Prescribing Information for Equine Use

Lutalyse® Injection

(dinoprost tromethamine 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 F_2 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 and water for injection.

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

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.

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.

Residue Warnings: 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. 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

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

For a copy of the Safety Data Sheet or to report adverse reactions, call 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 www.fda.gov/reportanimalae.

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 $PGF_{2\alpha}$, 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 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 $PGF_{2\alpha}$ 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 (^3H PGF_2 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 ^3H PGF_2 alpha Tham and ^3H PGF_2 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 ^3H PGF_2 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 ^3H PGF_2 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 $PGF_{2\alpha}$ 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.

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

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).
Use contents within 12 weeks of first vial puncture. Protect from freezing.

Approved by FDA under NADA # 108-901

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