradually until the smallest effective (ie, individualized) dose is established. MEDROL® Tablets containing methylprednisolone may also be used for maintenance in dogs and cats, administered according to the recommended dose.

When treatment is to be withdrawn after prolonged and intensive therapy, the dose should be reduced gradually.

If signs of stress are associated with the condition being treated, the dose should be increased. If a rapid hormonal effect of maximum intensity is required, as in anaphylactic shock, the intravenous administration of highly soluble SOLU-DELTA-CORTEF® Sterile Powder containing prednisolone sodium succinate is indicated.

INTRASYNOVIAL

Methylprednisolone acetate, a slightly soluble ester of methylprednisolone, is capable of producing a more prolonged local anti-inflammatory effect than equimolar doses of hydrocortisone acetate. Following intrasynovial injection, relief from pain may be experienced within 12 to 24 hours. The duration of relief varies, but averages three to four weeks, with a range of one to five or more weeks. Injections of methylprednisolone acetate have been well tolerated. *Intrasynovial (intra-articular) injections may occasionally result in an increased localized inflammatory response.*

Intrasynovial injection is recommended as an adjuvant to general therapeutic measures to effect suppression of inflammation in one or a few peripheral structures when (1) the disease is limited to one or a few peripheral structures; (2) the disease is widespread with one or a few peripheral structures actively inflamed; (3) systemic therapy with other corticoids or corticotropin controls all but a few of the more actively involved structures; (4) systemic therapy with cortisone, hydrocortisone, or corticotropin is contraindicated; (5) joints show early but actively progressing deformity (to enhance the effect of physiotherapy and corrective procedures); and (6) surgical or other orthopedic corrective measures are to be or have been done.

The action of DEPO-MEDROL Sterile Aqueous Suspension injected intrasynovially appears to be well localized since significant metabolic effects characteristic of systemic administration of adrenal steroids have not been observed. In a few instances mild and transient improvement of structures other than those injected have been reported. No other systemic effects have been noted. However, it is possible that mild systemic effects may occur following intrasynovial administration, and this possibility is greater the larger the number of structures injected and the higher the total dose employed.

Procedure for Intrasynovial Injection. The anatomy of the area to be injected should be reviewed in order to assure that the suspension is properly placed and to determine that large blood vessels or nerves are avoided. The injection site is located where the synovial cavity is most superficial. The area is prepared for aseptic injection of the medicament by the removal of hair and cleansing of the skin with alcohol or Mercresin® tincture. A sterile 18- to 21-gauge needle for horses, 20- to 22-gauge needle for dogs, on a dry syringe is quickly inserted into the synovial space and a small amount of synovial fluid withdrawn. If there is an excess of synovia and more than 1 mL of suspension is to be injected, it is well to aspirate a volume of fluid comparable to that which is to be injected. With the needle in place, the aspirating syringe is removed and replaced by a second syringe containing the proper amount of suspension which is then injected. In some animals a transient pain is elicited immediately upon injection into the affected cavity. This pain varies from mild to severe and may last for a few minutes up to 12 hours. After injection, the structure may be moved gently a few times to aid mixing of the synovial fluid and the suspension. The site may be covered with a small sterile dressing.

Areas not suitable for injection are those that are anatomically inaccessible such as spinal joints and those like the sacroiliac joints, which are devoid of synovial space. Treatment failures are most frequently the result of failure to enter the synovial space. If failures occur when injections into the synovial spaces are certain, as determined by aspiration of fluid, repeated injections are usually futile. Local therapy does not alter the underlying disease process, and whenever possible comprehensive therapy including physiotherapy and orthopedic correction should be employed.

The single intrasynovial dose depends on the size of the part, which corresponds to the size of the animal. The interval between repeated injections depends on the duration of relief obtained.

Horses. The average initial dose for a large synovial space in horses is 120 mg with a range from 40 to 240 mg. Smaller spaces will require a correspondingly lesser dose.

Dogs. The average initial dose for a large synovial space in dogs is 20 mg. Smaller spaces will require a correspondingly lesser dose.

Store at controlled room temperature 20° to 25° C (68° to 77° F).

Contents should be used within 12 weeks after the first dose is removed.

HOW SUPPLIED

DEPO-MEDROL Sterile Aqueous Suspension, 20 mg/mL is available in 20 mL vials, and 40 mg/mL is available in 5 mL vials.

NADA 12-204, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: March 2013

PAA034682A&P
GEQ14006

NADA 32-168, Approved by FDA

Domoso®

(DIMETHYL SULFOXIDE)

Solution

90% Dimethyl Sulfoxide — Medical Grade

For Animal Use Only

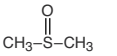
CAUTION

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

GENERAL

Dimethyl sulfoxide (DMSO), an oxidation product of dimethyl sulfide, is an exceptional solvent possessing a number of commercial uses.

DMSO is the lowest member of the group of alkyl sulfoxides with a general formula of RSOR. Its structural formula is:



It freely mixes with water with the evolution of heat and lowers the freezing point of aqueous solutions. It is soluble in many other compounds including ethanol, acetone, diethyl ether, glycerin, toluene, benzene and chloroform. DMSO is a solvent for many aromatic and unsaturated hydrocarbons as well as inorganic salts and nitrogen-containing compounds. DMSO has a high dielectric constant due to the polarity of the sulfur-oxygen bond. Its basicity is slightly greater than water due to enhanced electron density at the oxygen atom. It forms crystalline salts with strong protic acids and coordinates with Lewis acids. It modifies hydrogen bonding.

DMSO is a hygroscopic stable organic liquid essentially odorless and water white in color. Other physical characteristics include:

Molecular weight	78.13
Melting point	18.45°C
Boiling point	189°C

Each mL of DOMOSO (dimethyl sulfoxide) Solution contains 90% dimethyl sulfoxide and 10% water.

METABOLISM

Dimethyl sulfoxide when administered topically or orally is rapidly absorbed and distributed in living material.

Using S^{35}-labeled DMSO (1) the maximal blood concentration after cutaneous application was achieved in approximately 10 minutes in rats and less than 1 hour in dogs. In rats and dogs the substance did not accumulate in the organs but the concentration in the treated skin and underlying muscle was increased. The main route of excretion is via the urine partially dependent on the species and route of application. In rats there was no significant difference in the elimination half-time of 6 to 8 hours after intravenous or cutaneous administration; in the dog, the elimination half-time was 1.5 to 2 days after intravenous or oral administration. In the dog, however, after cutaneous application about 55% of the administered material was eliminated within 14 days. The radioactivity eliminated via the lungs, and identified as dimethyl sulfide, was about 3% of the administered dose.

In another S^{35}-labeled study (2) with DMSO, following intravenous or cutaneous administration, the only metabolite detectable in the urine of humans and rats, was dimethyl sulfone ($DMSO_2$).

In another S^{35}-labeled rat study (3), DMSO was administered by the oral, intraperitoneal and dermal routes at a level of 500 mg/kg body weight. Plasma radioactivity after an intraperitoneal dose was highest at 0.5 hours, the half-time being 5 to 6 hours. When applied dermally, levels remained constant for 6 hours. Radioactivity in the urine collected for 22 hours represented 60% to 85% of the intraperitoneal and oral doses and 36% to 50% of the dermal dose. The skin contained 3% to 7% of the labeled dosage in all cases.

A peculiar sweetish odor was noted in the exhaled breath of cats treated with dimethyl sulfoxide (4). The compound responsible for this was identified as dimethyl sulfide. The same odor has been noted in all species treated with the compound.

In rabbits, dimethyl sulfone was detected in the urine following treatment with DMSO (5).

It has been shown that dimethyl sulfone is a constituent of normal cow's milk (6).

PHARMACOLOGY

The original biological applications of DMSO were primarily confined to its use in preserving various tissues and cellular elements including blood (7), blood cells and bone marrow (8), leukocytes (9), lymphocytes (10), platelets (11), spermatozoa (12, 13, 14), corneal grafts (15, 16), skin (17), tissue culture cells (18, 19, 20, 21) and trypanosomes (22), by freezing techniques. DMSO has also been investigated as a radioprotective agent (23, 24).

In early studies with plants it was claimed that DMSO exerted a profound effect on the biologic membrane, altering their natural selectivity and enhancing the penetration of antibiotics and fungicides (25).

In one of the first studies reported in animals, various drugs were added to 15% solution of DMSO instilled into the urinary bladder of intact, anesthetized dogs through which an enhancement of absorption was demonstrated (25). Utilizing a similar technique the transport of physiologically active insulin across the intact bladder mucosa was demonstrated. Results were judged on a decrease in blood sugar levels over that of controls (26).

In vivo and in vitro methods demonstrated that DMSO enhanced human percutaneous absorp-tion of various compounds including steroids, vasoconstrictors, antiperspirants and dyes, as well as an anthelmintic (thiabendazole) and a skin antiseptic (hexachlorophene) (27, 28, 29, 60, 61, 62). Enhancement was not due to irreversible damage to the stratum corneum (28).

DMSO has been stated to increase the penetration of low molecular weight allergens such as penicillin G but not large molecular weight allergens such as house dust (30).

The rate of passage of tritiated water in the presence of DMSO on the epidermis of the hairless mouse was measured in vitro. DMSO did not appear to promote the passage of water by its presence, but when concentrated solutions (60% to 100%) were used, permanent changes were produced in the rate of passage of water. It was concluded that the concentration of DMSO used seemed more significant than the time of exposure in establishing the effect on the water barrier (31).

When the tails of mice were immersed in a 5% solution of various psychoactive drugs in DMSO, the drugs appeared to exert their usual pharmacological effects, indicating drug penetration as judged by the behavioral effects observed in the experimental subjects. Other solvents, including water, also appeared to permit some drug penetration in this study (32).

Using ten quaternary ammonium salts as test compounds and either water or DMSO as solvents, the oral LD_{50} values were determined in rats and mice. Toxicity changes were obtained in some instances by 50% DMSO and more changes were observed in rats than mice although the results in the two species were not always parallel. When toxicity was altered by DMSO it increased in all instances except one (33).

When administered systemically in another study, however, various drugs dissolved in DMSO did not differ significantly in their lethality or cellular penetration as compared to the same drug administered in saline (34).

When evaluated as a solvent for biologic screening tests, low doses of hormones in DMSO stimulated a response similar to that of the hormone in the control vehicle. Higher doses of hormone, however, failed to give the expected response, suggesting a partition coefficient in favor of the solvent (35). DMSO was also shown to carry physostigmine and phenylbutazone through the skin of the rat (36).

The absorption of phenylbutazone dissolved in an aqueous solution of DMSO was impaired when administered orally to the rabbit. Absorption of the same drug was not improved using the subcutaneous route simultaneously with DMSO.

However, phenylbutazone could be detected in the rabbit's blood for several hours when an ointment containing DMSO and 5% phenylbutazone was applied to the skin. When the DMSO content of the ointment was increased, the phenylbutazone levels increased. An increase of phenylbutazone in the muscle tissues underlying the site of application over a control ointment containing phenylbutazone without DMSO could be demonstrated in rats (37).

When 1% fluorescein was injected intradermally at several different concentrations of DMSO in man, the dermal clearance of this substance was considerably decreased as compared to saline control solutions. This was believed due to reduced diffusion through the dermis (29).

The addition of 50% DMSO to solutions containing 1% old tuberculin (OT) abolished positive patch test reactions in tuberculin sensitive human subjects, and 50% DMSO also prevented the dermatitis produced by 1% trypsin. A possible explanation of these phenomena is the formation of complexes with proteins causing their denaturation (28). DMSO has also been reported to alter the Schwartzman reaction (30). It is believed that, similar to chelating agents, DMSO can form complexes with certain metallic salts (25, 38).

Based on the above evidence as well as gas chromatographic and radio-isotope studies it is established that DMSO can effectively penetrate the stratum corneum of the epidermis and enter the systemic circulation. DMSO also has the ability to allow some substances ordinarily unable to penetrate the skin barrier to be carried through it. The mechanism of penetrant action is not yet understood although some theories have been advanced as explanations (25, 38).

DMSO has been claimed to show anti-inflammatory activity against the baker's yeast granuloma in guinea pigs, and when administered orally, against the carrageenin granuloma in rats. The dose needed to achieve these effects is quite high, requiring 1 to 5 g/kg body weight (39).

In a number of other studies in experimental animals (32, 36, 40) where DMSO has been chiefly administered orally or by injection, no anti-inflammatory or analgesic activity could be established.

Following experimental hypersensitization to human gamma globulin in the horse, antigen challenge resulted in massive erythema, necrosis and slough. This reaction could be markedly reduced by the hourly application of undiluted DMSO to the reaction site, after challenge (30).

In the human, DMSO did not exert any beneficial effects on experimentally induced thermal burns, contact dermatitis or ultraviolet burns. It was noted in this study that the burns were of a non-infected nature (28, 29).

In experimentally induced thermal edema of the legs of rabbits, the leg volume was the same for DMSO treated and untreated groups at 3 and 24 hours, but less at 6 hours for the treated group. The DMSO in this experiment was applied at a site distant to the injury (30).

Sedative effects have been noted in dogs when 90% DMSO was administered at 10 mg/kg dosage levels and mild reserpine-like actions of the drug have also been described in mice (30).

DMSO, by itself, at concentrations of 100%, 66% and 33% has been shown to produce neurolysis following perineural injection in the rat's sciatic nerve (41).

The conflicting reports cited above for the anti-inflammatory and analgesic properties of DMSO are partially dependent upon the experimental models and methods used to measure these parameters. DMSO fails to show analgesic or anti-inflammatory activity in certain of these situations, particularly when used by the systemic route or when administered topically preceded by an irritant substance. In clinical studies in the horse, it was noted that when iodine, liniments or other strong irritants were present on the skin from previous therapy and DMSO applied, a temporary but marked local reaction would occur. This was due to the ability of DMSO to carry these substances into the underlying skin tissues where their irritant actions could be displayed. When DMSO was used clinically, it was applied topically to the involved area, while in the experimental situation this procedure was seldom used. In clinical situations, a marked reduction of pain and edema has often been noted following topical application. The mechanism of action, although not understood, may be partially related to the heat of dissolution of DMSO. It has been demonstrated that following cutaneous application of DMSO in dogs, the skin, dermis and underlying muscle tissues show a local rise in temperature (30).

The analgesic and anti-inflammatory activity of DMSO, as observed clinically and the differences noted by classical pharmacological methods, may be partially due to the ability of the compound to alter the underlying pathology of the disease state under treatment (42).

Using the isolated guinea pig heart it was found that DMSO did not influence the amplitude of cardiac contractions, heart rate or coronary flow, although high intravenous doses in the rat and cat resulted in a transient lowering of blood pressure (36).

Isolated, innervated guinea pig preparations were also used to study the effects of DMSO on skeletal, smooth and cardiac muscles. The compound depressed diaphragm response to both muscle and nerve stimulation and also caused spontaneous skeletal muscle fasciculations. Actual contraction amplitude was augmented although contraction rate appeared unaffected. Vagal threshold was lowered almost 50% by a bath concentration of 6% DMSO. The fasciculations and increased tone of skeletal muscle, and lowering of the vagal threshold by DMSO could be due to cholinesterase inhibition (43). Intravenous doses of 50% DMSO in doses as high as 1 g/kg failed to alter the EKG of anesthetized dogs and monkeys (26).

With single intravenous doses of 200 mg/kg of DMSO to anesthetized cats, apnea and a transient fall in blood pressure were produced. Subsequent doses caused only a transient hypotension and apnea was no longer observed. Vagotomy failed to influence the course of DMSO-induced hypotension and bradycardia but atropine (1 mg/kg) significantly attenuated these effects. Repeated intravenous administration of DMSO where each succeeding dose was doubled, led to a gradually lowered blood pressure until death ensued at about 4 g/kg. Myoneural transmission, ganglionic transmission and force of cardia contraction also deteriorated gradually with repeated doses until death. The transient fall in blood pressure occurred only rarely after intraperitoneal administration. One cat exhibited hypotension following a 1 g/kg dose of DMSO but the remainder received dosages of 4 g/kg without showing this effect (44).

The *in vitro* oxygen consumption of liver, brain and hemidiaphragm tissues of rats is not affected by the intravenous administration of 75 mg DMSO/100 g body weight during the 7 subsequent days. Urease, trypsin and chymotrypsin are inhibited by DMSO, dependent upon its concentration. The *in vitro* metabolism of corticosterone by rat liver slices is not affected by the intravenous administration of 100 mg DMSO/100 g body weight during 3 subsequent days (2).

DMSO treatment administered intraperitoneally to rats for 35 days decreased experimentally induced intestinal adhesions by 80% over controls as compared to saline, cortisone acetate or a combination of cortisone and DMSO administered separately (45).

In rabbits the application of 70% DMSO, adjacent to but not on the wound incision site, appeared to increase the development of wound tensile strength over controls (46).

Increasing the concentration of DMSO resulted in an increasing inhibition of fibroblast proliferation, *in vitro,* which was reversible (30).

There is an increase in urinary production following the dermal or systemic administration of DMSO, and a transient doubling of urine volume after the intravenous administration of the drug (48).

Some studies have indicated that DMSO may potentiate the action of certain compounds including insulin (39), endogenous steroids and others. It was suggested that in the case of steroids it might be due to improved penetration at their sites of action on lysosomal membranes (30).

The minimal inhibitory concentration (MIC) of DMSO to the nearest 10% was determined for two isolates each of *Staphylococcus aureus, Staphylococcus aureus* var. albus, β-hemolytic Streptococci, *Corynebacterium acnes,* Corynebacterium species, *Alcaligenes faecalis, Escherichia coli* and Proteus species. Twenty percent DMSO was found to be bacteriostatic. For *Staphylococcus aureus,* the bactericidal concentration of 50% was 2.5 times that of the MIC; for the remainder, it ranged from 30% to 40% with the gram negative bacteria being somewhat more susceptible (29).

No growth of Staphylococci, Pseudomonas or Escherichia coli occurred in the presence of 36%, 25%, 33% or greater concentrations, respectively, of DMSO (49).

The minimal inhibitory concentration of DMSO in Sabouraud's broth to the nearest 10% was determined for three dermatophytes: *Trichophyton mentagrophytes, Microsporum gypseum* and *Microsporum canis.* Ten percent DMSO was inhibitory to all three species. The fungicidal concentrations were 30% for the Microsporum species, while *T. mentagrophytes* survived the highest test concentrations of 50% (29).

TOXICOLOGY

Absorption of topically applied DMSO results in degranulation of the mast cells at the site of application and a release of histamine followed by characteristic histamine whealing of the overlying skin. Following repeated applications of the compound to the same skin area, the mast cells are eventually depleted and the wheal no longer occurs (28).

The erythema of the skin following topical application of DMSO is considered to be partially due to the release of histamine. In addition, DMSO has the typical action of most solvents in causing drying and defatting of the skin.

In a study designed to evaluate the effects of DOMOSO (dimethyl sulfoxide) Solution at a total daily dose of 100–300 mL administered for a total period of 90 days, no essential or clinically meaningful ophthalmological effects were seen in the horse. There were no significant variations in glucose, sodium, potassium, SGOT or SGPT measurements. There were a few fluctuations in hematologic values but no changes appear to be drug-related or of significance.

Another study was conducted in the dog to determine the effects of DOMOSO Solution at a total daily dose of 20–60 mL administered topically for 21 consecutive days. No clinically meaningful ophthalmological effects were noted. No significant variations were observed in blood measurements, including glucose, BUN, SGOT and plasma electrophoresis. Hematologic values were similar to control animals used in this study.

Long-term topical applications of the drug to guinea pigs resulted in histopathologic changes similar to those observed in allergic contact dermatitis. The observed clinical changes were compatible with either an allergic contact dermatitis or a primary irritant effect (50). DMSO was shown to cause erythema and blistering of human and rat skin resulting in increased permeability of venules and capillaries (51).

In most cases the local irritation of the skin characterized by erythema, vesicle or blister formation and scurfing abates even with continued treatment. This phenomenon has been described as "accommodation" or "hardening" of the skin, and has been noted with other solvents.

The undiluted compound has low systemic toxicity but a marked local necrotizing and inflammatory effect when it is injected subcutaneously. In rats the subcutaneous injection of 10 g/kg or the intravenous injection of 2.5 g/kg of undiluted DMSO for 2 weeks showed no definite indication of systemic toxicity. The local necrotizing effects produced at these dose levels, however, prevented a longer period of treatment. No significant hematologic or biochemical changes were noted in 3 dogs receiving 0.4 g/kg for 33 days (35).

Four dogs were administered topical DMSO at 1 g/kg of body weight, 5 days weekly for 18 months. Serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), prothrombin time, alkaline phosphatase, bilirubin, total protein and albumin globulin (AG) ratio, and blood urea nitrogen (BUN) were determined at the beginning of treatment and at monthly intervals. Significant abnormalities did not occur (39).

Upon injection of DMSO into the rat pleura, there is an accumulation of fluid, initially appearing as a transudate, but later as a protein-rich exudate. Exudate formation is thought to be due to increased vascular permeability, predominantly in venules, brought about by a delayed release of histamine together with activation of a vaso-active slow contracting substance (51).

Rats are orally dosed 5 days a week for 2 weeks at levels of 1, 3.5, 5 and 10 mg/kg of DMSO. The only deaths in this group were due to dosing injuries. No signs of dermal sensitization were noted following a course of intradermal injection of a 10% v/v aqueous solution of DMSO in guinea pigs, nor did the same species show signs of injury following 28 daily applications of the undiluted drug to the clipped skin of the back (52).

A compilation of the results for a number of acute toxicity (LD_{50}) determinations derived from several published reports (35, 52, 53, 54, 55) in several experimental animal species is as follows:

Species	Rt. of Administr.	LD_{50} g/kg
Mouse	SQ	13.9 – 20.5
Mouse	IV	3.82 – 10.73
Mouse	Oral	15.0 – 22
Mouse	IP	20.06
Rat	IV	5.25 – 5.36
Rat	Oral	16.0 – 28.3
Rat	IP	6.5 – 13.621
Dog	IV	2.5
Guinea Pig	IP	6.5
Chicken	Oral	12.5

Hemolysis resulting in hemoglobinuria and methemoglobinuria was noted in anesthetized cats following single intravenous doses of 200 mg/kg DMSO. The intraperitoneal administration of DMSO or the dilution of DMSO with isotonic saline prior to intravenous administration reduced its hemo-lytic activity (44).

