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 of 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 foetal debris and other non-lactating cattle
- For use with FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-date artificial insemination (FTAI) in dairy cows
- For use with EAZI-BREED™ CIDR (propogestere intravaginal insert) Cattle Insert for synchronization of estrus in lactating dairy cows
- For use with EAZI-BREED™ CIDR (propogestere 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 postpartum estrus in beef heifers

Swine:
- For parturition induction in swine

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

DOSEAGE 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 estrus 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; however, these factors are important. Often the time of breeding is 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 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 estrus cycling and clinically anestrous mares that have a corpus luteum in the following circumstances:

1. Controlling Time of Estrus of Estrus Cyclic 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 anestru. Many mares described as anestru 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 bronchiopasms. 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. In cases of infection, the first sign of infection is usually 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 swine and/or gilt prior to 3 days of normal gestation.

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

<table>
<thead>
<tr>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
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<tbody>
<tr>
<td>Day 0 (Monday)</td>
<td>1st FACTREL</td>
<td>1st FACTREL</td>
</tr>
<tr>
<td>Day 7 (the following Monday)</td>
<td>LUTALYSE</td>
<td>LUTALYSE</td>
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<tr>
<td>Day 9 (Wednesday)</td>
<td>2nd FACTREL + FTAI at 48 hours after LUTALYSE</td>
<td>2nd FACTREL</td>
</tr>
<tr>
<td>Day 10 (Thursday)</td>
<td>FTAI 24 hours after 2nd FACTREL</td>
<td>FTAI 18 hours after 2nd FACTREL</td>
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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 show any signs of parturition or if there are other complications of the vascular system, gastrointestinal tract, respiratory system, or reproductive tract.

ADVERSE REACTIONS

Cattle: Limited salivation has been reported in some instances. Sweine: The most frequently observed side effects were erythema and pruritus, slight incoordination, nesting behavior, itching, urination, defecation, abdominal muscle spasms, tail movements, hyperperspiration or dyspnea, increased vocalization, salivation, and at the 100 mg (10x) dose only, possible vomiting. The most common side effect was the transient, 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 side effects are transient in all cases observed and have not been detrimental to the animal. Other reactions seen have been increase in heart rate, increase in respiratory 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 when used as a luteolytic agent in cattle. Release of ovulation from the ovary and the ovary to the ovarian artery (sheep), 3) be related to IUD induced luteal regression (sheep), and 4) be capable of reversing the corpus luteum in the majority of 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 (‘H PGF2α) in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study determined that equimolar doses of ‘H PGF2α Tham and ‘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 ‘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 ‘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-keo 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. Dinoprost was non-teratogenic in rats when administered orally at 1.25, 3.2, 10.0 and 20.0 mg dinoprost/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 or 14, 15, 16 and 17 or orally at doses of 0.01, 0.1 and 1.0 mg dinoprost/kg/day on days 6-15 or 0.5 mg/kg/day on days 16-18 of gestation. Luteal 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/kg body weight indicated prostaglandins of the F series could induce bone deposition. However, such bone changes were not detected. Rectal temperature was elevated about 1.5˚ F through the 6th hour after injection with doses up to 250 mg dinoprost administered twice intramuscularly at a 10 day interval or doses of 10 mg PGF2α administered 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 0.25, 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 0.25, 0.5, 0.75, 1.0, 2.5, 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 8, and 9 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 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 determined during the interval 0.5 until 1.0, 3, 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 98.6, 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 FACTREX™ (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAII) in lactating dairy cows: For a full description of the studies conducted for the use of FACTREX Injection and LUTALYSE Injection, please refer to the labeling for FACTREX Injection.

Cows: 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 50 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

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Revised: August 2014

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