

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_{2α} 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 in Beef Cows, Beef Heifers and Replacement Dairy Heifers: 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). Use contents within 12 weeks of first vial puncture. Protect from freezing.

Approved by FDA under NADA # 108-901

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

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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 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 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

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 cows, beef heifers and replacement dairy heifers
- For unobserved (silent) estrus in lactating dairy cows with a corpus luteum
- For treatment of pyometra (chronic endometritis) in cattle
- For abortion in beef cows, beef heifers and replacement dairy heifers
- 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 anestrus mares that have a corpus luteum)

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.

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 Cows, Beef Heifers and Replacement 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.

3. For Treatment of Pyometra (chronic endometritis) in Cattle. Inject a dose of 5 mL LUTALYSE Injection (25 mg dinoprost) intramuscularly.

4. For Abortion in Beef Cows, Beef Heifers and Replacement Dairy Heifers. LUTALYSE Injection is indicated for its abortifacient effect in beef cows, beef heifers and replacement dairy heifers 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)	1 st FACTREL	1 st FACTREL	1 st FACTREL
Day 7 (the following Monday)	LUTALYSE	LUTALYSE	LUTALYSE
Day 9 (Wednesday)	2 nd FACTREL + FTAI at 48 hours after LUTALYSE	2 nd FACTREL at 48 hours after LUTALYSE	2 nd FACTREL 56 hours after LUTALYSE
Day 10 (Thursday)		FTAI 24 hours after 2 nd FACTREL	FTAI 18 hours after 2 nd 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 anestrous 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 bronchospasms. 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 Safety Data Sheet (SDS) 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 PGF_{2α}, 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 PGF_{2α} 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 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 equine alpha doses of 3H PGF₂ alpha Tham and 3H PGF₂ alpha Tham and 3H PGF₂ alpha 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 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 3H 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