Tests *in vitro* showed that washed rabbit erythrocytes are hemolyzed in a short time with 40% to 60% DMSO solution. Higher concentrations caused, without hemolysis, an agglutination of the erythrocytes (55).

Teratology

The intraperitoneal administration of 5.5 g/kg of DMSO as a single dose to pregnant hamsters induced developmental malformations of their embryos (56). Both dimethyl sulfoxide and diethyl sulfoxide are teratogenic when injected into the chick embryo, the classification of malformations being dependent upon the stage of embryonic development at the time of treatment. The same drugs when administered by various techniques to mice, rats and rabbits in which fertility had been established did not cause any embryonic malformations (57).

Ocular Effects

In a variety of experimental animals including rats, dogs, swine, rabbits and primates, following oral or topical administration of DMSO, certain eye changes have been noted. These consist mainly of a change in the refractive index of the lens described as a "lens within a lens". The lens changes are characterized by a decrease in the normal relucency of the lens cortex, causing the normal central zone of the lens to act as a biconvex lens. When viewing the fundus of affected animals, it is necessary to interpose biconcave lenses in order to see the retinal vessels clearly. The functional effect would be a tendency toward myopia (58).

The lens changes were first observed in dogs receiving 5 g DMSO/kg after 9 weeks of administration. At lower dose levels the change was observed later. In rabbits these changes were seen after 90 days of dermal application, (8 mg 50% DMSO/kg/day and 4 mg 100% DMSO/kg/day and higher). In swine, dermal application of 4.5 g 90% DMSO/kg twice daily caused similar lens changes by 90 days of treatment (59).

The lens changes appear earlier with oral administration, and also bear a relation to the dosage employed; the higher the dose the more rapid their appearance.

The eye changes are slowly reversible but with a definite species difference, the dog being the slowest to exhibit improvement.

No effects were seen following direct application of aqueous solutions varying from 10% to full strength into the eyes of albino rabbits for a total dosage of DMSO between 0.1 and 0.2 g/kg body weight per day for six months. Rabbits which received daily doses as high as 10 g/kg orally or topically showed lines of discontinuity in their lenses. No cataract was seen after ten weeks of such daily treatment, although discontinuous lens lines could be detected in about two weeks by slit lamp examination. Chemical studies on these lenses revealed reduction in the usual concentrations of urea, glutathione, uric and amino acids (30).

INDICATIONS

Canine and Equine

DOMOSO (dimethyl sulfoxide) Solution is recommended as a topical application to reduce acute swelling due to trauma.

ADMINISTRATION AND DOSAGE

DOMOSO Solution is to be administered topically to the skin over the affected area. The spray pump should be initially held approximately 6 inches from the animal and the distance adjusted to provide a uniform coverage of the area. The volume delivered by depressing the spray pump is approximately 1/3 mL. Refer to user precautions below under **PRECAUTIONS AND CONTRAINDICATIONS.**

Dogs — Liberal application should be administered three to four times daily. Total daily dosage should not exceed 20 mL. Total duration of therapy should not exceed 14 days.

Horses — Liberal application should be administered two to three times daily. Total daily dosage should not exceed 100 mL. Total duration of therapy should not exceed 30 days.

SIDE EFFECTS

In general, adverse reactions are local, and while they may prove to be annoying to some patients, they are usually not of a serious nature. Upon topical application, an occasional animal may develop transient erythema, associated with local "burning" or "smarting". Even when erythema or vesiculation occurs, they are self-limiting reversible states, and not necessarily an indication to discontinue medication. Dryness of the skin and an oyster-like breath odor have been reported. These effects are temporary and are not considered to be of serious consequence. Changes in the refractive index of the lens of the eye and nuclear cataracts have been observed in animals, with the use of this drug. This appears to be related to dosage and duration of therapy.

WARNING

Do not use in horses intended for human consumption.

PRECAUTIONS AND CONTRAINDICATIONS

Contact between DOMOSO Solution and the skin should be avoided. Protective gloves should be worn while applying this drug. Forceps and swabs may be used to facilitate application. If absorbed through the skin, DOMOSO Solution will cause odorous breath and unpleasant mouth taste. Mild sedation or drowsiness, sensations of warmth, burning, irritation, itching and mild erythematous localized or generalized dermatitis have been reported in some persons following exposure to DOMOSO Solution. Treatment of such side effects is symptomatic. Consult a physician immediately if adverse effects appear.

DOMOSO Solution may mask certain disease signs such as are seen in fractures, etc.; this does not obviate the need for specific therapy in such conditions. DOMOSO Solution should not be used directly prior to racing or other physical stress wherein the drug might mask existing pathology, such as a fracture.

Since DOMOSO Solution effectively alters the biologic membrane, it will in some cases facilitate the systemic absorption of other topically applied drugs and may have a potentiating effect on drugs administered systemically. Therefore, great care should be exercised in use of other drugs at the DOMOSO Solution application site because of the demonstrated—if variable—ability of DMSO to carry other chemicals through the dermis into the general circulation. If other topical medications are indicated they should not be applied until DOMOSO Solution is thoroughly dry. Frequently, due to the heat of resolution, a "smoking" effect following application is noted due to vaporization of the drug.

DOMOSO Solution should also be judiciously used when administered in conjunction with other pharmaceutical preparations, especially those affecting the cardiovascular and central nervous systems. DMSO may potentiate the activity of atropine, insulin, endogenous steroids and certain other drugs.

Lowering of the vagal threshold, spontaneous skeletal muscle fasciculation, and increased smooth muscle tone in the stomach following DMSO exposure may be due to cholinesterase inhibition. Therefore, DOMOSO Solution should not be used on dogs, or horses, simultaneously or within a few days before or after treatment with, or exposure to, cholinesterase-inhibiting pesticides or drugs.

DOMOSO SOLUTION IS RECOMMENDED FOR TOPICAL APPLICATION ONLY. THE APPLICATION OF DOMOSO SOLUTION SHOULD TAKE PLACE ONLY IN WELL VENTILATED QUARTERS. INHALATION OF THE DRUG SHOULD BE AVOIDED. AVOID CONTACT OF THE MEDICATION WITH THE EYES.

Keep DOMOSO Solution out of the reach of children.

DO NOT ADMINISTER BY ANY OTHER ROUTE.

DOMOSO Solution should not be used under occlusive dressings. DOMOSO Solution is contraindicated in horses and dogs intended for breeding purposes.

DOMOSO Solution is a potent solvent and may have a deleterious effect on fabrics, plastics and other materials. Care should be taken to prevent physical contact with DOMOSO Solution and these materials, either alone or until drying of the treated skin surface has occurred when applied to an animal.

CAUTION: EXTREMELY HYGROSCOPIC! CLOSE BOTTLE CAP TIGHTLY AFTER USE. AVOID FREEZING. DUE TO THE RAPID PENETRATING ABILITY OF DOMOSO, PROTECTIVE GLOVES SHOULD BE WORN WHEN APPLYING THIS DRUG.

HOW SUPPLIED

DOMOSO (dimethyl sulfoxide) Solution is supplied in 1 Pint (473 mL) and 1 Gallon (3785 mL) bottles.

Store at controlled room temperature 20-25°C (68-77°F) with permissible excursions 15-30°C (59-86°F).

REFERENCES

1. Kolb, K.H., Janicke, G., Kramer, M., Schulze, P.E. and Raspe, G., DAS VERHALTEN VON 35S MARKIERTEM DIMETHYLSULFOXID IM MENSCHLICHEN UND TIERISCHEN ORGANISMUS. 1965 Arzneimittelforschung 15 1292–1295 Nov 1965
2. Gerhands, E., Gibian, H. and Raspe, G., STOFFWECHSEL UND STOFFWECHSELWIRKUNGEN VON DIMETHYLSULFOXID. 1965 Arzneimittel-forschung 15 1295–1297 Nov 1965
3. Hucker, H.B., Ahmad, P.M. and Miller, E.A., PHYSIOLOGICAL DISPOSITION AND METABOLISM OF DIMETHYL SULFOXIDE, DMSO. Federation of American Societies for Experimental Biology, 49th Annual Meeting. 9–14 Apr 1965, Atlantic City. 1965 Fed. Proc. 24, 546 Mar–Apr 1965, Abstr. No. 2310
4. DiStefano, V. and Borgstedt, H.H., REDUCTION OF DIMETHYL SULFOXIDE TO DIMETHYL SULFIDE IN THE CAT. 1964 Science 144, 1137–1138 29 May 1964
5. Williams, K.I., Whittemore, K.S., Mellin, T.N. and Layne, D.S., OXIDATION OF DIMETHYL SULFOXIDE TO DIMETHYL SULFONE IN THE RABBIT. 1965 Science 149, 203–204 9 Jul 1965
6. Williams, K.E., Burstein, S.H. and Layne, D.S., DIMETHYL SULFONE, ISOLATION FROM COWS MILK. 1966 Proc. Soc. Exp. Biol. Med. 122, 865–866 Jul 1966
7. Huggins, C.E., PRESERVATION OF BLOOD FOR TRANSFUSIONS BY FREEZING WITH DIMETHYL SULFOXIDE AND A NOVEL WASHING TECHNIQUE. 1963 Surgery 54, 191–194 Jul 1963
8. Pyle, H.M. and Boyer, H.F., EFFECTS OF DIMETHYL SULFOXIDE ON BLOOD CELLS AND BONE MARROW. 1961 Vox Sang 6, 199–200 1961
9. Rowe, A.W., Kaczmarek, C.S. and Cohen, E., LOW TEMPERATURE PRESERVATION OF LEUKOCYTES IN DIMETHYL SULFOXIDE. Federation of American Societies for Experimental Biology, 47th Annual Meeting. 16–20 Apr 1963. Atlantic City 1963 Fed. Proc. 22, 170 1963 Abstr. No. 60
10. Ashwood-Smith, M.J., LOW TEMPERATURE PRESERVATION OF MOUSE LYMPHOCYTES WITH DIMETHYL SULFOXIDE. 1964 Blood 23, 494–501 Apr 1964
11. Djerassi, I. and Roy, A., A METHOD FOR PRESERVATION OF VIABLE PLATELETS, COMBINED EFFECTS OF SUGARS AND DIMETHYL SULFOXIDE. 1963 Blood 22, 703–717 1963
12. Sawada, Y. and Chang, M.C., MOTILITY AND FERTILIZING CAPACITY OF RABBIT SPERMATOZOA AFTER FREEZING IN A MEDIUM CONTAINING DIMETHYL SULFOXIDE. 1964 Fertil. Steril. 15, 222–229 Mar–Apr 1964
13. Zimmerman, S.J., Maude, M.B. and Moldawer, M., FREEZING AND STORAGE OF HUMAN SEMEN IN 50 HEALTHY MEDICAL STUDENTS. A Comparative Study of Glycerol and Dimethyl Sulfoxide as a Preservative. 1964 Fertil. Steril. 15, 505–510 Sep–Oct 1964
14. Sherman, J.K., DIMETHYL SULFOXIDE AS A PROTECTIVE AGENT DURING FREEZING AND THAWING OF HUMAN SPERMATOZOA. 1964 Proc. Soc. Exp. Biol. Med. 177, 261–264 1964
15. Mueller, F.O., Casey, T.A. and Trevor-Roper, P.D., USE OF DEEP-FROZEN HUMAN CORNEA IN FULL-THICKNESS GRAFTS. 1964 Brit. Med. J. No. 5407, 473–475 22 Aug 1964
16. Platts, S. and Reed, H., USE OF DIMETHYL SULFOXIDE FOR PRESERVING CORNEAL TISSUE. 1963 Brit. J. Ophthal. 47, 334–338 1963
17. Barlyn, L.W., Berggren, R.B. and Lehr, H.B., FROZEN SKIN AUTOGRAFTS PROTECTED BY DIMETHYL SULFOXIDE. 1964 Surg. Forum 15, 475–476 1964
18. Nagington, J. and Greaves, R.I., PRESERVATION OF TISSUE CULTURE CELLS WITH LIQUID NITROGEN. 1962 Nature 194, 993–994 9 Jun 1962
19. Porterfield, J.S. and Ashwood-Smith, M.J., PRESERVATION OF CELLS IN TISSUE CULTURE BY GLYCEROL AND DIMETHYL SULFOXIDE. 1962 Nature 193, 548–550 10 Feb 1962
20. Lovelock, J.E. and Bishop, M.W., PREVENTION OF FREEZING DAMAGE TO LIVING CELLS BY DIMETHYL SULFOXIDE. 1959 Nature 183, 1394–1395 16 May 1959
21. Dougherty, R.M., USE OF DIMETHYL SULFOXIDE FOR PRESERVATION OF TISSUE CULTURE CELLS BY FREEZING. 1962 Nature 193, 550–552 10 Feb 1962
22. Walker, P.J. and Ashwood-Smith, M.J., DIMETHYL SULFOXIDE, AN ALTERNATIVE TO GLYCEROL, FOR THE LOW-TEMPERATURE PRESERVATION OF TRYPANOSOMES. 1961 Ann. Trop. Med. Parasit. 55, 93–96 1961
23. Ashwood-Smith, M.J., INABILITY OF DIMETHYL SULFOXIDE TO PROTECT MOUSE TESTIS AGAINST THE EFFECT OF X-RADIATION. 1961 Int. J. Radiat. Biol. 3, 101–103 1961
24. Ashwood-Smith, M.J., RADIOPROTECTIVE EFFECT OF COMBINATION OF AET OR CYSTEAMINE WITH DIMETHYL SULFOXIDE. 1962 Int. J. Radiat. Biol. 5, 201–202 May 1962
25. Jacob, S.W., Bischel, M. and Herschler, R.J., DIMETHYL SULFOXIDE, EFFECTS ON THE PERMEABILITY OF BIOLOGIC MEMBRANES. Preliminary Report. 1964 Curr. Ther. Res. 6, 193–198 Mar 1964
26. Jacob, S.W., Bischel, M.D., Eberle, G.A. and Herschler, R.J., THE INFLUENCE OF DIMETHYL SULFOXIDE ON THE TRANSPORT OF INSULIN ACROSS A BIOLOGIC MEMBRANE. Federation of American Societies for Experimental Biology, 48th Annual Meeting. 12–17 Apr 1964 Chicago. 1964 Fed. Proc. 23, 410 Mar–Apr 1964 Abstr. No. 1850
27. Stoughton, R.B. and Fritsch, W., INFLUENCE OF DIMETHYL SULFOXIDE (DMSO) ON HUMAN PERCUTANEOUS ABSORPTION. Archives of Dermatology 90:512 Nov 1964
28. Kligman, A.M., TOPICAL PHARMACOLOGY AND TOXICOLOGY OF DIMETHYL SULFOXIDE – PART I. 1965 J. Amer. Med. Assoc. 193, 796–804 6 Sep 1965
29. Kligman, A.M., TOPICAL PHARMACOLOGY AND TOXICOLOGY OF DIMETHYL SULFOXIDE – PART II. 1965 J. Amer. Med. Assoc. 193, 923–928 13 Sep 1965
30. Leake, C.D., DIMETHYL SULFOXIDE. Science 152, 1646–1649 17 Jun 1966
31. Sweeney, T.M., Downes, A.M. and Matoltsy, A.G., THE EFFECT OF DIMETHYL SULFOXIDE ON THE EPIDERMAL WATER BARRIER. 1966 J. Invest. Derm. 46, 300–302 Mar 1966
32. Horita, A. and Weber, L.J., SKIN PENETRATING PROPERTY OF DRUGS DISSOLVED IN DIMETHYL SULFOXIDE, DMSO, AND OTHER VEHICLES. 1964 Life Sci. 3, 1389–1395 Dec 1964
33. Rosen, H., Blumenthal, A., Panasevich, R. and McCallum, J., DIMETHYL SULFOXIDE (DMSO) AS A SOLVENT IN ACUTE TOXICITY DETERMINATIONS. 1965 Proc. Soc. Exp. Biol. Med. 120, 511–514 Nov 1965
34. Dixon, R.L., Adamson, R.H., Ben, M. and Rall, D.P., APPARENT LACK OF INTERACTION BETWEEN DIMETHYL SULFOXIDE AND A VARIETY OF DRUGS. 1965 Proc. Soc. Exp. Biol. Med. 118, 756–759 Mar 1965
35. Rosenkrantz, H., Hadidian, Z., Seay, H. and Mason, M.M., DIMETHYL SULFOXIDE, ITS STEROID SOLUBILITY AND ENDOCRINOLOGIC AND PHARMACOLOGIC-TOXICOLOGIC CHARACTERISTICS. 1963 Cancer Chemother. Rep. No. 31, 7–24 Sep 1963
36. Haeusler, G. and Jahn, U., UNTERSUCHUNGEN ZUR PHARMAKOLOGIE VON DIMETHYLSULFOXYD (DMSO). 1966 Arch. Int. Pharmacodyn 159, 386–400 Feb 1966
37. Pantio, M. and Kaerki, N.T., THE INFLUENCE OF DIMETHYL SULFOXIDE ON THE ABSORPTION OF PHENYLBUTAZONE. Spanish Translation. 1965 Air 8, 133–147 1965
38. Block, L.H., DMSO. MEDICINAL AND PHARMACEUTICAL ASPECTS. 1964 Drug Cosmet. Industr. 95, 342–346, 462–464 Sep 1964
39. Jacob, S.W., Herschler, R.J. and Rosenbaum, E.E., DIMETHYL SULFOXIDE (DMSO) LABORATORY AND CLINICAL EVALUATION. 1965 J. Amer. Vet. Med. Assoc. 147, 1350–1359 1965
40. Preziosi, P. and Scapagnini, U., ACTION OF DIMETHYL SULFOXIDE ON ACUTE INFLAMMATORY REACTIONS. 1966 Curr. Ther. Res. 8, 261–264 May 1966
41. Katz, J., Knott, L.W. and Rubinstein, L.J., THE NEUROHISTOLOGICAL CHANGES INDUCED BY PHENOL, DIMETHYL SULFOXIDE, AND HYALURONIDASE ON THE SCIATIC NERVE OF THE RAT. Special Abstract From Fall Pharmacology Meeting April 1966
42. Pope, D.C. and Oliver, W.T., DIMETHYL SULFOXIDE (DMSO). 1966 Canad. J. Comp. Med. 30, 3–8 Jan 1966
43. Sams, W.M., Carroll, N.V. and Crantz, P.L., EFFECTS OF DIMETHYL SULFOXIDE ON ISOLATED-INNERVATED SKELETAL, SMOOTH, AND CARDIAC MUSCLE. 1966 Proc. Soc. Exp. Biol. Med. 122, 103–107 May 1966
44. DiStefano, V. and Klahn, J.J., OBSERVATIONS ON THE PHARMACOLOGY AND HEMOLYTIC ACTIVITY OF DIMETHYL SULFOXIDE. 1965 Toxic. Appl. Pharmacol. 7, 660–666 Sep 1965
45. Mayer, J.H., Anido, H., Almond, C.H. and Seaber, A., DIMETHYL SULFOXIDE IN PREVENTION OF INTESTINAL ADHESIONS. 1965 Arch. Surg., Chicago, 91, 920–923 Dec 1965
46. Huu, N. and Albert, H.M., EFFECT OF DMSO ON WOUND HEALING TENSILE STRENGTH MEASUREMENTS IN RABBITS. 1966 Amer. Surg. 32, 421–424 Jun 1966
47. Scherbel, A.L., McCormack, L.J. and Poppo, M.J., ALTERATION OF COLLAGEN IN GENERALIZED SCLERODERMA (PROGRESSIVE SYSTEMIC SCLEROSIS) AFTER TREATMENT WITH DIMETHYL SULFOXIDE. 1965 Cleveland Clin. Quart. 32, 47–56 Apr 1965
48. Jacob, S.W., Bischel, M. and Herschler, R.J., DIMETHYL SULFOXIDE, DMSO: A NEW CONCEPT IN PHARMACOTHERAPY. 1964 Curr. Ther. Res. 6, 134–135 Feb 1964
49. Krizek, T.J. and Davis, J.H., BACTERIOSTATIC QUALITIES OF DIMETHYL SULFOXIDE. American Federation for Clinical Research, Annual Meeting of the Midwestern Section, 5 Nov 1964, Chicago. 1964 Clin. Res. 21, 349 1964 Abstr.
50. Wright, E.T. and Winer, L.H., TOPICAL APPLICATION OF DIMETHYL SULFOXIDE (DMSO) TO SKIN OF GUINEA PIGS, A Histopathological Study. 1966 J. Invest. Derm. 46, 409–414 Apr 1966
51. Willoughby, D.A., Walters, M.N. and Spector, W.G., AN ANALYSIS OF THE IRRITANT ACTION OF DIMETHYL SULFOXIDE. 1966 J. Path. Bact. 91, 195–205 Jan 1966
52. Brown, V.K., Robinson, J. and Stevenson, D.E., A NOTE ON THE TOXICITY AND SOLVENT PROPERTIES OF DIMETHYL SULFOXIDE. 1963 J. Pharm. Pharmacol. 15, 688–692 Oct 1963
53. Willson, J.E., Brown, D.E. and Timmens, E.K., A TOXICOLOGIC STUDY OF DIMETHYL SULFOXIDE. 1965 Toxic. Appl. Pharmacol. 7, 104–112 Jan 1965
54. Caujolle, F., Caujolle, D., Bouyssou, H. and Calvert, M.M., PHARMACODYNAMIE-TOXICITE ET APTITUDES PHARMACOLOGIQUES DU DIMETHYLSULFOXYDE. PHARMACODYNAMICS-TOXICITY AND PHARMACOLOGICAL PROPERTIES OF DIMETHYL SULFOXIDE. 1964 C.R. Acad. Sci. Paris, 258, 2224–2226 17 Feb 1964
55. Sommer, S. and Tauberger, G., TOXIKOLOGISCHE UNTERSUCHUNGEN MIT DIMETHYLSULFOXYD. TOXICOLOGIC INVESTIGATIONS WITH DIMETHYL SULFOXIDE. 1964 Arzneimittelforschung 14, 1050–1055 1964
56. Marin-Padilla, M., MESODERMAL ALTERATIONS INDUCED BY DIMETHYL SULFOXIDE. 1966 Proc. Soc. Exp. Biol. Med. 122, 717–720 Jul 1966
57. Caujolle, F., Caujolle, D., Cros, S., Calvert, M. and Tollon, Y., TERATOGENESE POUVOIR TERATOGENE DU DIMETHYLSULFOXIDE ET DU DIETHYLSULFOXYDE. TERATOGENESIS-TESTS OF THE TERATOGENY OF DIMETHYL SULFOXIDE AND OF DIETHYL SULFOXIDE. 1965 C.R. Acad. Sci. Paris, 260, 327–330 4 Jan 1965
58. Rubin, L.F. and Mattis, P.A., DIMETHYL SULFOXIDE, LENS CHANGES IN DOGS DURING ORAL ADMINISTRATION. 1966 Science 153, 83–84 1 Jul 1966
59. Unpublished data 1966
60. Stoughton, R.B., HEXACHLOROPHENE DEPOSITION IN HUMAN STRATUM CORNEUM. ENHANCEMENT BY DIMETHYLACETAMIDE, DIMETHYLSULFOXIDE, AND METHYLETHYL-ETHER. 1966 Arch. Derm. 94, 646–648 Nov 1966
61. Katz, R. and Hood, R.W., TOPICAL THIABENDAZOLE FOR CREEPING ERUPTION. 1966 Arch. Derm. 94, 643–645 Nov 1966
62. Sperber, P.A., TREATMENT OF CREEPING ERUPTION WITH ORALLY AND TOPICALLY ADMINISTERED THIABENDAZOLE. 1967 J. Fla. M.A., 1059–1061, Nov 1967

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Revised: March 2013 8DOM400 Rev: 04/13 GEQ14007

DORMOSEDAN®

(detomidine hydrochloride)

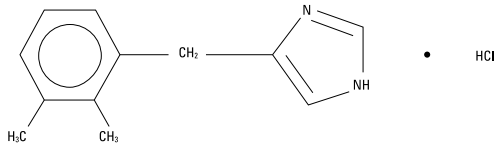
Sedative and Analgesic For Use in Horses Only

Sterile Solution
10 mg/mL

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

DESCRIPTION: Dormosedan® is a synthetic alpha-2 adrenoreceptor agonist with sedative and analgesic properties. The chemical name is 1H imidazole, 4-[(2,3-dimethylphenyl) methyl]- hydrochloride and the generic name is detomidine hydrochloride. It is a white, crystalline, water-soluble substance having a molecular weight of 222.7. The molecular formula is $C_{12}H_{14}N_2$•HCl.

CHEMICAL STRUCTURE:



Each mL of Dormosedan® contains 10.0 mg detomidine hydrochloride, 1.0 mg methyl paraben, 5.9 mg sodium chloride, and water for injection, q.s.

CLINICAL PHARMACOLOGY: Dormosedan®, a non-narcotic sedative and analgesic, is a potent α_2-adrenoreceptor agonist which produces sedation and superficial and visceral analgesia which is dose dependent in its depth and duration. Profound lethargy and a characteristic lowering of the head with reduced sensitivity to environmental stimuli (sounds, etc.) are seen with detomidine. A short period of incoordination is characteristically followed by immobility and a firm stance with front legs well spread. The analgesic effect is most readily seen as an increase in the pain threshold at the body surface. Sensitivity to touch is little affected and in some cases may actually be enhanced.

With detomidine administration, heart rate is markedly decreased, blood pressure is initially elevated, and then a steady decline to normal is seen. A transient change in the conductivity of the cardiac muscle may occur, as evidenced by partial atrioventricular (AV) and sinoauricular (SA) blocks. This change in the conductivity of the cardiac muscle may be prevented by IV administration of atropine at 0.02 mg/kg of body weight.

No effect on blood clotting time or other hematological parameters was encountered at dosages of 20 or 40 mcg/kg of body weight. Respiratory responses include an initial slowing of respiration within a few seconds to 1–2 minutes after administration, increasing to normal within 5 minutes. An initial decrease in tidal volume is followed by an increase.

INDICATIONS: Dormosedan® is indicated for use as a sedative and analgesic to facilitate minor surgical and diagnostic procedures in mature horses and yearlings. It has been used successfully for the following: to calm fractious horses, to provide relief from abdominal pain, to facilitate bronchoscopy, bronchoalveolar lavage, nasogastric intubation, nonreproductive rectal palpations, suturing of skin lacerations, and castrations. Additionally, an approved, local infiltration anesthetic is indicated for castration.

CONTRAINDICATIONS: Dormosedan® should not be used in horses with pre-existing AV or SA block, with severe coronary insufficiency, cerebrovascular disease, respiratory disease, or chronic renal failure. Intravenous potentiated sulfonamides should not be used in anesthetized or sedated horses as potentially fatal dysrhythmias may occur.

Information on the possible effects of detomidine hydrochloride in breeding horses is limited to uncontrolled clinical reports; therefore, this drug is not recommended for use in breeding animals.

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

HUMAN SAFETY INFORMATION: Care should be taken to assure that detomidine hydrochloride is not inadvertently ingested as safety studies have indicated that the drug is well absorbed when administered orally. Standard ocular irritation tests in rabbits using the proposed market formulation have shown detomidine hydrochloride to be nonirritating to eyes. Primary dermal irritation tests in guinea pigs using up to 5 times the proposed market concentration of detomidine hydrochloride on intact and abraded skin have demonstrated that the drug is nonirritating to skin and is apparently poorly absorbed dermally. However, in accordance with prudent clinical procedures, exposure of eyes or skin should be avoided and affected areas should be washed immediately if exposure does occur. As with all injectable drugs causing profound physiological effects, routine precautions should be employed by practitioners when handling and using loaded syringes to prevent accidental self-injection.

PRECAUTIONS: Before administration, careful consideration should be given to administering Dormosedan® to horses approaching or in endotoxic or traumatic shock, to horses with advanced liver or kidney disease, or to horses under stress from extreme heat, cold, fatigue, or high altitude. Protect treated horses from temperature extremes. Some horses, although apparently deeply sedated, may still respond to external stimuli. Routine safety measures should be employed to protect practitioners and handlers. Allowing the horse to stand quietly for 5 minutes before administration and for 10–15 minutes after injection may improve the response to Dormosedan®.

Dormosedan® is a potent α_2-agonist, and extreme caution should be exercised in its use with other sedative or analgesic drugs for they may produce additive effects.

When using any analgesic to help alleviate abdominal pain, a complete physical examination and diagnostic work-up are necessary to determine the etiology of the pain.

Food and water should be withheld until the sedative effect of Dormosedan® has worn off.

ADVERSE REACTIONS: Occasional reports of anaphylactic-like reactions have been received, including 1 or more of the following: urticaria, skin plaques, dyspnea, edema of the upper airways, trembling, recumbency, and death. **The use of epinephrine should be avoided since epinephrine may potentiate the effects of α_2-agonists.** Reports of mild adverse reactions have resolved uneventfully without treatment. Severe adverse reactions should be treated symptomatically. As with all α_2-agonists, the potential for isolated cases of hypersensitivity exist, including paradoxical response (excitation).

SIDE EFFECTS: Horses treated with Dormosedan® exhibit hypertension. Bradycardia routinely occurs 1 minute after injection. The relationship between hypertension and bradycardia is consistent with an adaptive baroreceptor response to the increased pressure and inconsistent with a primary drug-induced bradycardia. Piloerection, sweating, salivation, and slight muscle tremors are frequently seen after administration. Partial transient penis prolapse may be seen. Partial AV and SA blocks may occur with decreased heart and respiratory rates. Urination typically occurs during recovery at about 45–60 minutes posttreatment, depending on dosage. Incoordination or staggering is usually seen only during the first 3–5 minutes after injection, until animals have secured a firm footing.

Because of continued lowering of the head during sedation, mucus discharges from the nose and, occasionally, edema of the head and face may be seen. Holding the head in a slightly elevated position generally prevents these effects.

OVERDOSAGE: Detomidine hydrochloride is tolerated in horses at up to 200 mcg/kg of body weight (10 times the low dosage and 5 times the high dosage). In safety studies in horses, detomidine hydrochloride at 400 mcg/kg of body weight administered daily for 3 consecutive days produced microscopic foci of myocardial necrosis in 1 of 8 horses.

DOSAGE AND ADMINISTRATION:

For Sedation: Administer Dormosedan® IV or IM at the rates of 20 or 40 mcg detomidine hydrochloride per kg of body weight (0.2 or 0.4 mL of Dormosedan® per 100 kg or 220 lb), depending on the depth and duration of sedation required. Onset of sedative effects should be reached within 2–4 minutes after IV administration and 3–5 minutes after IM administration. Twenty mcg/kg will provide 30–90 minutes of sedation and 40 mcg/kg will provide approximately 90 minutes to 2 hours of sedation.

For Analgesia: Administer Dormosedan® IV at the rates of 20 or 40 mcg detomidine hydrochloride per kg of body weight (0.2 or 0.4 mL of Dormosedan® per 100 kg or 220 lb), depending on the depth and duration of analgesia required. Twenty mcg/kg will usually begin to take effect in 2–4 minutes and provide 30–45 minutes of analgesia. The 40 mcg/kg dose will also begin to take effect in 2–4 minutes and provide 45–75 minutes of analgesia.

For Both Sedation and Analgesia: Administer Dormosedan® IV at the rates of 20 or 40 mcg detomidine hydrochloride per kg of body weight (0.2 or 0.4 mL of Dormosedan® per 100 kg or 220 lb), depending on the depth and duration of sedation and analgesia required.

Before and after injection, the animal should be allowed to rest quietly.

STORAGE: Store at controlled room temperature 15°–30°C (59°–86°F) in the absence of light.

HOW SUPPLIED: Dormosedan® is supplied in 5- and 20-mL multidose vials.

NADA #140-862, Approved by FDA

Manufactured by:
Orion Corporation
Espoo, Finland

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: January 2013

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107224US-10
Made in Finland

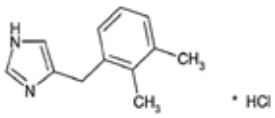
NADA #141-306, Approved by FDA

DORMOSEDAN GEL®

(detomidine hydrochloride)
Alpha$_2$-agonist oromucosal gel
Rx only
For Sedation and Restraint in Horses Only

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

DESCRIPTION:
DORMOSEDAN (detomidine hydrochloride) GEL is a synthetic alpha$_2$-adrenoreceptor agonist with sedative properties. Each mL of DORMOSEDAN GEL contains 7.6 mg detomidine hydrochloride. The chemical name is 1H imidazole, 4-[(2,3-dimethylphenyl) methyl]-hydrochloride. Detomidine hydrochloride is a white, crystalline, water-soluble substance having a molecular weight of 222.7. The molecular formula is $C_{12}H_{14}N_2$•HCl and the structural formula is



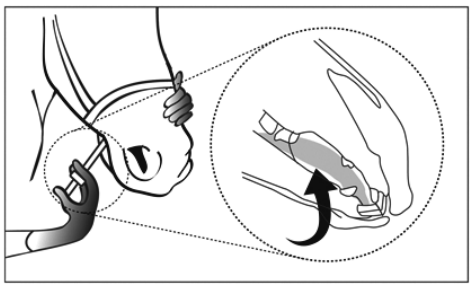
INDICATIONS:
DORMOSEDAN GEL is indicated for sedation and restraint in horses.

DOSAGE AND ADMINISTRATION:
DORMOSEDAN GEL produces sedation when administered sublingually at 0.018 mg/lb (0.040 mg/kg). DORMOSEDAN GEL must be placed beneath the tongue of the horse and is not meant to be swallowed. The dosing syringe delivers the product in 0.25 mL increments. The following dosing table may be used to determine the correct dose of DORMOSEDAN GEL (Table 1).
Table 1: Sublingual dosing of DORMOSEDAN GEL

Approximate body weight (lb)	Range of doses (mg/lb)	Approximate body weight (kg)	Range of doses (mg/kg)	Dose volume (mL)
330 - 439	0.023 – 0.017	150 – 199	0.051 – 0.038	1.00
440 - 549	0.022 – 0.017	200 – 249	0.047 – 0.038	1.25
550 – 659	0.021 – 0.017	250 – 299	0.046 – 0.038	1.50
660 - 769	0.020 – 0.017	300 – 349	0.044 – 0.038	1.75
770 - 879	0.019 – 0.017	350 – 399	0.043 – 0.038	2.00
880 - 989	0.019 – 0.017	400 – 449	0.043 – 0.038	2.25
990 - 1099	0.019 – 0.017	450 – 499	0.042 – 0.038	2.50
1100 - 1209	0.019 – 0.017	500 – 549	0.042 – 0.038	2.75
1210 - 1320	0.019 – 0.017	550 – 600	0.041 – 0.038	3.00

Use impermeable gloves when handling the product. Remove the syringe from the outer carton. While holding the plunger, turn the ring-stop on the plunger until the ring is able to slide freely up and down the plunger. Position the ring in such a way that the side nearest the barrel is at the desired volume marking. Turn the ring to secure it in place. Make sure that the horse's mouth contains no feed. Remove the cap from the tip of the syringe and save for cap replacement. Insert the syringe tip into the horse's mouth from the side of the mouth, placing the syringe tip beneath the tongue at the level of the commisure of the mouth. Depress the plunger until the ring-stop contacts the barrel, depositing the product beneath the tongue.

The following picture demonstrates correct administration of DORMOSEDAN GEL beneath the tongue.



Take the syringe out of the horse's mouth, recap the syringe and return it to the outer carton for disposal. Remove gloves for disposal.

For the best results, allow adequate time (a minimum of 40 minutes) between administration of DORMOSEDAN GEL and beginning the procedure. In general, horses show sedative effects lasting approximately 90-180 minutes.

Withhold food and water until the sedative effects of the product wear off.

CONTRAINDICATIONS:
DORMOSEDAN GEL is contraindicated in horses with known hypersensitivity to detomidine. Intravenous potentiated sulfonamides should not be used in anesthetized or sedated horses as potentially fatal dysrhythmias may occur.

Do not use DORMOSEDAN GEL in horses with pre-existing atrioventricular (AV) or sino-atrial (SA) blocks, respiratory disease, or chronic renal failure.

WARNINGS:
For sublingual use in horses only. Do not use in horses intended for human consumption.

HUMAN WARNINGS: Not for human use. Keep out of the reach of children. **Use impermeable gloves during drug administration and during procedures that require contact with the horse's mouth.** Following sublingual administration of detomidine oromucosal gel, drug concentrations up to 0.072 mg/mL were measured at 30 minutes post dose in equine saliva, equivalent to less than one percent of the original detomidine concentration in the gel. Mean drug concentrations fall to less than 0.010 mg/mL by 2 hours after drug administration, after which a slow decline occurs for several additional hours.

DORMOSEDAN GEL can be absorbed following direct exposure to skin, eyes, or mouth, and may cause irritation. Skin and mucosal contact with the product should be avoided. Use impermeable gloves at all times.

In case of accidental eye exposure, rinse abundantly with fresh water. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing.

Appropriate precautions should be taken while handling and using gel syringes. Accidental exposure could cause adverse reactions, including sedation, hypotension, and bradycardia. Seek medical attention immediately but do not drive because sedation or changes in blood pressure may occur.

Individuals with cardiovascular disease (for example, hypertension or ischemic heart disease) should take special precautions to avoid exposure to this product.

Caution should be exercised when handling sedated horses. Handling or any other sudden stimuli, including noise, may cause a defense reaction in an animal that appears to be heavily sedated.

Rare cases of human abuse of detomidine products have been reported. DORMOSEDAN GEL should be managed to prevent the risk of diversion, through such measures as restriction of access and the use of drug accountability procedures appropriate to the clinical setting.

The material safety data sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in users or to obtain a copy of the MSDS for this product call 1-888-963-8471.

Note to physician: This product contains an alpha$_2$-adrenoceptor agonist.

PRECAUTIONS:
DORMOSEDAN GEL must be placed beneath the tongue of the horse. Unlike most oral veterinary products, this product is not meant to be swallowed. Swallowing could result in ineffectiveness.

DORMOSEDAN GEL does not provide analgesia. Do not use for painful procedures.

Do not use with other sedative drugs because the effects may be additive.

Repeat dosing has not been evaluated.

The use of an alpha$_2$-agonist reversal agent with DORMOSEDAN GEL has not been evaluated.

Before initiating any procedure, allow sedation to fully develop. Nervous or excited horses with high levels of endogenous catecholamines may exhibit a reduced pharmacological response to alpha$_2$-adrenoceptor agonists like detomidine. In agitated horses, the onset of sedative effects could be slowed, or the depth and duration of effects could be diminished or nonexistent. When the product is administered, the animal should be allowed to rest in a quiet place for a minimum of 40 minutes.

Do not use DORMOSEDAN GEL in horses with cardiovascular disease, respiratory disorders, liver or kidney diseases, or in conditions of shock, severe debilitation, or stress due to extreme heat, cold, fatigue, or high altitude. Protect treated horses from temperature extremes. As with all alpha$_2$-adrenoceptor agonists, the potential for isolated cases of hypersensitivity, including paradoxical response (excitation), exists.

DORMOSEDAN GEL has not been evaluated in ponies, miniature horses, or horses younger than one year of age.

DORMOSEDAN GEL has not been evaluated for use in breeding, pregnant, or lactating horses.

ADVERSE REACTIONS:
Clinical field study:
In a US field study of 270 horses sedated to facilitate completion of various veterinary and husbandry procedures, the following adverse reactions were reported in 202 horses treated with DORMOSEDAN GEL and 68 horses treated with placebo:

Table 2: Adverse reactions (number of horses) during the clinical field study

Clinical Sign	DORMOSEDAN GEL N = 202	Placebo N =68
Sweating	20	0
Penile relaxation	12	0
Bradycardia (≤ 20 bpm)	11	0
Second degree AV block	9	0
Frequent urination	9	0
Piloerection	4	0
Marked ataxia	3	0
Facial/oral edema	3	0
Hypersalivation	2	0
Nasal discharge	2	0
Flatulence	1	0
Muscle tremors	1	1
Epiphora	1	0
Pale mucous membranes	1	0
Swollen sheath	1	0

In a laboratory study, transient erythema of the mucous membranes was seen in 2 (of 8) horses that received the recommended dose of detomidine gel.

Mild ataxia (horse stable but swaying slightly) was observed in 54% of DORMOSEDAN GEL-treated horses and in 4% of the placebo-treated horses at 40 minutes post treatment administration. Moderate ataxia was observed in 25% of DORMOSEDAN GEL-treated horses (0% placebo) at 40 minutes post treatment. Moderate to marked ataxia continued to 90 minutes for 5% and to 120 minutes for 4% of DORMOSEDAN GEL-treated horses.

CLINICAL PHARMACOLOGY:
Detomidine is a potent non-narcotic alpha$_2$-adrenoceptor agonist which produces sedation with a central effect inhibiting the transmission of noradrenalin-mediated nervous impulses. Blood pressure is initially increased due to peripheral vasoconstriction, subsequently dropping to normal or slightly below normal levels. Vasoconstriction may cause mucous membranes to appear pale or mildly cyanotic. This initial vasopressor response is accompanied by a compensatory marked decrease in heart rate mediated by a vagal baroreceptor. The peripheral pulse may feel weak and a transient change in the conductivity of the cardiac muscle may occur, as evidenced by first and second degree atrioventricular blocks. Other arrhythmias may occur. Detomidine also decreases the respiratory rate and decreases body temperature. Detomidine causes depression of gastrointestinal motility due to decrease in smooth muscle activity, increases blood glucose levels due to inhibition of insulin release, and increases production of urine 2 to 4 hours after treatment. In some horses, sweating, salivation and slight muscle tremors may be seen. Partial, transient penis prolapse may occur in stallions and geldings. Because of continued lowering of the head during sedation, mucus discharges from the nose with occasional swelling of the head, particularly around the eyes, may be seen.

Detomidine is oxidized mainly in the liver. Most metabolites are excreted in the urine. Halflife (T½) is 1-2 hours. Detomidine is rapidly distributed; volume of distribution (Vd) varies between 0.69 L/kg and 1.89 L/kg. Protein binding is about 85%.
Detomidine is a high extraction ratio drug. Alterations in liver blood flow (the site of detomidine metabolism) can change the rate of drug clearance and, consequently, drug exposure. The sedative effects of detomidine (using head droop as a marker for sedation) are highly correlated to blood concentration, regardless of the route of administration.

First pass effect results in a very small portion of drug reaching the systemic circulation if it is swallowed. Sedation achieved with the DORMOSEDAN GEL is attributable to sublingual drug absorption. Peak concentrations occur approximately 1.83 hours after sublingual administration of DORMOSEDAN GEL. The peak concentrations observed after administration of DORMOSEDAN GEL are approximately 40% of those observed after intramuscular injection of detomidine solution. The absolute bioavailability of detomidine in DORMOSEDAN GEL is 22%.

EFFECTIVENESS:
A prospective, randomized, masked, multi-center study was conducted to evaluate under field conditions, whether DORMOSEDAN GEL provided sufficient sedation and restraint in horses to successfully conduct procedures requiring administration of a sedative. Two hundred and seventy client-owned horses of any breed or sex were sedated to facilitate grooming (including cleaning of the prepuce), hoof care, floating teeth (manually), passage of a nasogastric tube or endoscope, or radiography. Horses were enrolled in the study if they were a yearling or older, in satisfactory body condition, and had a history of requiring sedation or other means of strong restraint to enable similar procedures to be carried out. Horses were randomly assigned to receive DORMOSEDAN GEL sublingually at 0.040 mg/kg or placebo gel.

After administration of treatment, each horse's level of sedation, degree of ataxia, heart rate and rhythm, and respiratory rate were assessed and measured to recovery. After an appropriate period of time elapsed to allow sedation to develop, a study veterinarian assessed and scored the ability to attempt and to complete the veterinary or husbandry procedure.

One hundred and twenty-nine DORMOSEDAN GEL-treated and 42 placebo-treated horses were included in the statistical analysis of effectiveness. Ninety-nine horses were excluded from the analysis due to failure to meet inclusion criteria or due to major protocol deviations. The veterinary or husbandry procedure was successfully completed for 98 of 129 DORMOSEDAN GEL-treated horses (76%) but only 3 of 42 placebo-treated horses (7%) (Table 3). The difference between the two treatments was statistically significant (p=0.0005).

Table 3: Treatment success rates (number of horses) by treatment group

Ability to perform the procedure score*	DORMOSEDAN GEL N=129	Placebo N=42
0	16	38
1	15	1
2	44	2
3	54	1
Success (score 2 or 3)	98	3

* 0: Poor – Strong resistance. 1: Fair. Moderate resistance. 2: Good. Some resistance, but the procedure could be performed. 3: Excellent. Procedure could be easily performed with insignificant resistance.

The following success rates with DORMOSEDAN GEL were recorded for electric clipping of hair (48%), cleaning the prepuce (81%), manual floating of teeth (89%), hoof trimming or shoeing (86%), passage of a nasogastric tube or endoscope (80%), or radiography (74%). At 40 minutes post dosing, 94% of DORMOSEDAN GEL-treated horses showed minimal, moderate or marked sedation compared with 14% of the horses treated with placebo. All DORMOSEDAN GEL-treated horses had recovered from sedation by 240 minutes post treatment.

DORMOSEDAN GEL was correctly administered sublingually (beneath the tongue) in 97% of horses with mild or no objection.

ANIMAL SAFETY:

In a multiple dose target animal safety study, DORMOSEDAN GEL was administered on three consecutive days to 6 horses per treatment group at 0, 1, 3 and 5 times the recommended label dose of 0.040 mg/kg.

The recommended dose (1X) induced sedation. Head droop caused transient edema of the head area, nasal/ocular discharge, and congestion of oral mucous membranes. Ataxia, sweating, and reversible penile prolapse were observed. Erythematous mucous membranes were seen at the area of dose application in 2/6 horses. Transient reductions were seen in heart rate, respiratory rate, and gut motility. Electrocardiography revealed increased incidences of vagally mediated arrhythmias (sinus arrhythmia, sinus block, 1st and 2nd degree atrioventricular block) as well as atrial or ventricular premature beats in the majority of horses. No clinical abnormalities were associated with the transient arrhythmias. Excessive or erratic urination were seen in isolated cases.

Similar treatment related findings were seen in horses receiving 3X and 5X doses. In most cases the incidence, severity, and duration of the findings were dose dependent. All findings in all dose groups were representative of the alpha$_2$-adrenoreceptor drugs used in horses.

STORAGE INFORMATION:

Store at controlled room temperature 20-25°C (68-77°F), with excursions permitted to 15-30°C (59-86°F), in the original package.

HOW SUPPLIED:

3.0 mL graduated oral dosing syringe, 7.6 mg/mL detomidine hydrochloride.

DORMOSEDAN® is a trademark of Orion Corporation.

TAKE TIME  OBSERVE LABEL DIRECTIONS

Mfd by:

ORION PHARMA Orion Corporation
Turku, Finland

Distributed by:
zoetis Zoetis Inc.
Kalamazoo, MI 49007

Made in Finland
Date: January 2013

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DOR14004

CLIENT INFORMATION SHEET FOR OWNER/HANDLER USE AND SAFETY:

This summary contains important information about Dormosedan Gel. You should read this information before you administer Dormosedan Gel to your horse. This sheet is provided only as a summary and does not take the place of instructions from your veterinarian. Talk to your veterinarian if you do not understand any of this information or if you want to know more about Dormosedan Gel.

What is Dormosedan Gel?

Dormosedan Gel is an oromucosal sedative containing detomidine hydrochloride. It is prescribed by veterinarians to allow procedures to be done in an anxious horse. Dormosedan Gel has not been shown to provide analgesia and should not be used for painful procedures.

How should the product be handled?

Always wear impermeable gloves when handling the dosing syringe with detomidine hydrochloride gel. Ask the veterinarian whether the gloves you plan to use are impermeable. For a minimum of 2 hours after administration, wear impermeable gloves when performing any tasks that require contact with the horse's mouth.

If you have or have had a history of cardiovascular disease (for example, hypertension or heart attack) take special precautions and avoid direct exposure to the dosing syringe. Do not come in contact with the mouth or any saliva of any horse that was treated with detomidine gel for a minimum of 2 hours.

What if I get the gel in my eyes or mouth?

Detomidine hydrochloride can be absorbed into your body after direct exposure through the eyes or mouth, and may cause irritation to these areas. In case of accidental eye exposure, flush with water for 15 minutes. If detomidine is exposed to the mucous membranes of the mouth, rinse without swallowing. In all cases of accidental exposure and possible ingestion, seek medical attention immediately. Accidental exposure could result in the drug affecting you, causing symptoms that include sleepiness, low blood pressure, and slower heart rate. DO NOT DRIVE because detomidine may cause you to feel drowsy or sleepy. Share the package information with your physician and tell the physician that the product contains an alpha$_2$-adrenoceptor agonist.

What if I get the gel on my skin?

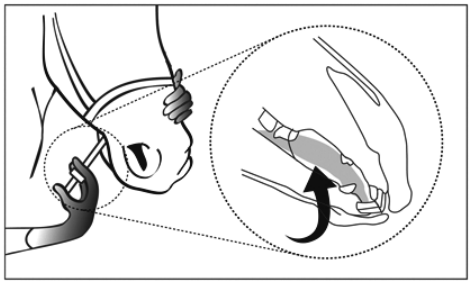
Detomidine hydrochloride can be absorbed into your body after direct exposure through the skin. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. Contact your physician if you have any questions or concerns.

The material safety data sheet (MSDS) contains more detailed occupational safety information. To report adverse reactions in humans or horses or to obtain an MSDS for this product call 1-888-963-8471.

How is Dormosedan Gel administered?

Dormosedan Gel should be given according to your veterinarian's instructions. Your veterinarian will tell you what amount of gel you should give to your horse. The appropriate dose is delivered beneath the tongue (sublingually) and is not meant to be swallowed. Make sure there is no food in the horse's mouth prior to administration.

The following drawing demonstrates correct administration of Dormosedan Gel beneath the tongue.



Following appropriate dosing of the gel, your horse should be kept in a quiet area until sedation is achieved.

If after 40 minutes there is inadequate sedation and you suspect that the horse swallowed or spit out some of the gel, contact your prescribing veterinarian. Do not repeat the dose.

If you believe the correct dose of detomidine gel was administered but the horse remains inadequately sedated, contact the prescribing veterinarian. Do not repeat the dose.

Contact your prescribing veterinarian immediately if the dosing syringe fails during the administration of detomidine gel and you are unsure if too much or too little of the dose was given.

Do not re-use partial dosing syringes. Any unused product or waste material should be disposed of in accordance with local requirements and Federal prescription drug disposal guidelines. Ask your veterinarian for this information.

What should I expect after administering Dormosedan Gel?

Following appropriate dosing of the gel, your horse should be kept in a quiet area. As the drug takes effect, you will typically see the head lower and the front legs plant in a firm stance. This will usually take about 40 minutes. You may also notice slight swaying, sweating, salivation and slight muscle tremors. Be careful when handling sedated horses. Handling or any other sudden stimuli, including noise, may cause a defense reaction (for example, kicking) even in a horse that appears to be fully sedated. It may take up to 3-4 hours for the horse to recover from sedation. Withhold food and water until the horse has recovered.

What else should I know about Dormosedan Gel?

As with all prescribed medicines, Dormosedan Gel should only be given to the horse for which it was prescribed. This sheet provides a summary of information about Dormosedan Gel. If you have any questions or concerns about Dormosedan Gel or its effects on your horse or yourself, talk to your veterinarian.

EXCEDE®
(Ceftiofur Crystalline Free Acid)
Sterile Suspension

For intramuscular injection in the horse.

CAUTION

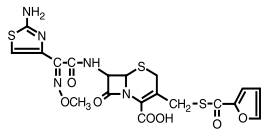
Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal Law prohibits extra-label use of this drug in cattle for disease prevention purposes; at unapproved doses; frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION

EXCEDE Sterile Suspension is a ready-to-use formulation that contains the crystalline free acid of ceftiofur, which is a broad spectrum cephalosporin antibiotic active against Gram-positive and Gram-negative bacteria including ß-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal, *in vitro*, resulting from inhibition of cell wall synthesis.

Each mL of this ready-to-use sterile suspension contains ceftiofur crystalline free acid equivalent to 200 mg ceftiofur, in a caprylic/capric triglyceride (Miglyol®) and cottonseed oil based suspension.

Figure 1. Structure of ceftiofur crystalline free acid:



Chemical name of ceftiofur crystalline free acid:
7-[[2-(2-Amino-4-thiazolyl)-2-(methoxyimino)acetyl] amino]- 3-[[(2-furanylcarbonyl)thio]methyl]-8-oxo-5-thia-1- azabicyclo[4.2.0]oct-2-ene 2-carboxylic acid

INDICATION

EXCEDE Sterile Suspension is indicated for the treatment of lower respiratory tract infections in horses caused by susceptible strains of *Streptococcus equi* ssp. *zooepidemicus*.

DOSAGE AND ADMINISTRATION

Shake well before using.

Administer two intramuscular injections to horses, 4 days apart, at a dose of 3.0 mg/lb (6.6 mg/kg). A maximum of 20 mL per injection site may be administered. Therapeutic drug concentrations are maintained for 6 days after the second injection (or a total of 10 days from the beginning of treatment) against *Streptococcus equi* ssp. *zooepidemicus*.

Table 1. Dosing Schedule for EXCEDE Sterile Suspension.

Weight (lb)	Dose Volume (mL)
100	1.5
200	3.0
300	4.5
400	6.0
500	7.5
600	9.0
700	10.5
800	12.0
900	13.5
1000	15.0

Weight (lb)	Dose Volume (mL)
1100	16.5
1200	18.0
1300	19.5
1400	21.0
1500	22.5
1600	24.0
1700	25.5
1800	27.0
1900	28.5
2000	30.0

CONTRAINDICATIONS

EXCEDE Sterile Suspension is contraindicated in horses with known allergy to ceftiofur or to ß-lactam (penicillins and cephalosporins) group antimicrobials. Due to the extended exposure in horses, based on the drug's pharmacokinetic properties, adverse reactions may require prolonged care.

WARNINGS

Not for use in humans. For use in animals only. Keep this and all drugs out of reach of children. Consult a physician in case of accidental human exposure.

Do not use in horses intended for human consumption.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposure to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth and clothing. Sensitization of the skin may be avoided by wearing protective gloves. Persons with a known sensitivity to penicillin or cephalosporins should avoid exposure to this product. In the case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g. skin rash, hives, difficult breathing) seek medical attention.

ANTIBACTERIAL WARNINGS

Use of antibacterial drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant bacteria.

PRECAUTIONS

The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that can be fatal. If acute diarrhea is observed, additional doses of EXCEDE should not be administered and appropriate therapy should be initiated.

Due to the extended exposure in horses, based on the drug's pharmacokinetic properties, adverse reactions may require prolonged care. EXCEDE is slowly eliminated from the body, with approximately 17 days needed to eliminate 97% of the dose from the body. Animals experiencing adverse reactions may need to be monitored for this duration of time.

The use of ceftiofur has not been evaluated in horses less than 4 months of age and in breeding, pregnant, or lactating horses. The long term effects on injection sites have not been evaluated.

ADVERSE REACTIONS

The injection of EXCEDE Sterile Suspension in the horse may cause firmness, swelling, sensitivity, and/or edema at the injection site (see **ANIMAL SAFETY**).

A total of 373 horses of various breeds, ranging in age from 4 months to 20 years, were included in the field study safety analysis. Adverse reactions reported in horses treated with EXCEDE and the placebo control are summarized in Table 2.

Injection site swelling (edema) was reported in 10 of 278 (3.6%) EXCEDE-treated horses and 1 of 95 (1%) of the placebo-treated horses. Of the 10 EXCEDE-treated horses with injection site swelling, 8 horses had swellings of 4 cm or less in diameter, one horse had a 10 cm diameter swelling and one horse had injection site reactions to both injections measuring 25 x 12 cm each. The injection site reactions in EXCEDE-treated horses resolved over 1 to 20 days.

At least one episode of diarrhea, loose, soft, or cowpie stools were observed in 25 of 278 (9%) of the EXCEDE-treated horses and 7 of 95 (7%) of the placebo-treated horses. The duration of episodes in EXCEDE-treated horses ranged from a single observation of loose stool to observations lasting 6 days. All cases were self-limiting and resolved with minimal (a single dose of loperamide) or no treatment.

Table 2. Number of Horses with Adverse Reactions During the Field Study with EXCEDE.

Adverse Reaction	EXCEDE (n=278)	Placebo (n=95)
Diarrhea/Soft Stool	25 (9%)	7 (7%)
Injection Site Swelling	10 (4%)	1 (1%)

The material safety data sheet (MSDS) contains more detailed occupational safety information. To obtain a material safety data sheet or to report any adverse event please call 1-888-963-8471.

CLINICAL PHARMACOLOGY

Ceftiofur is a beta-lactam antibiotic from the cephalosporin class. Beta lactams exert their inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins, which are essential for synthesis of the bacterial wall. Ceftiofur administered as either ceftiofur sodium (NAXCEL® Sterile Powder) or ceftiofur crystalline free acid (EXCEDE Sterile Suspension) is rapidly metabolized to desfuroylceftiofur, the primary metabolite with antimicrobial activity. Two intramuscular injections of EXCEDE Sterile Suspension at a dose of 6.6 mg/kg body weight in the horse provide concentrations of ceftiofur and desfuroylceftiofur related metabolites in plasma above the therapeutic target of 0.2 µg/mL for the entire 96 hour (4 day) dosing interval and for 6 days after the second injection (or a total of 10 days from the beginning of treatment) (see Figure 2 and Table 3).

Figure 2. Average plasma concentration of ceftiofur and desfuroylceftiofur related metabolites in horses following the intramuscular administration of either EXCEDE Sterile Suspension at a dose of 3.0 mg/lb (6.6 mg/kg) administered twice at a 96 hour interval or NAXCEL Sterile Powder at a dose of 1.0 mg/lb (2.2 mg/kg BW) once daily for 10 consecutive days.

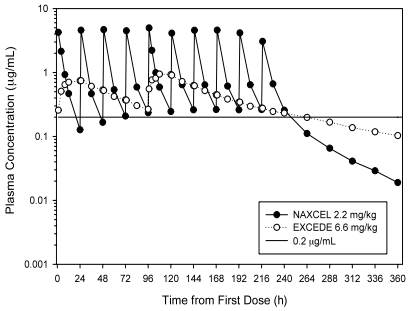


Table 3. Pharmacokinetic parameters measured after either two intramuscular injections of EXCEDE Sterile Suspension at a dose of 3.0 mg/lb (6.6 mg/kg) BW at a 96 hour interval or NAXCEL Sterile Powder at a dose of 1.0 mg/lb (2.2 mg/kg) BW once daily for 10 consecutive days are summarized in the following table.

PK Parameter	CCFA-SS at 6.6 mg/kg BW administered twice 96 h apart (Mean ± SD; n=12)		Ceftiofur sodium at 2.2 mg/kg BW once daily for 10 days (Mean ± SD; n=11)	
$AUC_{0-\infty}$ (µg•h/mL)	157 (19.1)		353 (44.9)	
$t_{\lambda 0.2}$ (h)	262 (29.0)		ND	
	Dose 1	**Dose 2**	**Dose 1**	**Dose 10**
T_{max} (h)	21.6 (5.8)	15.6 (6.3)	1.0	2.0 (3.3)
C_{max} (µg/mL)	0.78 (0.19)	1.0 (0.24)	4.31 ± 0.78	3.99 (1.23)

MICROBIOLOGY

Ceftiofur is a cephalosporin antibiotic. Like other ß-lactam antimicrobials, ceftiofur exerts its inhibitory effect by interfering with bacterial cell wall synthesis. This interference is primarily due to its covalent binding to the penicillin-binding proteins (PBPs) (i.e., transpeptidase and carboxypeptidase), which are essential for synthesis of the bacterial wall. Ceftiofur is not active against *Pseudomonas* spp. and enterococci.

The minimum inhibitory concentration (MIC) values for ceftiofur against label-claim pathogens isolated from lower respiratory tract infections in horses enrolled in a 2007-2008 field effectiveness study are presented in Table 4. All MICs were determined in accordance with the *Clinical and Laboratory Standards Institute* (CLSI) standards.

Table 4. Activity of EXCEDE Against Pathogens Isolated from Horses Treated With EXCEDE in Field Studies in the U.S. During 2007-2008.

Disease	Pathogen	Treatment Outcome	# of Isolates	Time of Sample Collection	MIC_{50} µg/mL	MIC_{90} µg/mL	MIC Range µg/mL
Lower Respiratory Tract Infection	*Streptococcus equi* ssp. *zooepidemicus*	Success	93*	Pre-Treatment	0.06	0.12	0.03-0.5
		Failure	42	Pre-Treatment	0.06	0.25	0.03-0.5

* One horse cultured *Staphylococcus aureus* (successfully treated) and is not represented in the table.

EFFECTIVENESS

A double masked, randomized, negative control, field study evaluated the effectiveness of two intramuscular doses of 6.6 mg/kg EXCEDE Sterile Suspension administered 4 days apart for the treatment of lower respiratory infections caused by *Streptococcus equi* ssp. *zooepidemicus* in the horse. In this study, a total of 278 horses were treated with EXCEDE, and 95 horses were treated with saline injections. One hundred ninety-three horses (136 EXCEDE and 57 saline placebo) were included in the statistical analysis. Therapeutic success was characterized by no worsening of clinical signs at Day 4, clinical improvement at Day 9, resolution of the clinical signs by Day 15, and no recurrence of clinical signs by Day 25 after initial dosing. EXCEDE was superior to the saline control. Table 5 summarizes the clinical success rates obtained 15 and 25 days after the first dose.

Table 5. Clinical success rates at Day 15 and 25.

Effectiveness parameter	EXCEDE	Saline Control	P-value
Clinical success Day 15	73.53%	38.60%	N/A
Clinical success Day 25	69.12%	31.58%	0.0215

ANIMAL SAFETY

Two studies, a target animal safety (TAS) study and a pharmacokinetic (PK) study (see **CLINICAL PHARMACOLOGY** section), were conducted to assess the safety of EXCEDE in the horse.

In the TAS study, healthy adult horses received 6 intramuscular (lateral neck) injections of EXCEDE Sterile Suspension at doses of either 3.0 (1X), 6.0 (2X) or 9.0 (3X) mg/lb with a 4 day interval between each injection. In the TAS study, there were no treatment related gastrointestinal findings for the three EXCEDE Sterile Suspension treatment groups. In the PK study, one horse treated with 6.0 mg/lb (2X) EXCEDE experienced a mild episode of colic the day after the second injection of EXCEDE. The horse recovered without treatment.

Injection sites were observed in both studies. In both studies, the largest injection volume administered was 20 mL per injection site. There were no observations of erythema, necrosis or drainage at the injection sites in these studies. Firmness, swelling, and/or sensitivity were observed in at least one injection site in all horses treated at the label dose. In the TAS study, injection site reaction measurements ranged from no measurable reaction to 16 x 33 x 1.5 cm. In the PK study, the largest area of edema associated with the injection site ranged from no detectable reaction to a 30 x 36 cm area of edema. Injection site reactions developed within 2 days of injection and resolved within 1-18 days. In the PK study, 2 horses had small areas of firmness that had not resolved at the end of the study (21 days after injection). In both studies, a greater incidence of injection site reactions occurred after the second injection, and in several horses, swelling at the injection site resolved then recurred 1-5 days later.

In the PK study, several horses developed clinical signs consistent with foot pain (stiff in the front limbs when turned in tight circles, and increased pulses and heat to the front feet). One horse in the NAXCEL group and one horse in the 6.0 mg/lb (2X) EXCEDE group were euthanized due to laminitis. Clinical signs of foot pain (stiff front limbs and increased heat and pulses in feet) affected more horses, for a longer period of time, in all EXCEDE-treated groups as compared to the NAXCEL-treated group. The study housing (multi-horse pens on concrete slabs) and diet (free choice alfalfa/grass mix and once a day pellets) may have contributed to the development of foot pain. The prevalence and severity of injection site reactions in EXCEDE-treated horses may also have contributed to the development of a stiff gait. A causal relationship between ceftiofur and foot pain could not be definitively determined.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F). Shake well before using. Contents should be used within 12 weeks after the first dose is removed.

HOW SUPPLIED

EXCEDE Sterile Suspension is available in the following package sizes:
100 mL vial
250 mL vial

NADA #141-209, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

www.EXCEDE.com or call 1-888-963-8471

Revised: November 2013

10423902A&P

ANADA 200-387, Approved by FDA

Flunixamine®

(flunixin meglumine)

Injectable Solution

50 mg/mL ***Sterile Solution***
VETERINARY ***Multi-Dose Vial***

NOT FOR USE IN HUMANS
KEEP OUT OF REACH OF CHILDREN

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

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

DESCRIPTION
Each milliliter of FLUNIXAMINE Injectable
Solution contains flunixin meglumine equivalent to 50 mg flunixin, 0.1 mg edetate disodium, 2.2 mg sodium formaldehyde sulfoxylate, 4.0 mg diethanolamine, 207.2 mg propylene glycol, 5.0 mg phenol as preservative, hydrochloric acid, water for injection q.s.

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 (V_{ss} 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: FLUNIXAMINE 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: FLUNIXAMINE Injectable Solution is indicated for the control of pyrexia associated with bovine respiratory disease, endotoxemia and acute bovine mastitis. FLUNIXAMINE 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 1.0 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 FLUNIXAMINE 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 WARNINGS: 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 FLUNIXAMINE Injectable Solution with other anti-inflammatory drugs, such as other NSAIDs and corticosteroids, should be avoided or closely monitored.

Horse: The effect of FLUNIXAMINE Injectable Solution on pregnancy has not been determined. Studies to determine activity of FLUNIXAMINE 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 FLUNIXAMINE Injectable Solution in these classes of cattle have not been investigated. NSAIDs are known to have potential effects on both parturition 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. The effects of flunixin on imminent parturition have not been evaluated in a controlled study. NSAIDs are known to have the potential to delay parturition through a tocolytic effect. Do not exceed the recommended dose.

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 flunixin meglumine. 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
FLUNIXAMINE Injectable Solution, 50 mg/mL, is available in 100 mL and 250 mL multi-dose vials.

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

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_{2a} 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.

Manufactured by:
Bimeda-MTC Animal Health Inc.
Cambridge, ON Canada

zoetis

Distributed by: Zoetis Inc.
Kalamazoo, MI 49007

Revised: March 2014

11952603A&P

HYLARTIN® V
sodium hyaluronate injection

10 mg/mL

Product Information

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

DESCRIPTION:
HYLARTIN® V is a sterile pyrogen-free solution of a highly purified, specific fraction of the sodium salt of hyaluronic acid extracted from rooster combs. HYLARTIN® V is supplied in disposable glass syringes, each of which contains 20 mg (10 mg/mL) of sodium hyaluronate in 2.0 mL physiological sodium chloride-phosphate buffer with a pH of 7.0-7.5.

CHEMISTRY:
Sodium hyaluronate is a high molecular weight polymer made up of repeating disaccharide units of N-acetylglucosamine and sodium glucuronate linked by beta 1-3 and beta 1-4 glycosidic bonds. HYLARTIN® V contains only traces of protein.

PHARMACOLOGY:
Sodium hyaluronate is a natural, physiological substance which occurs extracellularly in connective tissue in both animals and man and is chemically identical in different species. High concentrations (>0.2 mg/mL) of hyaluronate are found in the synovial fluid, the vitreous of the eye and the umbilical cord.

Sodium hyaluronate is a normal component of connective tissue matrix and it is injected therapeutically only in compartments where it constitutes a normal component, specifically the joint cavity.

ANIMAL SAFETY:
Acute, sub-acute and chronic toxicity studies in mice, rats, rabbits, dogs, monkeys and horses have not demonstrated any significant adverse reactions or sensitization.

In an acute toxicity study in horses, HYLARTIN® V was injected intra-articularly at dosages corresponding to five times the recommended dose per animal (200 mg total). In a sub-acute study, horses were injected intra-articularly with the recommended dose per joint (20 mg) at weekly intervals for nine weeks. The results of both investigations showed that hematological and blood chemistry values remained within normal ranges. In mice, the intravenous LD_{100} was found to be of the order of 50 mg/kg body weight.

There is always a potential immunological risk with repeated parenteral administration of biological material. However, as shown by Richter (1974), sodium hyaluronate, of both human and avian origin, did not produce any antibodies after repeated immunization, nor did intense stimulation of the immunization process by coupling of protein to the hyaluronate and simultaneous administration of Freund's adjuvant give rise to antibodies.

CLINICAL STUDIES:
Clinical field trials with thoroughbred and standardbred race horses were undertaken at four separate clinics. A total of 252 joints were injected with HYLARTIN® V in these investigations. In one study, only horses which were conventional treatment failures were included and the overall improvement rate following HYLARTIN® V treatment approached 90 percent. In the other studies, the improvement rate surpassed this figure.

In another case, electrogoniometry was used to objectively show that HYLARTIN® V can improve the function of arthritic carpal and fetlock joints. HYLARTIN® V brought return to symmetry with respect to timing and duration of various angular motions of the joints. In cases where HYLARTIN® V was not able to achieve contralateral symmetry of the joint motion pattern, blocking of the joint with anesthetic also had no effect, indicating that most probably mechanical damage was responsible for the joint dysfunction.

INDICATIONS:
HYLARTIN® V, is indicated in the treatment of joint dysfunction in horses due to non-infectious synovitis associated with equine osteoarthritis.

CONTRAINDICATIONS:
None known.

WARNING:
Do not use in horses intended for human consumption. HYLARTIN® V must not be administered intravascularly.

PRECAUTIONS:
Used or partially used syringes should be crushed and disposed of in an approved landfill.
Do not use if numerous small air bubbles are present throughout the solution.

ADVERSE REACTIONS:
The side effects observed in clinical trials were heat (15%), transient edema (12%), and pain (9%) around the treated joint. These side effects have been observed after intra-articular injection. Most of these reactions were of mild nature and in no case did they require the discontinuance of treatment. These reactions subsided in 24 to 48 hours.
For a copy of the Material Safety Data Sheet (MSDS) or to report adverse reactions call Zoetis Inc. at 1-888-963-8471.

DOSAGE AND ADMINISTRATION:
2 mL (20 mg) of HYLARTIN® V given to horses intra-articularly in small and medium size joints (carpal, fetlock). In the treatment of larger joints (hock), the dosage is 4 mL (40 mg). The treatment may be repeated at weekly intervals for a total of three treatments.

HYLARTIN® V should be injected in horses intra-articularly under strict aseptic conditions. Effusion should be removed prior to injection. When performing the injections, care should be taken not to scratch the cartilage surface, as this may result in diffuse swelling lasting for 24 to 48 hours. This transient swelling, however, will have no effect on the ultimate clinical result. For best results, the horse should be given two days stall rest before gradually resuming normal activity.

STORAGE CONDITIONS:
Store at 2° to 8°C. The expiration date is stated on the package.
Protect from freezing. Protect from light.

HOW SUPPLIED:
HYLARTIN® V, is supplied sterile in disposable glass syringes, each containing 20 mg (10 mg/mL) of sodium hyaluronate in 2.0 mL physiological sodium chloride-phosphate buffer. Each mL contains: Sodium hyaluronate 10.0 mg, sodium chloride 8.5 mg, disodium hydrogen phosphate dihydrate 0.28 mg, sodium dihydrogen phosphate hydrate 0.04 mg, water for injection USP q.s.

REFERENCE:
Richter, W., "Non-immunogenicity of purified hyaluronic acid preparations tested by passive cutaneous anaphylaxis", Int. Arch. Allergy 47:211-217, 1974.

NADA 112-048, Approved by FDA

Made in Sweden by:
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zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: October 2014
52-0241-00A&P

NADA 140-269, Approved by FDA

KETOFEN®
(ketoprofen)

Sterile Solution, 100 mg/mL

For intravenous use in horses only.

CAUTION

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

DESCRIPTION

Ketoprofen is a non-steroidal anti-inflammatory agent of the propionic acid class that includes ibuprofen, naproxen and fenoprofen. Each mL of KETOFEN (ketoprofen) contains 100 mg of ketoprofen in an aqueous formulation containing: L-Arginine, 70 mg; citric acid (to adjust pH); benzyl alcohol, 0.025 g (as preservative).

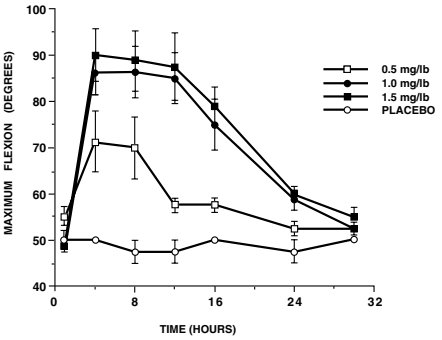
It is packaged in a multiple dose bottle.

PHARMACOLOGY

KETOFEN is a non-narcotic, non-steroidal anti-inflammatory agent with analgesic and antipyretic properties.

In horses, intravenous dosages of ketoprofen ranging from 0.5 to 1.5 mg/lb resulted in dosage dependent anti-inflammatory effects in the chronic adjuvant carpitis model as depicted in the following graph.

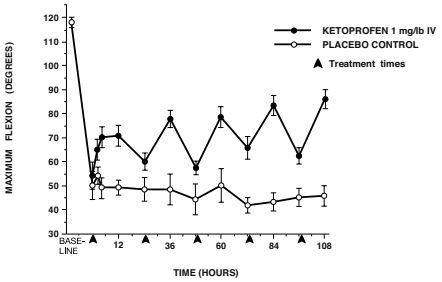
MAXIMUM FLEXION (intravenous ketoprofen, mean ± sem, n = 4)*



***sem = standard error of the mean**
n = number of animals

Additional studies using the same model in horses have shown that the effects of ketoprofen are maximal by 12 hours and still measurable at 24 hours after each dosage as depicted in the following graph.

MAXIMUM FLEXION (mean ± sem, n = 6)*



***sem = standard error of the mean**
n = number of animals

TOXICITY

Horses were found to tolerate ketoprofen given intravenously at dosages of 0, 1, 3 and 5 mg/lb once daily for 15 consecutive days (up to five times the recommended dosage for three times the usual duration) with no evidence of toxic effects. In clinical studies, intravenous injection of 1 mg/lb/day for five days resulted in no injection site irritation or other side effects.

At 15-fold overdose (15 mg/lb/day) for five days one of two horses developed severe laminitis, but no gross lesions or histologic changes were observed. The toxic effects observed in the horses given a 25-fold overdose (25 mg/lb/day) for five days included inappetence, depression, icterus, abdominal swelling and postmortem findings of gastritis, nephritis and hepatitis.

INDICATION

KETOFEN® (ketoprofen) is recommended for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse.

ADMINISTRATION AND DOSAGE

The recommended dosage is 1 mg/lb (1 mL/100 lbs) of body weight once daily. Treatment is administered by intravenous injection and may be repeated for up to five days. Onset of activity is within two hours with peak response by 12 hours.

CONTRAINDICATIONS

There are no known contraindications to this drug when used as directed. Intra-arterial injection should be avoided. Do not use in a horse if it has previously shown hypersensitivity to ketoprofen.

CAUTION

This product should not be used in breeding animals since the effects of KETOFEN on fertility, pregnancy or fetal health in horses have not been determined.

PRECAUTIONS

Studies to determine activity of KETOFEN when administered concomitantly with other drugs have not been conducted. Drug compatibility should be monitored closely in patients requiring adjunctive therapy.

WARNING

Do not use in horses intended for human consumption.

SIDE EFFECTS

During investigational studies, no significant side effects were reported.

HOW SUPPLIED

KETOFEN (ketoprofen) Solution 100 mg/mL is available in 50 mL and 100 mL multidose bottles.

Store at controlled room temperature 20° to 25°C (68° to 77°F).

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: January 2013

4390L
14053600A&P
GEQ14008

Lutalyse® Injection

(dinoprost injection)

5 mg dinoprost/mL as dinoprost tromethamine

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

LUTALYSE® Injection (5 mg dinoprost/mL) is a sterile solution containing the naturally occurring prostaglandin F2 alpha (dinoprost) as the tromethamine salt. Each mL contains dinoprost tromethamine equivalent to 5 mg dinoprost: also, benzyl alcohol, 16.5 mg added as preservative. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid. Dinoprost tromethamine is a white or slightly off-white crystalline powder that is readily soluble in water at room temperature in concentrations to at least 200 mg/mL.

INDICATIONS FOR USE

Cattle: LUTALYSE Injection is indicated as a luteolytic agent. LUTALYSE Injection is effective only in those cattle having a corpus luteum, i.e., those which ovulated at least five days prior to treatment. Future reproductive performance of animals that are not cycling will be unaffected by injection of LUTALYSE Injection.

- For estrus synchronization in beef cattle and non-lactating dairy heifers
- For unobserved (silent) estrus in lactating dairy cows with a corpus luteum
- For treatment of pyometra (chronic endometritis) in cattle
- For abortion of feedlot and other non-lactating cattle
- For use with FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows
- For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in lactating dairy cows
- For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in suckled beef cows and replacement beef and dairy heifers, advancement of first postpartum estrus in suckled beef cows, and advancement of first pubertal estrus in beef heifers

Swine:

- For parturition induction in swine

Mares:

- For controlling the timing of estrus in estrous cycling mares
- For difficult-to-breed mares (clinically anestrous mares that have a corpus luteum)

DOSAGE AND ADMINISTRATION

As with any multi-dose vial, practice aseptic techniques in withdrawing each dose to decrease the possibility of post-injection bacterial infections. Adequately clean and disinfect the vial stopper prior to entry with a sterile needle and syringe. Use only sterile needles, and use each needle only once.

No vial stopper should be entered more than 20 times. For this reason, the 100 mL bottle should only be used for cattle. The 30 mL bottle may be used for cattle, swine, or mares.

Cattle:

1. **For Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers.** LUTALYSE Injection is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum. Inject a dose of 5 mL LUTALYSE Injection (25 mg dinoprost) intramuscularly either once or twice at a 10 to 12 day interval. With the single injection, cattle should be bred at the usual time relative to estrus. With the two injections cattle can be bred after the second injection either at the usual time relative to detected estrus or at about 80 hours after the second injection of LUTALYSE Injection. Estrus is expected to occur 1 to 5 days after injection if a corpus luteum was present. Cattle that do not become pregnant to breeding at estrus on days 1 to 5 after injection will be expected to return to estrus in about 18 to 24 days.
2. **For Unobserved (Silent) Estrus in Lactating Dairy Cows with a Corpus Luteum.** Inject a dose of 5 mL LUTALYSE Injection (25 mg dinoprost) intramuscularly. Breed cows as they are detected in estrus. If estrus has not been observed by 80 hours after injection, breed at 80 hours. If the cow returns to estrus, breed at the usual time relative to estrus.

   Management Considerations: Many factors contribute to success and failure of reproduction management, and these factors are important also when time of breeding is to be regulated with LUTALYSE Injection. Some of these factors are:

   a. Cattle must be ready to breed—they must have a corpus luteum and be healthy;
   b. Nutritional status must be adequate as this has a direct effect on conception and the initiation of estrus in heifers or return of estrous cycles in cows following calving;
   c. Physical facilities must be adequate to allow cattle handling without being detrimental to the animal;
   d. Estrus must be detected accurately if timed AI is not employed;
   e. Semen of high fertility must be used;
   f. Semen must be inseminated properly.

   A successful breeding program can employ LUTALYSE Injection effectively, but a poorly managed breeding program will continue to be poor when LUTALYSE Injection is employed unless other management deficiencies are remedied first. Cattle expressing estrus following LUTALYSE Injection are receptive to breeding by a bull. Using bulls to breed large numbers of cattle in heat following LUTALYSE Injection will require proper management of bulls and cattle.
3. **For Treatment of Pyometra (chronic endometritis) in Cattle.** Inject a dose of 5 mL LUTALYSE Injection (25 mg dinoprost) intramuscularly.
4. **For Abortion of Feedlot and Other Non-Lactating Cattle.** LUTALYSE Injection is indicated for its abortifacient effect in feedlot and other non-lactating cattle during the first 100 days of gestation. Inject a dose of 25 mg dinoprost (5 mL) intramuscularly. Cattle that abort will abort within 35 days of injection.
5. **For use with FACTREL® (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows:** Administer 2 to 4 mL FACTREL Injection (100-200 mcg gonadorelin) per cow as an intramuscular injection in a treatment regimen with the following framework:
   - Administer the first dose of FACTREL Injection (2-4 mL) at Day 0
   - Administer LUTALYSE (25 mg dinoprost, as dinoprost tromethamine) Injection by intramuscular injection 6-8 days after the first dose of FACTREL Injection.
   - Administer a second dose of FACTREL Injection (2-4 mL) 30 to 72 hours after the LUTALYSE injection.
   - Perform FTAI 0 to 24 hours after the second dose of FACTREL Injection, or inseminate cows on detected estrus using standard herd practices.

Below are three examples of treatment regimens for FTAI that fit within the dosage regimen framework described immediately above:

	Example 1	Example 2	Example 3
Day 0 (Monday)	1st FACTREL	1st FACTREL	1st FACTREL
Day 7 (the following Monday)	LUTALYSE	LUTALYSE	LUTALYSE
Day 9 (Wednesday)	2nd FACTREL + FTAI at 48 hours after LUTALYSE	2nd FACTREL 48 hours after LUTALYSE	2nd FACTREL 56 hours after LUTALYSE
Day 10 (Thursday)		FTAI 24 hours after 2nd FACTREL	FTAI 18 hours after 2nd FACTREL

6. **For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for Synchronization of Estrus in Lactating Dairy Cows:**
   - Administer one EAZI-BREED CIDR Cattle Insert per animal and remove 7 days later (for example if administered on a Monday remove the following Monday).
   - Administer 5 mL LUTALYSE Injection at the time of removal of the EAZI-BREED CIDR Cattle Insert.
   - Observe animals for signs of estrus on Days 2 to 5 after removal of the EAZI-BREED CIDR Cattle Insert and inseminate animals found in estrus following normal herd practices.
7. **For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in suckled beef cows and replacement beef and dairy heifers, advancement of first postpartum estrus in suckled beef cows, and advancement of first pubertal estrus in beef heifers:**
   - Administer one EAZI-BREED CIDR Cattle Insert per animal for 7 days (for example, if administered on a Monday remove on the following Monday).
   - Inject 5 mL LUTALYSE Injection (equivalent to 5 mg/mL dinoprost) 1 day prior to EAZI-BREED CIDR Cattle Insert removal, on Day 6 of the 7 day administration period.
   - Observe animals for signs of estrus on Days 1 to 3 after removal of the EAZI-BREED CIDR Cattle Insert and inseminate animals about 12 hours after onset of estrus.

Swine:

For Parturition Induction in Swine: For intramuscular use for parturition induction in swine. LUTALYSE Injection is indicated for parturition induction in swine when injected within 3 days of normal predicted farrowing. The response to treatment varies by individual animals with a mean interval from administration of 2 mL LUTALYSE Injection (10 mg dinoprost) to parturition of approximately 30 hours. This can be employed to control the time of farrowing in sows and gilts in late gestation.

Management Considerations: Several factors must be considered for the successful use of LUTALYSE Injection for parturition induction in swine. The product must be administered at a relatively specific time (treatment earlier than 3 days prior to normal predicted farrowing may result in increased piglet mortality). It is important that adequate records be maintained on (1) the average length of gestation period for the animals on a specific location, and (2) the breeding and projected farrowing dates for each animal. This information is essential to determine the appropriate time for administration of LUTALYSE Injection.

Mares: LUTALYSE Injection is indicated for its luteolytic effect in mares. Administer a single intramuscular injection of 1 mg per 100 lbs (45.5 kg) body weight which is usually 1 mL to 2 mL LUTALYSE Injection. This luteolytic effect can be utilized to control the timing of estrus in estrous cycling and clinically anestrous mares that have a corpus luteum in the following circumstances:

1. **Controlling Time of Estrus of Estrous Cycling Mares:** Mares treated with LUTALYSE Injection during diestrus (4 or more days after ovulation) will return to estrus within 2 to 4 days in most cases and ovulate 8 to 12 days after treatment. This procedure may be utilized as an aid to scheduling the use of stallions.
2. **Difficult-to-Breed Mares:** In extended diestrus there is failure to exhibit regular estrous cycles which is different from true anestrus. Many mares described as anestrus during the breeding season have serum progesterone levels consistent with the presence of a functional corpus luteum. A proportion of "barren", maiden, and lactating mares do not exhibit regular estrous cycles and may be in extended diestrus. Following abortion, early fetal death and resorption, or as a result of "pseudopregnancy", there may be serum progesterone levels consistent with a functional corpus luteum. Treatment of such mares with LUTALYSE Injection usually results in regression of the corpus luteum followed by estrus and/or ovulation. Treatment of "anestrous" mares which abort subsequent to 36 days of pregnancy may not result in return to estrus due to presence of functional endometrial cups.

WARNINGS AND PRECAUTIONS

User Safety: Not for human use. Keep out of the reach of children. Women of childbearing age, asthmatics, and persons with bronchial and other respiratory problems should exercise **extreme caution** when handling this product. In the early stages, women may be unaware of their pregnancies. Dinoprost tromethamine is readily absorbed through the skin and can cause abortion and/or bronchiospasms. Accidental spillage on the skin should be washed off **immediately** with soap and water.

To report suspected adverse events, for technical assistance or to obtain a copy of the Material Safety Data Sheet (MSDS) contact Zoetis Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

Residue Warnings: No milk discard or preslaughter drug withdrawal period is required for labeled uses in cattle. No preslaughter drug withdrawal period is required for labeled uses in swine. Use of this product in excess of the approved dose may result in drug residues. Do not use in horses intended for human consumption.

Animal Safety Warnings: Severe localized clostridial infections associated with injection of LUTALYSE Injection have been reported. In rare instances, such infections have resulted in death. Aggressive antibiotic therapy should be employed at the first sign of infection at the injection site whether localized or diffuse. Do not administer intravenously (IV) as this route may potentiate adverse reactions. Non-steroidal anti-inflammatory drugs may inhibit prostaglandin synthesis; therefore this class of drugs should not be administered concurrently. Do not administer to pregnant cattle, unless abortion is desired. Cattle administered a progestin would be expected to have a reduced response to LUTALYSE Injection. Do not administer to sows and/or gilts prior to 3 days of normal

predicted farrowing as an increased number of stillbirths and postnatal mortality may result. In mares, LUTALYSE Injection is ineffective when administered prior to day-5 after ovulation. Mare pregnancy status should be determined prior to treatment since LUTALYSE Injection has been reported to induce abortion and parturition when sufficient doses were administered. Mares should not be treated if they suffer from either acute or subacute disorders of the vascular system, gastrointestinal tract, respiratory system, or reproductive tract.

ADVERSE REACTIONS

Cattle: Limited salivation has been reported in some instances.

Swine: The most frequently observed side effects were erythema and pruritus, slight incoordination, nesting behavior, itching, urination, defecation, abdominal muscle spasms, tail movements, hyperpnea or dyspnea, increased vocalization, salivation, and at the 100 mg (10x) dose only, possible vomiting. These side effects are transitory, lasting from 10 minutes to 3 hours, and were not detrimental to the health of the animal.

Mares: The most frequently observed side effects are sweating and decreased rectal temperature. However, these have been transient in all cases observed and have not been detrimental to the animal. Other reactions seen have been increase in heart rate, increase in respiration rate, some abdominal discomfort, locomotor incoordination, and lying down. These effects are usually seen within 15 minutes of injection and disappear within one hour. Mares usually continue to eat during the period of expression of side effects. One anaphylactic reaction of several hundred mares treated with LUTALYSE Injection was reported but was not confirmed.

Contact Information: To report adverse reactions call Zoetis Inc. at 1-888-963-8471.

CLINICAL PHARMACOLOGY

General Biologic Activity: Prostaglandins occur in nearly all mammalian tissues. Prostaglandins, especially PGE's and PGF's, have been shown, in certain species, to 1) increase at time of parturition in amniotic fluid, maternal placenta, myometrium, and blood, 2) stimulate myometrial activity, and 3) to induce either abortion or parturition. Prostaglandins, especially PGF2α, have been shown to 1) increase in the uterus and blood to levels similar to levels achieved by exogenous administration which elicited luteolysis, 2) be capable of crossing from the uterine vein to the ovarian artery (sheep), 3) be related to IUD induced luteal regression (sheep), and 4) be capable of regressing the corpus luteum of most mammalian species studied to date. Prostaglandins have been reported to result in release of pituitary tropic hormones. Data suggest prostaglandins, especially PGE's and PGF's, may be involved in the process of ovulation and gamete transport. Also PGF2α has been reported to cause increase in blood pressure, bronchoconstriction, and smooth muscle stimulation in certain species.

Metabolism: A number of metabolism studies have been done in laboratory animals. The metabolism of tritium labeled dinoprost (^{3}H PGF2 alpha) in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study demonstrated that equimolar doses of ^{3}H PGF2 alpha Tham and ^{3}H PGF2 alpha free acid administered intravenously to rats demonstrated no significant differences in blood concentration of dinoprost. An interesting observation in the above study was that the radioactive dose of ^{3}H PGF2 alpha rapidly distributed in tissues and dissipated in tissues with almost the same curve as it did in the serum. The half-life of dinoprost in bovine blood has been reported to be on the order of minutes. A complete study on the distribution of decline of ^{3}H PGF2 alpha Tham in the tissue of rats was well correlated with the work done in the cow. Cattle serum collected during 24 hours after doses of 0 to 250 mg dinoprost have been assayed by RIA for dinoprost and the 15-keto metabolites. These data support previous reports that dinoprost has a half-life of minutes. Dinoprost is a natural prostaglandin. All systems associated with dinoprost metabolism exist in the body; therefore, no new metabolic, transport, excretory, binding or other systems need be established by the body to metabolize injected dinoprost.

TARGET ANIMAL SAFETY

Laboratory Animals: Dinoprost was non-teratogenic in rats when administered orally at 1.25, 3.2, 10.0 and 20.0 mg dinoprost/kg/day from day 6th-15th of gestation or when administered subcutaneously at 0.5 and 1.0 mg/kg/day on gestation days 6, 7 and 8 or 9, 10 and 11 or 12, 13 and 14. Dinoprost was non-teratogenic in the rabbit when administered either subcutaneously at doses of 0.5 and 1.0 mg dinoprost/kg/day on gestation days 6, 7 and 8 or 9, 10 and 11 or 12, 13 and 14 or 15, 16 and 17 or orally at doses of 0.01, 0.1 and 1.0 mg dinoprost/kg/day on days 6-18 or 5.0 mg/kg/day on days 8-18 of gestation. A slight and marked embryo lethal effect was observed in dams given 1.0 and 5.0 mg dinoprost/kg/day respectively. This was due to the expected luteolytic properties of the drug.

A 14-day continuous intravenous infusion study in rats at 20 mg PGF2α per kg body weight indicated prostaglandins of the F series could induce bone deposition. However, such bone changes were not observed in monkeys similarly administered LUTALYSE Injection at 15 mg dinoprost per kg body weight for 14 days.

Cattle: In cattle, evaluation was made of clinical observations, clinical chemistry, hematology, urinalysis, organ weights, and gross plus microscopic measurements following treatment with various doses up to 250 mg dinoprost administered twice intramuscularly at a 10 day interval or doses of 25 mg administered daily for 10 days. There was no unequivocal effect of dinoprost on the hematology or clinical chemistry parameters measured. Clinically, a slight transitory increase in heart rate was detected. Rectal temperature was elevated about 1.5˚ F through the 6th hour after injection with 250 mg dinoprost, but had returned to baseline at 24 hours after injection. No dinoprost associated gross lesions were detected. There was no evidence of toxicological effects. Thus, dinoprost had a safety factor of **at least 10X** on injection (25 mg luteolytic dose vs. 250 mg safe dose), based on studies conducted with cattle. At luteolytic doses, dinoprost had no effect on progeny. If given to a pregnant cow, it may cause abortion; the dose required for abortion varies considerably with the stage of gestation. Induction of abortion in feedlot cattle at stages of gestation up to 100 days of gestation did not result in dystocia, retained placenta or death of heifers in the field studies. The smallness of the fetus at this early stage of gestation should not lead to complications at abortion. However, induction of parturition or abortion with any exogenous compound may precipitate dystocia, fetal death, retained placenta and/or metritis, especially at latter stages of gestation.

Swine: In pigs, evaluation was made of clinical observations, food consumption, clinical pathologic determinations, body weight changes, urinalysis, organ weights, and gross and microscopic observations following treatment with single doses of 10, 30, 50 and 100 mg dinoprost administered intramuscularly. The results indicated no treatment related effects from dinoprost treatment that were deleterious to the health of the animals or to their offspring.

Mares: Dinoprost tromethamine was administered to adult mares (weighing 320 to 485 kg; 2 to 20 years old), at the rates of 0, 100, 200, 400, and 800 mg per mare per day for 8 days. Route of administration for each dose group was both intramuscularly (2 mares) and subcutaneously (2 mares). Changes were detected in all treated groups for clinical (reduced sensitivity to pain; locomotor incoordination; hypergastromotility; sweating; hyperthermia; labored respiration), blood chemistry (elevated cholesterol, total bilirubin, LDH, and glucose), and hematology (decreased eosinophils; increased hemoglobin, hematocrit, and erythrocytes) measurements. The effects in the 100 mg dose, and to a lesser extent, the 200 mg dose groups were transient in nature, lasting for a few minutes to several hours. Mares did not appear to sustain adverse effects following termination of the side effects.

Mares treated with either 400 mg or 800 mg exhibited more profound symptoms. The excessive hyperstimulation of the gastrointestinal tract caused a protracted diarrhea, slight electrolyte imbalance (decreased sodium and potassium), dehydration, gastrointestinal irritation, and slight liver malfunction (elevated SGOT, SGPT at 800 mg only). Heart rate was increased but pH of the urine was decreased. Other measurements evaluated in the study remained within normal limits. No mortality occurred in any of the groups. No apparent differences were observed between the intramuscular and subcutaneous routes of administration. Luteolytic doses of dinoprost tromethamine are on the order of 5 to 10 mg administered on one day, therefore, LUTALYSE Injection was demonstrated to have a wide margin of safety. Thus, the 100 mg dose gave a safety margin of 10 to 20X for a single injection or 80 to 160X for the 8 daily injections.

Additional studies investigated the effects in the mare of single intramuscular doses of 0, 0.25, 1.0, 2.5, 3.0, 5.0, and 10.0 mg dinoprost tromethamine. Heart rate, respiration rate, rectal temperature, and sweating were measured at 0, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 6.0 hr. after injection. Neither heart rate nor respiration rates were significantly altered ($P > 0.05$) when compared to contemporary control values. Sweating was observed for 0 of 9, 2 of 9, 7 of 9, 9 of 9, and 8 of 9 mares injected with 0.25, 1.0, 2.5, 3.0, 5.0, or 10.0 mg dinoprost tromethamine, respectively. Sweating was temporary in all cases and was mild for doses of 3.0 mg or less but was extensive (beads of sweat over the entire body and dripping) for the 10 mg dose. Sweating after the 5.0 mg dose was intermediate between that seen for mares treated with 3.0 and 10.0 mg. Sweating began within 15 minutes after injection and ceased by 45 to 60 minutes after injection. Rectal temperature was decreased during the interval 0.5 until 1.0, 3 to 4, or 5 hours after injection for 0.25 and 1.0 mg, 2.5 and 3.0, or 5.0 and 10.0 mg dose groups, respectively. Average rectal temperature during the periods of decreased temperature was on the order of 97.5 to 99.6, with the greatest decreases observed in the 10 mg dose group.

EFFECTIVENESS

Cattle:

For Treatment of Pyometra (chronic endometritis) in Cattle: In studies conducted with LUTALYSE Injection, pyometra was defined as presence of a corpus luteum in the ovary and uterine horns containing fluid but not a conceptus based on palpation per rectum. Return to normal was defined as evacuation of fluid and return of the uterine horn size to 40mm or less based on palpation per rectum at 14 and 28 days. Most cattle that recovered in response to LUTALYSE Injection recovered within 14 days after injection. After 14 days, recovery rate of treated cattle was no different than that of non-treated cattle.

For Abortion of Feedlot and Other Non-Lactating Cattle: Commercial cattle were palpated per rectum for pregnancy in six feedlots. The percent of pregnant cattle in each feedlot less than 100 days of gestation ranged between 26 and 84; 80% or more of the pregnant cattle were less than 150 days of gestation. The abortion rates following injection of LUTALYSE Injection increased with increasing doses up to about 25 mg. As examples, the abortion rates, over 7 feedlots on the dose titration study, were 22%, 50%, 71%, 90% and 78% for cattle up to 100 days of gestation when injected IM with LUTALYSE Injection doses of 0,1 (5 mg), 2 (10 mg), 4 (20 mg) and 8 (40 mg) mL, respectively. The statistical predicted relative abortion rate based on the dose titration data, was about 93% for the 5 mL (25 mg) LUTALYSE Injection dose for cattle injected up to 100 days of gestation.

For use with FACTREL® (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows: For a full description of the studies conducted for the use of FACTREL Injection and LUTALYSE Injection, please refer to the labeling for FACTREL Injection.

Mares:

For Difficult-to-Breed Mares: In one study with 122 Standardbred and Thoroughbred mares in clinical anestrus for an average of 58 days and treated during the breeding season, behavioral estrus was detected in 81 percent at an average time of 3.7 days after injection with 5 mg LUTALYSE Injection; ovulation occurred an average of 7.0 days after treatment. Of those mares bred, 59% were pregnant following an average of 1.4 services during that estrus.

HOW SUPPLIED

LUTALYSE Injection is available in 30 and 100 mL vials.

STORAGE, HANDLING, AND DISPOSAL

Store at controlled room temperature 20° to 25°C (68° to 77°F). Protect from freezing.

NADA 108-901, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: August 2014

30196601A&P

Naxcel®

brand of ceftiofur sodium
sterile powder

For intramuscular and subcutaneous injection in cattle only. For intramuscular injection in swine, sheep, goats, and horses. For subcutaneous injection only in dogs, day-old chickens and day-old turkey poults. This product may be used in lactating dairy cattle, sheep, and goats.

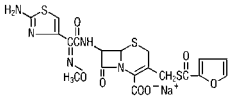
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian. Federal law prohibits extra-label use of this drug in cattle, swine, chickens and turkeys for disease prevention purposes; at unapproved doses, frequencies, durations, or routes of administration; and in unapproved major food producing species/production classes.

DESCRIPTION

NAXCEL Sterile Powder contains the sodium salt of ceftiofur which is a broad spectrum cephalosporin antibiotic active against gram-positive and gram-negative bacteria including β-lactamase-producing strains. Like other cephalosporins, ceftiofur is bactericidal *in vitro*, resulting from inhibition of cell wall synthesis.

Each mL of the reconstituted drug contains ceftiofur sodium equivalent to 50 mg ceftiofur. The pH was adjusted with sodium hydroxide and monobasic potassium phosphate.

Chemical Structure of Ceftiofur Sodium



Chemical Name of Ceftiofur Sodium

5-Thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2-amino-4-thiazolyl)(methoxyimino)-acetyl]amino]-3-[[(2-furanylcarbonyl)thio] methyl]-8-oxo-, monosodium salt, [6R-[6α,7β(Z)]]-

RECONSTITUTION OF THE STERILE POWDER

NAXCEL Sterile Powder should be reconstituted as follows:

1 gram vial–Reconstitute with 20 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

4 gram vial–Reconstitute with 80 mL Sterile Water for Injection. Each mL of the resulting solution contains ceftiofur sodium equivalent to 50 mg ceftiofur.

Shake thoroughly prior to use.

INDICATIONS

Cattle

NAXCEL Sterile Powder is indicated for treatment of bovine respiratory disease (shipping fever, pneumonia) associated with *Mannheimia haemolytica, Pasteurella multocida* and *Histophilus somni.* NAXCEL Sterile Powder is also indicated for treatment of acute bovine interdigital necrobacillosis (foot rot, pododermatitis) associated with *Fusobacterium necrophorum* and *Bacteroides melaninogenicus.*

Swine

NAXCEL Sterile Powder is indicated for treatment/control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis* and *Streptococcus suis.*

Sheep

NAXCEL Sterile Powder is indicated for treatment of sheep respiratory disease (sheep pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida.*

Goats

NAXCEL Sterile Powder is indicated for treatment of caprine respiratory disease (goat pneumonia) associated with *Mannheimia haemolytica* and *Pasteurella multocida.*

Horses

NAXCEL Sterile Powder is indicated for treatment of respiratory infections in horses associated with *Streptococcus zooepidemicus.*

Dogs

NAXCEL Sterile Powder is indicated for the treatment of canine urinary tract infections associated with *Escherichia coli* and *Proteus mirabilis.*

Day-Old Chicks

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old chicks.

Day-Old Turkey Poults

NAXCEL Sterile Powder is indicated for the control of early mortality, associated with *E. coli* organisms susceptible to ceftiofur, in day-old turkey poults.

DOSAGE AND ADMINISTRATION

Cattle

Administer to cattle by intramuscular or subcutaneous injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., for respiratory disease, extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite; and for foot rot, extent of swelling, lesion and severity of lameness).

Swine

Administer to swine by intramuscular injection at the dosage of 1.36 to 2.27 mg ceftiofur per pound (3.0 to 5.0 mg/kg) of body weight (1 mL of reconstituted sterile solution per 22 to 37 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days.

Sheep

Administer to sheep by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite).

Goats

Administer to goats by intramuscular injection at the dosage of 0.5 to 1.0 mg ceftiofur per pound (1.1 to 2.2 mg/kg) of body weight (1-2 mL reconstituted sterile solution per 100 lbs body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days. Additional treatments may be given on days four and five for animals which do not show a satisfactory response (not recovered) after the initial three treatments. Selection of dosage (0.5 to 1.0 mg/lb) should be based on the practitioner's judgement of severity of disease (i.e., extent of elevated body temperature, depressed physical appearance, increased respiratory rate, coughing and/or loss of appetite). Pharmacokinetic data indicate that elimination of the drug is more rapid in lactating does. For lactating does, the high end of the dose range is recommended.

Horses

Administer to horses by intramuscular injection at the dosage of 1.0 to 2.0 mg ceftiofur per pound (2.2 to 4.4 mg/kg) of body weight (2-4 mL reconstituted sterile solution per 100 lbs body weight). A maximum of 10 mL may be administered per injection site. Treatment should be repeated at 24-hour intervals, continued for 48 hours after clinical signs have disappeared and should not exceed 10 days.

Dogs

Administer to dogs by subcutaneous injection at the dosage of 1.0 mg ceftiofur per pound (2.2 mg/kg) of body weight (0.1 mL reconstituted sterile solution per 5 lbs body weight). Treatment should be repeated at 24-hour intervals for 5-14 days.

Reconstituted NAXCEL Sterile Powder is to be administered to dogs by subcutaneous injection. No vial closure should be entered more than 20 times. Therefore, only the 1 gram vial is approved for use in dogs.

Day-Old Chicks

Administer by subcutaneous injection in the neck region of day-old chicks at the dosage of 0.08 to 0.20 mg ceftiofur/chick. One mL of the 50 mg/mL reconstituted solution will treat approximately 250 to 625 day-old chicks.

Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only. A sterile 26 gauge needle and syringe or properly cleaned automatic injection machine should be used.

Day-Old Turkey Poults

Administer by subcutaneous injection in the neck region of day-old turkey poults at the dosage of 0.17 to 0.5 mg ceftiofur/poult. One mL of the 50 mg/mL reconstituted solution will treat approximately 100 to 294 day-old turkey poults. Reconstituted NAXCEL Sterile Powder is to be administered by subcutaneous injection only.

CONTRAINDICATIONS

As with all drugs, the use of NAXCEL Sterile Powder is contraindicated in animals previously found to be hypersensitive to the drug.

WARNINGS

NOT FOR HUMAN USE. KEEP OUT OF REACH OF CHILDREN.

Penicillins and cephalosporins can cause allergic reactions in sensitized individuals. Topical exposures to such antimicrobials, including ceftiofur, may elicit mild to severe allergic reactions in some individuals. Repeated or prolonged exposure may lead to sensitization. Avoid direct contact of the product with the skin, eyes, mouth, and clothing.

Persons with a known hypersensitivity to penicillin or cephalosporins should avoid exposure to this product.

In case of accidental eye exposure, flush with water for 15 minutes. In case of accidental skin exposure, wash with soap and water. Remove contaminated clothing. If allergic reaction occurs (e.g., skin rash, hives, difficult breathing), seek medical attention.

The material safety data sheet contains more detailed occupational safety information. To obtain a material safety data sheet (MSDS) or to report any adverse event please call Zoetis Inc. at 1-888-963-8471.

RESIDUE WARNINGS:

Cattle: When used according to label indications, dosage and routes of administration, treated cattle must not be slaughtered for 4 days following the last treatment. When used according to label indications, dosage and routes of administration, a milk discard time is not required. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Swine: When used according to label indications, dosage and route of administration, treated pigs must not be slaughtered for 4 days following the last treatment. **Use of dosages in excess of those indicated or by unapproved routes of administration may result in illegal residues in edible tissues.**

Sheep: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Goats: Neither a pre-slaughter drug withdrawal interval nor a milk discard time is required when this product is used according to label indications, dosage, and route of administration. **Use of dosages in excess of those indicated or by unapproved routes of administration, such as intramammary, may result in illegal residues in edible tissues and/or in milk.**

Horses: Do not use in horses intended for human consumption.

PRECAUTIONS

The effects of ceftiofur on the reproductive performance, pregnancy, and lactation of cattle, swine, sheep, and goats have not been determined.

Cattle

Following subcutaneous administration of ceftiofur sodium in the neck, small areas of discoloration at the site may persist beyond five days, potentially resulting in trim loss of edible tissues at slaughter.

As with any parenteral injection, localized post-injection bacterial infections may result in abscess formation. Attention to hygienic procedures can minimize their occurrence.

Swine

The safety of ceftiofur has not been determined for swine intended for breeding.

Horses

The safety of ceftiofur has not been determined for horses intended for breeding. The administration of antimicrobials to horses under conditions of stress may be associated with acute diarrhea that could be fatal. If acute diarrhea is observed, discontinue use of this antimicrobial and initiate appropriate therapy.

Dogs

The safety of ceftiofur has not been determined for dogs intended for breeding, or pregnant dogs.

ADVERSE REACTIONS

The use of ceftiofur may result in some signs of immediate and transient local pain to the animal.

CLINICAL MICROBIOLOGY

Summaries of MIC data are presented in Tables 1 and 2. Testing followed Clinical and Laboratory Standards Institute (CLSI) Guidelines.

Table 1. Ceftiofur MIC Values of Bacterial Isolates from Clinical Field Studies in the USA

Animal	Organism	Number Tested	Date Tested	MIC_{90}* (μg/mL)	MIC Range (μg/mL)
Bovine	*Mannheimia haemolytica*	461	1988-1992	0.06	≤0.03-0.13
	Mannheimia haemolytica	42	1993	0.015	≤0.003-0.03
	Pasteurella multocida	318	1988-1992	0.06	≤0.03-0.25
	Pasteurella multocida	48	1993	≤0.003	≤0.003-0.015
	Histophilus somni	109	1988-1992	0.06	≤0.03-0.13
	Histophilus somni	59	1993	≤0.0019	no range
	Fusobacterium necrophorum	17	1994	≤0.06	no range
Swine	*Actinobacillus pleuropn.*	83	1993	≤0.03	≤0.03-0.06
	Pasteurella multocida	74	1993	≤0.03	≤0.03-0.06
	Streptococcus suis	94	1993	0.25	≤0.03-1.0
	Salmonella choleraesuis	50	1993	1.0	1.0-2.0
	beta-hemolytic *Streptococcus* spp.	24	1993	≤0.03	≤0.03-0.06
	Actinobacillus suis	77	1998	0.0078	0.0019-0.0078
	Haemophilus parasuis	76	1998	0.06	0.0039-0.25
Sheep	*Mannheimia haemolytica*	39	1992	0.13	≤0.03-0.13
	Pasteurella multocida	23	1992	≤0.03	no range
Canine	*Escherichia coli*	44	1992	4.0	0.06-64.0
	Escherichia coli	18	1990	0.25	0.13-0.5
	Proteus mirabilis	17	1990	≤0.06	≤0.06-0.5
	Proteus mirabilis	23	1992	1.0	≤0.06-4.0
Turkey	*Escherichia coli*	1204	1995	1.0	0.13->32.0

*Minimum inhibitory concentration (MIC) for 90% of the isolates.

Table 2. Ceftiofur MIC Values of Bacterial Isolates from Diagnostic Laboratories in the USA and Canada*

Animal	Organism Tested	Number Tested	Date (μg/mL)	MIC_{90}** (μg/mL)	MIC Range
Bovine	*Mannheimia haemolytica*	110	1997-1998	0.06	≤0.03-0.25
	Mannheimia haemolytica	139	1998-1999	≤0.03	≤0.03-0.5
	Mannheimia haemolytica	209	1999-2000	≤0.03	≤0.03-0.12
	Mannheimia haemolytica	189	2000-2001	≤0.03	≤0.03-0.12
	Pasteurella multocida	107	1997-1998	≤0.03	≤0.03-0.25
	Pasteurella multocida	181	1998-1999	≤0.03	≤0.03-0.5
	Pasteurella multocida	208	1999-2000	≤0.03	≤0.03-0.12
	Pasteurella multocida	259	2000-2001	≤0.03	≤0.03-0.12
	Histophilus somni	48	1997-1998	≤0.03	≤0.03-0.25
	Histophilus somni	87	1998-1999	≤0.03	≤0.03-0.125
	Histophilus somni	77	1999-2000	≤0.03	≤0.03-0.06
	Histophilus somni	129	2000-2001	≤0.03	≤0.03-0.12
	Bacteroides fragilis group	29	1994	16.0	≤0.06->16.0
	Bacteroides spp., non-*fragilis* group	12	1994	16.0	0.13->16.0
	Peptostreptococcus anaerobius	12	1994	2.0	0.13-2.0
Swine	*Actinobacillus pleuropn.*	97	1997-1998	≤0.03	no range
	Actinobacillus pleuropn.	111	1998-1999	≤0.03	≤0.03-0.25
	Actinobacillus pleuropn.	126	1999-2000	≤0.03	≤0.03-0.06
	Actinobacillus pleuropn.	89	2000-2001	≤0.03	≤0.03-0.06
	Pasteurella multocida	114	1997-1998	≤0.03	≤0.03-1.0
	Pasteurella multocida	147	1998-1999	≤0.03	≤0.03-0.5
	Pasteurella multocida	173	1999-2000	≤0.03	≤0.03-0.06
	Pasteurella multocida	186	2000-2001	≤0.03	≤0.03-0.12
	Streptococcus suis	106	1997-1998	0.5	≤0.03-4.0
	Streptococcus suis	142	1998-1999	0.25	≤0.03-1.0
	Streptococcus suis	146	1999-2000	0.06	≤0.03-4.0
	Streptococcus suis	167	2000-2001	0.06	≤0.03-4.0
	Salmonella choleraesuis	96	1999-2000	1.0	0.03->4.0
	Salmonella choleraesuis	101	2000-2001	1.0	0.5-2.0
Equine	*Streptococcus equi* subsp. *equi*	12	1994	≤0.0019	no range
	Streptococcus equi subsp. *equi*	29	2002	≤0.03	≤0.03-0.05
	Streptococcus zooepidemicus	48	1994	≤0.0019	no range
	Streptococcus zooepidemicus	59	2002	≤0.03	≤0.03-0.25
	Rhodococcus equi	66	1998	4.0	≤0.03-16.0
	Rhodococcus equi	42	2002	8.0	≤0.03->32.0
	Bacteroides fragilis group	32	1995	>16.0	0.13->16.0
	Bacteroides spp., non-*fragilis* group	12	1995	4.0	0.25-4.0
	Fusobacterium necrophorum	16	1995	≤0.06	no range
Canine	*Escherichia coli*	26	2000	32	0.25->32
	Proteus mirabilis	14	2000	0.25	0.06-0.25
Turkey	*Escherichia coli*	17	1998-1999	1.0	0.25-1.0
	Escherichia coli	25	1999-2000	0.50	0.12-0.5
	Escherichia coli	20	2000-2001	2.0	0.12-16.0
	Citrobacter spp.	37	1995	32.0	0.5->32.0
	Enterobacter spp.	51	1995	>32.0	0.13->32.0
	Klebsiella spp.	100	1995	1.0	0.13-2.0
	Proteus spp.	19	1995	1.0	0.06-32.0
	Pseudomonas spp.***	31	1995	>32.0	0.06->32.0
	Salmonella spp.	24	1995	1.0	0.5-1.0
	Staphylococcus spp. (coagulase positive)	17	1995	2.0	1.0-2.0
	Staphylococcus spp. (coagulase negative)	26	1995	8.0	0.13->32.0
Chicken	*Escherichia coli*	62	1997-1998	0.50	0.25-2.0
	Escherichia coli	53	1998-1999	4.0	0.25->4.0
	Escherichia coli	67	1999-2000	0.50	0.12-16.0
	Escherichia coli	90	2000-2001	1.0	≤0.03-8.0

* The following *in vitro* data are available but their clinical significance is unknown.
** Minimum inhibitory concentration (MIC) for 90% of the isolates.
*** MIC_{50} is 32 μg/mL

Based on the pharmacokinetic studies of ceftiofur in swine and cattle after a single intramuscular injection of 1.36 to 2.27 mg ceftiofur equivalents/lb (3.0 to 5.0 mg/kg) BW (swine) or 0.5 to 1.0 mg ceftiofur equivalents/lb (1.1 to 2.2 mg/kg) BW (cattle) and the MIC and disk (30 µg) diffusion data, the following breakpoints are recommended by CLSI.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 21	≤ 2.0	(S) Susceptible
18-20	4.0	(I) Intermediate
≤ 17	≥ 8.0	(R) Resistant

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" is a technical buffer zone and isolates falling into this category should be retested. Alternatively the organism may be successfully treated if the infection is in a body site where drug is physiologically concentrated. A report of "Resistant" indicates that the achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Based on the pharmacokinetic studies of ceftiofur in horses after a single intramuscular injection of 1 mg ceftiofur equivalents/lb (2.2 mg/kg) BW, clinical effectiveness data and MIC data, the following breakpoint is recommended by CLSI.

Zone Diameter (mm)	MIC (µg/mL)	Interpretation
≥ 22	≤ 0.25	(S) Susceptible

The susceptible only category is used for populations of organisms (usually one species) for which regression analysis (disk vs. MIC) cannot be performed. These breakpoints will permit detection of strains with decreased susceptibility as compared to the original population.

Standardized procedures[1] require the use of laboratory control organisms for both standardized diffusion techniques and standardized dilution techniques. The 30 µg ceftiofur sodium disk should give the following zone diameters and the ceftiofur sodium standard reference powder (or disk) should provide the following MIC values for the reference strain. Ceftiofur sodium disks or powder reference standard is appropriate for both ceftiofur salts.

Table 3. Acceptable quality control ranges for ceftiofur against Clinical and Laboratory Standards Institute recommended American Type Culture Collection (ATCC) reference strains

Organism Name (ATCC Number)	Zone Diameter* (mm)	MIC Range (µg/mL)
Escherichia coli (25922)	26–31	0.25–1.0
Staphylococcus aureus (29213)	—	0.25–1.0
Staphylococcus aureus (25923)	27–31	—
Pseudomonas aeruginosa (27853)	14–18	16.0–64.0
Actinobacillus pleuropneumoniae (27090)	34–42**	0.004–0.015***
Histophilus somni (700025)	36–46**	0.0005–0.004***

* All testing performed using a 30µg disk.

** Quality control ranges are applicable only to tests performed by disk diffusion test using a chocolate Mueller-Hinton agar, incubated in 5-7% CO_2 for 20-24 hours.

*** MIC quality control ranges are applicable only to tests performed by broth microdilution procedures using veterinary fastidious medium (VFM).

ANIMAL SAFETY

Cattle

Results from a five-day tolerance study in normal feeder calves indicated that formulated ceftiofur was well tolerated at 25 times (25 mg/lb/day) the highest recommended dose of 1.0 mg/lb/day for five consecutive days. Ceftiofur administered intramuscularly had no adverse systemic effects.

In a 15-day safety/toxicity study, five steer and five heifer calves per group were intramuscularly administered formulated ceftiofur at 0 (vehicle control), 1, 3, 5 and 10 times the highest recommended dose of 1.0 mg/lb/day to determine the safety factor. There were no adverse systemic effects indicating that the formulated ceftiofur has a wide margin of safety when injected intramuscularly into the feeder calves at 10 times (10 mg/lb/day) the recommended dose for three times (15 days) the recommended three to five days of therapy. The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at 1 and 3 times the highest recommended dose of 1.0 mg/lb/day. The histopathological evaluations were conducted at posttreatment days 1, 3, 7 and 14.

The injection of NAXCEL Sterile Powder at the recommended dose administered SC in the neck of cattle was well tolerated. However, a several square centimeter area of yellow-red discoloration resulting from a single SC injection persisted in many of the cattle beyond 4.5 days post-injection. Also, one of the animals developed an abscess at the injection site.

Swine

Results from a five-day tolerance study in normal feeder pigs indicated that formulated ceftiofur was well tolerated when administered at 57 mg/lb (more than 25 times the highest recommended daily dosage of 2.27 mg/lb of body weight) for five consecutive days. Ceftiofur administered intramuscularly to pigs produced no overt adverse signs of toxicity.

To determine the safety factor and to measure the muscle irritancy potential in swine, a safety/toxicity study was conducted. Five barrows and five gilts per group were intramuscularly administered formulated ceftiofur at 0, 2.27, 6.81 and 11.36 mg/lb of body weight for 15 days which is 0, 1, 3 and 5 times the highest recommended dose of 2.27 mg/lb of body weight/day and 5 times the recommended treatment length of 3 days. There were no adverse systemic effects indicating that formulated ceftiofur has a wide margin of safety when injected intramuscularly into feeder pigs at the highest recommended dose of 2.27 mg/lb/day for 3 days or at levels up to 5 times the highest recommended dose for 5 times the recommended length of treatment. The formulation was shown to be a slight muscle irritant based on results of histopathological evaluation of the injection sites at posttreatment days 1, 2, 3 and 4. By day 10 post injection the muscle reaction was subsiding and at day 15 post injection there was little evidence of muscle damage in any of the pigs in any of the treatment groups.

Sheep

In a 15-day safety/toxicity study in sheep, three wether and three ewe lambs per group were given formulated ceftiofur sodium by the intramuscular route 0 (sterile water vehicle), 1, 3 or 5 times the recommended dose of 1.0 mg/lb/day for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in sheep. Based on examination of injection sites from study days 9, 11, 13 and 15, a low incidence of visual changes and histopathologic findings of mild, reversible inflammation from all groups including the controls indicated that the formulation is a slight muscle irritant.

Goats

In a 15-day safety/toxicity study 5 lactating does, 5 dry does, and 5 wethers were given formulated ceftiofur by the intramuscular route with 11 mg/kg/day for 15 days. This constitutes 5 times the recommended dose for 3 times the recommended maximum duration of 5 days of treatment. There were no adverse systemic effects indicating that formulated ceftiofur is well tolerated and has a wide margin of safety in goats.

Horses

In a safety study, horses received a daily intramuscular injection of either 0 mg/lb/day (saline control), 1.0 mg/lb/day (50 mg/mL), 3.0 mg/lb/day (100 mg/mL), or 5.0 mg/lb/day (200 mg/mL) of an aqueous solution of ceftiofur sodium for 30 or 31 days. Ceftiofur sodium was well tolerated when administered intramuscularly to male and female horses at doses up to 5.0 mg/lb/day for 30 or 31 days. No clinical evidence of irritation was noted at any dose. The drug-related changes detected in this study were limited to a transient decrease in food consumption in horses receiving 3.0 or 5.0 mg/lb/day ceftiofur, and general mild skeletal muscle irritation at the injection sites which resolved by regeneration of muscle fibers.

In a tolerance study, horses received a single daily intravenous infusion of either 0 (saline), 10.0 or 25.0 mg/lb/day of an aqueous solution (50 mg/mL) of ceftiofur for 10 days. The results indicated that ceftiofur administered intravenously at a dose of 10.0 or 25.0 mg/lb/day apparently can change the bacterial flora of the large intestine thereby leading to inflammation of the large intestine with subsequent diarrhea and other clinical signs (loose feces, eating bedding straw, dehydration, rolling or colic and a dull, inactive demeanor). Decreased food consumption, a loss of body weight, hematologic changes related to acute inflammation and stress, and serum chemistry changes related to decreased food consumption and diarrhea were also associated with treatment at these doses. The adverse effects were most severe a few days after dosing was initiated and tended to become less severe toward the end of the 10-day dosing period.

Dogs

Ceftiofur sodium was well tolerated at the therapeutic dose and is safe for the treatment of urinary tract infections in dogs. In the acute safety study, ceftiofur was well tolerated by dogs at the recommended level (1.0 mg/lb) for 5-14 days. When administered subcutaneously for 42 consecutive days, one of four females developed thrombocytopenia (15 days) and anemia (36 days). Thrombocytopenia and anemia also occurred at the 3X and 5X dose levels. In the reversibility phase of the study (5X dose), the thrombocytopenia reversed within 8 days, and of the two anemic animals the male recovered within 6 weeks and the female was sacrificed due to the severity of the anemia.

In the 15-day tolerance study in dogs, high subcutaneous doses (25 and 125 times the recommended therapeutic dose) produced a progressive and dose-related thrombocytopenia, with some dogs also exhibiting anemia and bone marrow changes. The hematopoietic changes noted in dogs treated with ceftiofur were similar to those associated with long-term cephalosporin administration in dogs and also man. The hematopoietic effects are not expected to occur as a result of recommended therapy.

Day-Old Chicks

In an acute toxicity study of ceftiofur in day-old chicks, a total of 60 male and 60 female chicks were each given single subcutaneous injections of 10, 100 or 1,000 mg/kg of body weight. Treatment on day 1 was followed by 6 days of observation; body weight was determined on days 1, 4 and 7; and selected hematology parameters were evaluated on day 4. No meaningful differences were noted among the treated and control groups of chicks for the parameters evaluated. Histopathologic evaluation of all deaths and chicks surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 20 times (100 mg/kg) the intended highest use dosage.

Day-Old Turkey Poults

In an acute toxicity study of ceftiofur in day-old turkey poults, a total of 30 male and 30 female poults were each administered single subcutaneous injections of 100, 400 or 800 mg/kg body weight. Injection on day 1 was followed by 6 days of observation; body weight on days 1, 4, and 7; and selected hematology parameters on day 4. No meaningful differences were noted between the treated groups at 100 or 400 mg ceftiofur/kg and a negative control group for the parameters evaluated. Histopathologic evaluation of all deaths and poults surviving to termination did not reveal a target organ or tissue of potential toxicity of ceftiofur when administered at up to 50 times (400 mg/kg) the highest use dosage. A dose of 800 mg/kg (100 times the intended highest use dosage) was toxic, resulting in clinical signs and deaths accompanied by gross and microscopic morphologic tissue alterations.

TISSUE RESIDUE DEPLETION

Cattle

A radiolabeled residue metabolism study established tolerances for ceftiofur residues in cattle kidney, liver and muscle. These tolerances of ceftiofur residues are 0.4 ppm in kidney, 2.0 ppm in liver, 1.0 ppm in muscle, and 0.1 ppm in milk.

A pivotal tissue residue decline study was conducted in cattle. In this study, cattle received an intramuscular injection of 1.0 mg of ceftiofur per lb body weight (2.2 mg of ceftiofur per kg body weight) for five consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period in cattle when used according to label directions.

Swine

Radiolabeled residue metabolism studies established tolerances for ceftiofur residues in swine kidney, liver, and muscle. These tolerances of ceftiofur residues are 0.25 ppm in kidney, 3.0 ppm in liver and 2.0 ppm in muscle.

A pivotal tissue residue decline study was conducted in swine. In this study, pigs received 2.27 mg of ceftiofur per lb body weight (5 mg of ceftiofur per kg body weight) per day for three consecutive days. Ceftiofur residues in tissues were less than the tolerances for ceftiofur residues in tissues such as kidney, liver and muscle by 4 days after dosing. These data collectively support a 4-day pre-slaughter withdrawal period in swine when used according to label directions.

STORAGE CONDITIONS

Store **unreconstituted** product at controlled room temperature 20° to 25° C (68° to 77° F).

Store **reconstituted** product either in a refrigerator 2° to 8° C (36° to 46° F) for up to 7 days or at controlled room temperature 20° to 25° C (68° to 77° F) for up to 12 hours.

Protect from light. Color of the cake may vary from off-white to a tan color. Color does not affect potency.

ONE-TIME SALVAGE PROCEDURE FOR RECONSTITUTED PRODUCT

At the end of the 7-day refrigeration or 12-hour room temperature storage period following reconstitution, any remaining reconstituted product may be frozen for up to 8 weeks without loss in potency or other chemical properties. This is a one-time only salvage procedure for the remaining product. To use this salvaged product at any time during the 8-week storage period, hold the vial under warm running water, gently swirling the container to accelerate thawing, or allow the frozen material to thaw at room temperature. Rapid freezing or thawing may result in vial breakage. Any product not used immediately upon thawing should be discarded.

HOW SUPPLIED

NAXCEL Sterile Powder is available in the following package sizes:

1 gram vial
4 gram vial

[1] Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Disk and Dilution Susceptibility Tests for Bacteria Isolated from Animals; Approved Standard – Second Edition. NCCLS document M31-A2. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, 2002.

NADA # 140-338, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: January 2014

30146300A&P

Predef® 2X

isoflupredone acetate

Sterile Aqueous Suspension

For Intramuscular or Intrasynovial Use Only

FOR USE IN ANIMALS ONLY

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

DESCRIPTION

Each mL of PREDEF 2X Sterile Aqueous Suspension contains 2 mg of isoflupredone acetate; also 4.5 mg sodium citrate hydrous; 120 mg polyethylene glycol 3350; 1 mg povidone; 0.201 mg myristyl-gamma-picolinium chloride added as preservative. When necessary, pH was adjusted with hydrochloric acid and/or sodium hydroxide. It is for intramuscular or intrasynovial injection in animals and is indicated in situations requiring glucocorticoid, anti-inflammatory, and/or supportive effect.

Metabolic and Hormonal Effects

PREDEF 2X, a potent corticosteroid, has greater glucocorticoid activity than an equal quantity of prednisolone.

The glucocorticoid activity of PREDEF 2X is approximately 10 times that of prednisolone, 50 times that of hydrocortisone, and 67 times that of cortisone as measured by liver glycogen deposition in rats. The gluconeogenic activity is borne out by its hyperglycemic effect in both normal and ketotic cattle.

INDICATIONS

Bovine Ketosis. PREDEF 2X Sterile Aqueous Suspension, by its gluconeogenic and glycogen deposition activity, is an effective and valuable treatment for the endocrine and metabolic imbalance of primary bovine ketosis. The stresses of parturition and high milk production predispose the dairy cow to this condition. This adrenal steroid causes a prompt physiological effect, with blood glucose levels returning to normal or above within 8 to 24 hours following injection. There is a decrease in circulating eosinophils, followed by a reduction in blood and urine ketones. Usually the general attitude of the cow is much improved, appetite returns, and milk production rises to previous levels within 3 to 5 days. In secondary bovine ketosis, where the condition is complicated by pneumonia, mastitis, endometritis, traumatic gastritis, etc, PREDEF 2X should be used concurrently with proper local and parenteral antibacterial therapy, infusion solutions, and other accepted treatments for the primary conditions.

Musculoskeletal Conditions. As with other adrenal steroids, this preparation has been found useful in alleviating the pain and lameness associated with generalized and acute localized arthritic conditions in large animals. PREDEF 2X has been used successfully to treat laminitis, rheumatoid and traumatic arthritis, osteoarthritis, periostitis, tendinitis, tenosynovitis, bursitis, and myositis. Generalized muscular soreness, stiffness, depression, and anorexia resulting from overwork, shipping, unusual physical exertion, etc, respond promptly. Remission of symptoms may be permanent, or symptoms may recur, depending on the cause and extent of structural degeneration.

Allergic Reactions. PREDEF 2X is especially beneficial in treating acute hypersensitivity reactions resulting from treatment with a sensitizing drug or exposure to other allergenic agents. Usual manifestations are anaphylactoid reactions and urticaria. Less severe allergic manifestations, such as atopic and contact dermatitis, summer eczema, and conjunctivitis, may also be treated. Response is usually rapid and complete, although in severe cases with extensive lesions, more prolonged adrenocorticoid therapy and other appropriate treatment may be indicated.

Overwhelming Infections with Severe Toxicity. In animals moribund from overwhelmingly severe infections for which specific antibacterial therapy is available (eg, critical pneumonia, peritonitis, endometritis, septic mastitis), intensive PREDEF 2X therapy may aid in correcting the circulatory defect by counteracting the responsible inflammatory changes, thereby permitting the antibacterial agent to exert its full effect. As supportive therapy, this steroid combats the stress and improves the general attitude of the animal being treated. All necessary procedures for the establishment of a bacterial diagnosis should be carried out whenever possible before institution of therapy. PREDEF 2X Sterile Aqueous Suspension therapy in the presence of infection should be administered for the shortest possible time compatible with maintenance of an adequate response, and antibacterial therapy should be continued for at least three days after the hormone has been withdrawn. Combined hormone and antibacterial therapy does not obviate the need for indicated surgical treatment.

Shock. PREDEF 2X is indicated in adrenal failure and shocklike states occurring in association with severe injury or other trauma, emergency surgery, anaphylactoid reactions, and elective surgery in poor surgical risks. It is recommended as an adjuvant to standard methods of combating shock, including use of plasma expanders. Because of interrelated physiologic activities, beneficial effects may not be exhibited until all such procedures have been employed.

Other Indications. Exhaustion following surgery or dystocia, retained placenta, inflammatory ocular conditions, snakebite, and other stress conditions are also indications for use. Its employment in the treatment of these conditions is recommended as a supportive measure to standard procedures and time-honored treatments will give comfort to the animal and hasten complete recovery.

PREDEF 2X has been found useful as supportive therapy in the treatment of the stress associated with parturient paresis ie, milk fever. It should be given intramuscularly, before or after the administration of the calcium infusion solutions commonly employed in treating the disease. **PREDEF 2X is not to be added to the infusion solutions.**

WARNINGS

Animals intended for human consumption should not be slaughtered within 7 days of last treatment. Do not use in horses intended for human consumption. 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 human use.**

Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis.

Additionally, corticosteroids administered to dogs, rabbits, and rodents during pregnancy have resulted in cleft palate in offspring. Corticosteroids administered to dogs during pregnancy have also resulted in other congenital anomalies, including deformed forelegs, phocomelia, and anasarca.

PRECAUTIONS

PREDEF 2X Sterile Aqueous Suspension exerts an inhibitory influence on the mechanisms and the tissue changes associated with inflammation. Vascular permeability is decreased, exudation diminished, and migration of the inflammatory cells markedly inhibited. In addition, systemic manifestations such as fever and signs of toxemia may also be suppressed. While certain aspects of this alteration of the inflammatory reaction may be beneficial, the suppression of inflammation may mask the signs of infection and tend to facilitate spread of microorganisms. However, in infections characterized by overwhelming toxicity, PREDEF 2X therapy in conjunction with appropriate antibacterial therapy is effective in reducing mortality and morbidity. Without concurrent use of an antibiotic to which the invader-organism is sensitive, injudicious use of the adrenal hormones in animals with infections can be hazardous. As with other corticoids, continued or prolonged use is discouraged.

While no sodium retention nor potassium depletion has been observed at the doses recommended in animals receiving 9-fluoroprednisolone acetate, as with all corticoids, animals should be under close observation for possible untoward effects. If symptoms of hypopotassemia should occur, corticoid therapy should be discontinued and 5% solution of potassium chloride administered by continuous intravenous drip.

DOSAGE AND ADMINISTRATION

PREDEF 2X Sterile Aqueous Suspension is administered by deep intramuscular injection for systemic effect, or into joint cavity, tendon sheath, or bursa for local effect.

Cattle. The usual intramuscular dose for cattle is 10 to 20 mg, according to the size of the animal and severity of the condition. This dose may be repeated in 12 to 24 hours if indicated.

Ketosis studies have demonstrated that relatively high initial doses of corticoids produce a more prompt recovery with a lower incidence of relapse than when relatively low doses are used, even when these are repeated. Response of ketosis to PREDEF 2X therapy parallels that derived with prednisolone. PREDEF 2X is 10 times more glucogenic than prednisolone. Thus, 10 mg of isoflupredone acetate therapeutically equals 100 mg of prednisolone.

In the event of poor response or relapse, diagnosis should be reconfirmed by re-examining the animal for complications (ie, pneumonia, metritis, traumatic gastritis, mastitis).

Horses. The usual intramuscular dose for horses is 5 to 20 mg repeated as necessary. The usual intrasynovial dose in joint inflammation, tendinitis, or bursitis is 5 to 20 mg or more, depending on the size of the cavity to be injected.

Swine. The usual intramuscular dose for swine is 5 mg for a 300 pound animal. The dose for larger or smaller pigs is proportional to the weight of the animal.

HOW SUPPLIED

PREDEF 2X Sterile Aqueous Suspension, 2 mg per mL, is available in 100 mL vials.

Store at controlled room temperature 20° to 25° C (68° to 77° F).

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: March 2013

PAA036089A&P
GCE14017

Strongid® T

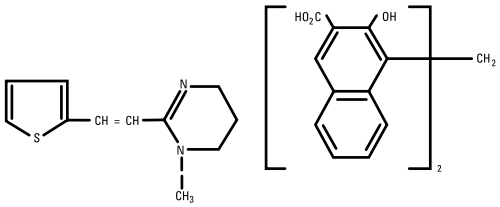
(pyrantel pamoate)

Equine Anthelmintic Suspension

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

DESCRIPTION: Strongid T is a suspension of pyrantel pamoate in a palatable caramel-flavored vehicle. Each mL contains 50 mg of pyrantel base as pyrantel pamoate.

Pyrantel pamoate is a compound belonging to a family classified chemically as tetrahydropyrimidines. It is a yellow, water-insoluble crystalline salt of the tetrahydropyrimidine base and pamoic acid containing 34.7% base activity. The chemical structure and name are given below:



(E)-1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl) vinyl] pyrimidine 4,4' methylenebis[3-hydroxy-2-naphthoate] (1:1)

INDICATIONS AND USAGE: For the removal and control of mature infections of large strongyles *(Strongylus vulgaris, S. edentatus, S. equinus);* pinworms *(Oxyuris equi);* large roundworms *(Parascaris equorum);* and small strongyles in horses and ponies.

CONTRAINDICATIONS: It is recommended that severely debilitated animals not be treated with this preparation.

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

PRECAUTION: This product is a suspension and as such will separate. To insure uniform resuspension and to achieve proper dosage, **it is extremely important that the product be shaken and stirred thoroughly before every use.**

DOSAGE AND ADMINISTRATION: Administer 3 mg pyrantel base per lb of body weight (6 mL Strongid T per 100 lb of body weight). For maximum control of parasitism, it is recommended that foals (2–8 months of age) be dosed every 4 weeks. To minimize potential hazard that the mare may pose to the foal, she should be treated 1 month prior to anticipated foaling date followed by retreatment 10 days to 2 weeks after birth of foal. Horses over 8 months of age should be routinely dosed every 6 weeks.

Directions for use: Strongid T may be administered by means of a stomach tube, dose syringe or by mixing into the feed.

Stomach Tube: Measure the appropriate dosage of Strongid T and mix in the desired quantity of water. Protect drench from direct sunlight and administer to the animal immediately following mixing. Do not attempt to store diluted suspension.

Strongid T is inactive against the common horse bot (*Gasterophilus* spp.) However, Strongid T may be administered concurrently with carbon disulfide observing the usual precautions with carbon disulfide.

Dose Syringe: Draw the appropriate dosage of Strongid T into a dose syringe and administer to the animal. Do not expose Strongid T to direct sunlight.

Feed: Mix the appropriate dosage of Strongid T in the normal grain ration. Fasting of animals prior to or following treatment is not required.

EFFICACY: Critical (worm-count) studies in horses demonstrated that Strongid T administered at the recommended dosage was efficacious against mature infections of *Strongylus vulgaris* (>90%), *S. edentatus* (69%), *S. equinus* (>90%), *Oxyuris equi* (81%), *Parascaris equorum* (>90%), and small strongyles (90%).

SAFETY: Strongid T is well tolerated by horses and ponies of all ages. No adverse drug response was observed when dose rates up to 60 mg of pyrantel base per lb of body weight were administered by stomach tube nor when 3 mg base per lb was given by intratracheal injection. The reproductive performance of pregnant mares and stud horses dosed with Strongid T has not been affected.

RECOMMENDED STORAGE: Store below 30°C (86°F).

HOW SUPPLIED: Strongid T is supplied in 1 quart (946 mL) bottles.

NADA #91-739, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

13911800A&P
Revised: January 2013
Printed in USA
STR14002

NADA 135-780, Approved by FDA

Torbugesic®

BUTORPHANOL TARTRATE

Veterinary Injection

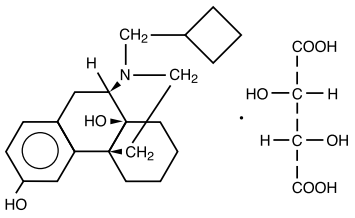
CAUTION

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

DESCRIPTION

TORBUGESIC (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 $C_{21}H_{29}NO_2 \cdot C_4H_6O_6$.

Chemical Structure



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

CLINICAL PHARMACOLOGY

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 the newborn, resulting in a decreased survival rate of the newborn. This nervousness was seen only in the rat species.

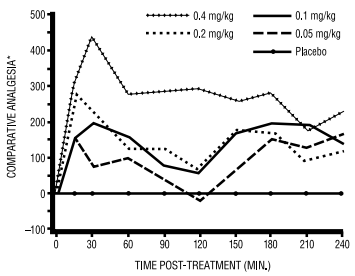
Equine Pharmacology

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, as illustrated in the following figure:

Analgesic Effects of Butorphanol Given at Various Dosages in Horses with Abdominal Pain



*Pain threshold in butorphanol-treated colicky horses relative to placebo controls.

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 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 three minutes. The same dosage administered after 10 successive daily 1 mg/kg dosages of butorphanol resulted only in transient sedative effects. During the 10-day course of administration at 1 mg/kg (10 times the recommended use level) in two 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 mg/kg (10 times the recommended dose) every four 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

TORBUGESIC (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 TORBUGESIC alleviates abdominal pain associated with torsion, impaction, intussusception, spasmodic and tympanic colic and postpartum pain.

WARNINGS

DO NOT USE IN HORSES INTENDED FOR HUMAN CONSUMPTION. NOT FOR HUMAN USE.

CAUTION

TORBUGESIC, 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 of butorphanol per kilogram of body weight (0.05 mg/lb) by intravenous injection. This is equivalent to 5 mL of TORBUGESIC for each 1000 lbs body weight.

The dose may be repeated within 3 to 4 hours but treatment should not exceed 48 hours. Pre-clinical model studies and clinical field trials in horses demonstrate that the analgesic effects of TORBUGESIC are seen within 15 minutes following injection and persist for about 4 hours.

HOW SUPPLIED

50 mL vials TORBUGESIC (butorphanol tartrate) Veterinary Injection, 10 mg base activity per mL.
10 mL vials TORBUGESIC (butorphanol tartrate) Veterinary Injection, 10 mg base activity per mL.

Store at controlled room temperature 20°-25°C (68°-77°F) with excursions between 15°-30°C (59°-86°F).

REFERENCES

1. Pircio, A.W. *et al.* "The Pharmacology of Butorphanol," *Arch. Int. Pharmacodyn. Ther.* 220 (2): 231–257, 1976.
2. Dobkin, A.B. *et al.* "Butorphanol and Pentazocine in Patients with Severe Postoperative Pain," *Clin. Pharmacol. Ther.* 18: 547–553, 1975.
3. Gilbert, M.S. *et al.* "Intramuscular Butorphanol and Meperidine in Postoperative Pain," *Clin. Pharmacol. Ther.* 20: 359–364, 1976.
4. Cavanagh, R.L. *et al.* "Antitussive Properties of Butorphanol," *Arch. Int. Pharmacodyn. Ther.* 220 (2): 258–268, 1976.
5. Schurig, J.E. *et al.* "Effect of Butorphanol and Morphine on Pulmonary Mechanics, Arterial Blood Pressure, and Venous Plasma Histamine in the Anesthetized Dog," *Arch. Int. Pharmacodyn. Ther.* 233: 296–304, 1978.
6. Nagashmina, H. *et al.* "Respiratory and Circulatory Effects of Intravenous Butorphanol and Morphine," *Clin. Pharmacol. Ther.* 19: 735–745, 1976.
7. Popio, K.A. *et al.* "Hemodynamic and Respiratory Effects of Morphine and Butorphanol," *Clin. Pharmacol. Ther.* 23: 281–287, 1978.
8. Robertson, J.T. and Muir, W.W.: "Cardiopulmonary Effects of Butorphanol Tartrate in Horses," *Am. J. Vet. Res.* 42: 41–44, 1981.
9. Kalpravidh, M. *et al.* "Effects of Butorphanol, Flunixin, Levorphanol, Morphine, Pentazocine and Xylazine in Ponies," *Am. J. Vet. Res.* 45: 217–223, 1984.

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Fort Dodge Animal Health
a division of Wyeth
a wholly owned subsidiary of Pfizer Inc
New York, NY 10017
Made in Spain

Revised: January 2012

P1106-308US/02-12A&P
GEQ14010

TUCOPRIM® (trimethoprim and sulfadiazine)

Powder

For Use in Horses

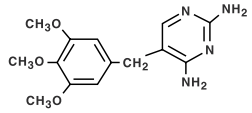
CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION

TUCOPRIM Powder contains 67 mg trimethoprim and 333 mg sulfadiazine per gram.

TUCOPRIM Powder is a combination of trimethoprim and sulfadiazine in the ratio of 1 part to 5 parts by weight, which provides effective antibacterial activity against a wide range of bacterial infections in animals.

The chemical structure of trimethoprim is



The chemical name of trimethoprim is 2,4 diamino-5-(3,4,5-trimethoxybenzyl) pyrimidine.

ACTIONS

Microbiology

Trimethoprim blocks bacterial production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase.

Sulfadiazine, in common with other sulfonamides, inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid.

Trimethoprim/sulfadiazine thus imposes a sequential double blockade on bacterial metabolism. This deprives bacteria of nucleic acids and proteins essential for survival and multiplication and produces a high level of antibacterial activity which is usually bactericidal.

Although both sulfadiazine and trimethoprim are antifolate, neither affects the folate metabolism of animals. The reasons are: animals do not synthesize folic acid and cannot, therefore, be directly affected by sulfadiazine; and although animals must reduce their dietary folic acid to tetrahydrofolic acid, trimethoprim does not affect this reduction because its affinity for dihydrofolate reductase of mammals is significantly less than for the corresponding bacterial enzyme.

Trimethoprim/sulfadiazine is active against a wide spectrum of bacterial pathogens, both gram-negative and gram-positive. The following in vitro data are available, but their clinical significance is unknown. In general, species of the following genera are sensitive to trimethoprim/sulfadiazine:

Very Sensitive	**Sensitive**	**Moderately Sensitive**	**Not Sensitive**
Escherichia	*Staphylococcus*	*Moraxella*	*Mycobacterium*
Streptococcus	*Neisseria*	*Nocardia*	*Leptospira*
Proteus	*Klebsiella*	*Brucella*	*Pseudomonas*
Salmonella	*Fusiformis*		*Erysipelothrix*
Pasteurella	*Corynebacterium*		
Shigella	*Clostridium*		
Haemophilus	*Bordetella*		

As a result of the sequential double blockade of the metabolism of susceptible organisms by trimethoprim and sulfadiazine, the minimum inhibitory concentration (MIC) of trimethoprim/sulfadiazine is markedly less than that of either of the components used separately. Many strains of bacteria that are not susceptible to one of the components are susceptible to the combination. A synergistic effect between trimethoprim and sulfadiazine in combination has been shown experimentally both *in vitro* and *in vivo* (in dogs).

Trimethoprim/sulfadiazine is bactericidal against susceptible strains and is often effective against sulfonamide-resistant organisms. *In vitro* sulfadiazine is usually only bacteriostatic.

The precise *in vitro* MIC of the combination varies with the ratio of the drugs present, but action of trimethoprim/sulfadiazine occurs over a wide range of ratios with an increase in the concentration of one of its components compensating for a decrease in the other. It is usual, however, to determine MICs using a constant ratio of 1 part trimethoprim in 20 parts of the combination.

The following table shows MICs using the above ratio, of bacteria which were susceptible to both trimethoprim (TMP) and sulfadiazine (SDZ). The organisms are those most commonly involved in conditions for which trimethoprim/sulfadiazine is indicated.

AVERAGE MINIMUM INHIBITORY CONCENTRATION (MIC-mcg/ml)

Bacteria	TMP	SDZ	TMP/SDZ	
			TMP	SDZ
Escherichia coli	0.31	26.5	0.07	1.31
Proteus species	1.3	24.5	0.15	2.85
Staphylococcus aureus	0.6	17.6	0.13	2.47
Pasteurella species	0.06	20.1	0.03	0.56
Salmonella species	0.15	61.0	0.05	0.95
β *Streptococcus*	0.5	24.5	0.15	2.85

The following table demonstrates the marked effect of the trimethoprim and sulfadiazine combination against sulfadiazine resistant strains of normally susceptible organisms:

AVERAGE MINIMUM INHIBITORY CONCENTRATION OF SULFADIAZINE-RESISTANT STRAINS (MIC-mcg/ml)

Bacteria	TMP Alone	SDZ Alone	TMP/SDZ	
			TMP	SDZ
Escherichia coli	0.32	> 245	0.27	5.0
Proteus species	0.66	> 245	0.32	6.2

Susceptibility Testing

In testing susceptibility to trimethoprim/sulfadiazine, it is essential that the medium used does not contain significant amounts of interfering substances which can bypass the metabolic blocking action, e.g., thymidine or thymine.

The standard SxT disc is appropriate for testing by the disc diffusion method.

Pharmacology

Following oral administration, trimethoprim/sulfadiazine is rapidly absorbed and widely distributed throughout body tissues. Concentrations of trimethoprim are usually higher in tissues than in blood. The levels of trimethoprim are high in lungs, kidneys and liver, as would be expected from its physical properties.

Serum trimethoprim concentrations in horses following oral administration indicate rapid absorption of the drug; peak concentrations occur in 1.5 hours. The mean serum elimination half-life is 2 to 2.5 hours. Sulfadiazine absorption is slower, requiring 2.5 to 6 hours to reach peak concentrations. The mean serum elimination halflife for sulfadiazine is 4 to 5.5 hours.

Usually, the concentration of an antibacterial in the blood and the *in vitro* MIC of the infecting organism indicate an appropriate period between doses of a drug. This does not hold entirely for trimethoprim/sulfadiazine because trimethoprim, in contrast to sulfadiazine, localizes in tissues and therefore, its concentration and ratio to sulfadiazine are higher there than in blood.

TUCOPRIM Powder

The following table shows the average concentration of trimethoprim and sulfadiazine, as measured in either serum or plasma, in 24 adult horses observed after a single dose of TUCOPRIM Powder:

AVERAGE PLASMA CONCENTRATION (mcg/ml)

Trimethoprim (5 mg/kg)					Sulfadiazine (25 mg/kg)				
1 hr	3 hr	6 hr	10 hr	24 hr	1 hr	3 hr	6 hr	10 hr	24 hr
0.82	0.69	0.36	0.12	< 0.25	9.9	18.8	17.3	9.0	1.6

Excretion of trimethoprim/sulfadiazine is chiefly by the kidneys, by both glomerular filtration and tubular secretion. Urine concentrations of both trimethoprim and sulfadiazine are severalfold higher than blood concentrations. Neither trimethoprim nor sulfadiazine interferes with the excretion pattern of the other.

INDICATIONS AND USAGE

Trimethoprim/sulfadiazine is indicated in horses where potent systemic antibacterial action against sensitive organisms is required. Trimethoprim/sulfadiazine is indicated where control of bacterial infections is required during treatment of:

- Acute Strangles
- Respiratory Tract Infections
- Acute Urogenital Infections
- Wound Infections and Abscesses

Trimethoprim/sulfadiazine is well tolerated by foals.

CONTRAINDICATIONS

Trimethoprim/sulfadiazine should not be used in horses showing marked liver parenchymal damage, blood dyscrasias or in those with a history of sulfonamide sensitivity.

WARNINGS

NOT FOR HUMAN USE. **KEEP OUT OF REACH OF CHILDREN.**

Do not use in horses intended for human consumption.

PRECAUTION

Water should be readily available to horses receiving sulfonamide therapy.

ADVERSE REACTIONS

During clinical trials, one case of anorexia and one case of loose feces following treatment with the drug were reported.

Individual animal hypersensitivity may result in local or generalized reactions, sometimes fatal. Anaphylactoid reactions, although rare, may also occur. **Antidote:** Epinephrine.

POST APPROVAL EXPERIENCE

Horses have developed diarrhea during trimethoprim /sulfadiazine treatment, which could be fatal. If fecal consistency changes during trimethoprim/sulfadiazine therapy, discontinue treatment immediately and contact your veterinarian.

ANIMAL SAFETY

Toxicity is low. The acute toxicity (LD_{50}) of trimethoprim/ sulfadiazine 50 is more than 5 g/kg orally in rats and mice. No significant changes were recorded in rats given doses of 600 mg/kg per day for 90 days.

Horses treated intravenously with trimethoprim/sulfadiazine 48% Injection have tolerated up to five times the recommended daily dose for 7 days or on the recommended daily dose for 21 consecutive days without clinical effects or histopathological changes.

Lengthening of clotting time was seen in some of the horses on high or prolonged dosing in one of two trials. The effect, which may have been related to a resolving infection, was not seen in a second similar trial.

Slight to moderate reductions in hematopoietic activity following high, prolonged dosage in several species have been recorded. This is usually reversible by folinic acid (leucovorin) administration or by stopping the drug. During long-term treatment of horses, periodic platelet counts and white and red blood cell counts are advisable.

In rare instances, horses have developed diarrhea during trimethoprim/sulfadiazine treatment. If fecal consistency changes during trimethoprim/sulfadiazine therapy, discontinue treatment immediately and institute appropriate symptomatic measures.

TERATOLOGY

The effect of trimethoprim/sulfadiazine 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 trimethoprim/sulfadiazine.

DOSAGE AND ADMINISTRATION

The recommended dose is 3.75 grams TUCOPRIM Powder per 50 kg (110 lbs) body weight per day. Each level, loose-filled scoop contains approximately 15 grams which is sufficient to treat 200 kg (440 lbs) of body weight. Since product contents may settle, gentle agitation during scooping is recommended. Administer orally once a day in a small amount of palatable feed.

The usual course of treatment is a single, daily dose for 5 to 7 days. Continue acute infection therapy for 2 or 3 days after clinical signs have subsided. If no improvement of acute infections is seen in 3 to 5 days, re-evaluate the diagnosis.

Trimethoprim/sulfadiazine may be used alone or in conjunction with intravenous dosing. Following treatment with trimethoprim/sulfadiazine 48% Injection, therapy can be maintained using oral powder.

A complete blood count should be done periodically in patients receiving trimethoprim/sulfadiazine for prolonged periods. If significant reduction in the count of any formed blood element is noted, treatment with trimethoprim/sulfadiazine should be discontinued.

STORAGE CONDITIONS

Store at or below 30 C.

HOW SUPPLIED

TUCOPRIM Powder is available in the following package sizes:

400 gram bottle
2000 gram pails

ANADA #200-244, Approved by FDA

Made in China

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007
Revised: January 2013

A73050-4A&P

GEQ14011

NOTES

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FRONT COVER: Zoetis employee Rachel Helmbold, photo courtesy of Hoof Print Images Photography.

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