Lutalyse® *HighCon* Injection

(dinoprost tromethamine injection)

12.5 mg dinoprost/mL as dinoprost tromethamine

For use in cattle only.

Not for use in horses and swine.

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

DESCRIPTION

LUTALYSE® HighCon Injection (12.5 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 12.5 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

LUTALYSE HighCon Injection is indicated as a luteolytic agent. LUTALYSE HighCon Injection is effective only in those cattle having a corpus luteum, i.e., those which ovulated at least five days prior to treatment.

- 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

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 HighCon 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 HighCon Injection effectively, but a poorly managed breeding program will continue to be poor when LUTALYSE HighCon Injection is employed unless other management deficiencies are remedied first. Cattle expressing estrus following LUTALYSE HighCon Injection are receptive to breeding by a bull. Using bulls to breed large numbers of cattle in heat following LUTALYSE HighCon Injection will require proper management of bulls and cattle. Future reproductive performance of animals that are not cycling will be unaffected by injection of LUTALYSE HighCon Injection.

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.

1. **For Estrus Synchronization in Beef Cows, Beef Heifers and Replacement Dairy Heifers.** LUTALYSE HighCon Injection is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum. Inject a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) intramuscularly or subcutaneously 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 HighCon 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 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramuscular or subcutaneous injection. 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 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramuscular or subcutaneous injection.
4. **For Abortion in Beef Cows, Beef Heifers and Replacement Dairy Heifers.** LUTALYSE HighCon 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 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramuscular or subcutaneous injection. 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 a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramuscular or subcutaneous 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 HighCon 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 HighCon	LUTALYSE HighCon	LUTALYSE HighCon
Day 9 (Wednesday)	2nd FACTREL + FTAI at 48 hours after LUTALYSE HighCon	2nd FACTREL 48 hours after LUTALYSE HighCon	2nd FACTREL 56 hours after LUTALYSE HighCon
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 a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramuscular or subcutaneous 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).
   - Administer a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramuscular or subcutaneous injection 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.

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: No milk discard or preslaughter drug withdrawal period is required for labeled uses in cattle. Use of this product in excess of the approved dose may result in drug residues.

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.

ADVERSE REACTIONS

Limited salivation has been reported in some instances.

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 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.

Relative Bioavailability Study: The requirement for substantial evidence of effectiveness was fulfilled by a pharmacokinetic study comparing the relative bioavailability of the subcutaneous (SC) administration of 25 mg of LUTALYSE HighCon Injection (12.5 mg dinoprost/mL) to the approved intramuscular (IM) administration of 25 mg of LUTALYSE Injection (5 mg dinoprost/mL). The effectiveness data for LUTALYSE Injection at doses of 25 and 35 mg IM were used to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for C_{max} and AUC to demonstrate therapeutic equivalence.

The pivotal relative bioavailability study was a randomized, non-replicated, three treatment, three period, six sequence crossover study in 24 cows (4 cows per sequence). Each cow received a single dose of 25 mg dinoprost administered as 5 mL of LUTALYSE Injection IM, 5 mL of LUTALYSE Injection SC, or 2 mL of LUTALYSE HighCon SC, with a washout period of 48 hours between doses. Plasma samples were collected at 60 and 10 minutes prior to dose administration, and at 5, 10, 15, 20, 30, 75 minutes, and at 2, 3, 4.5, 6, 7.5, and 12 hours after each dose. Samples were analyzed by UPLC-MS/MS for PGF2α (dinoprost) and PGFm (metabolite) concentrations. PGFm was chosen as the analyte of interest because its concentrations are reflective of exogenously administered dinoprost (after subtraction of endogenous concentrations), and it has a longer half-life and therefore less blood level fluctuations than PGF2α. The results of the relative bioavailability study are summarized in Table 1. The C_{max} and AUC_{last} of LUTALYSE HighCon were within the adjusted 90% Confidence Intervals. Therefore, the SC administration of 25 mg of LUTALYSE HighCon was considered to be equivalent to the IM administration of 25 mg of LUTALYSE Injection.

Table 1: Relative Bioavailability Results for LUTALYSE HighCon Injection

Parameter	Product/Route	LSMean	Ratio T/R†	Lower 90% CI	Upper 90% CI
C_{max} (ng/mL)	LUTALYSE Injection (IM)*	41.26			
	LUTALYSE Injection (SC)	50.80	1.23	110.99	136.60
	LUTALYSE HighCon Injection (SC)	55.12	1.34	120.42	148.20
AUC_{last} (hr*ng/mL)	LUTALYSE Injection (IM)*	66.85			
	LUTALYSE Injection (SC)	67.25	1.00	96.26	105.12
	LUTALYSE HighCon Injection (SC)	65.81	0.98	94.20	102.87

C_{max} - maximum plasma concentration

AUC_{last} - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay

* Reference product and route of administration

† Geometric means

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 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.

Injection Site Safety Summary: Eight non-lactating, non-pregnant dairy cows were injected with saline and eight animals were injected with LUTALYSE HighCon (12.5 mg dinoprost/mL @ 25 mg/animal) twice, at an interval of ten days. The first injection was administered in the left neck on Day 0 and the second injection was administered in the right neck on Day 10. Clinical observations were conducted on Days -14, -1, 0, 1, 2, 10, and 11, and injection site observations were conducted on all animals once on Days -14, -1, and once daily from Day 0 until Day 11. Animals were euthanized on Day 11. There were no abnormal clinical observations or general health observations related to drug administration during the conduct of the study. Injection site observations revealed no findings of erythema, heat, or sensitivity. No hardness was noted at the injection sites in any control animal post treatment administration. In the treated group, two animals had hardness noted on the right neck on Day 11. This hardness was probably a result of test article administration at that site on the previous day. No abnormal skin appearance was noted in any animal during this study. Swelling with a volume of 3.53 cm^3 was observed on Day 11 in the right neck in one treated animal. At necropsy discoloration (variations of dark red, tan, gray, or yellow mottled) in the subcutaneous tissue was observed at all dinoprost injection sites. More discolored subcutaneous tissue was present at the Day 10 injection sites compared to the Day 0 injection sites. There was no discoloration observed in the deep muscle tissue. In summary, this study demonstrated that subcutaneous injection of LUTALYSE HighCon was well tolerated when injected subcutaneously into dairy cows at a dose of 25 mg dinoprost/cow twice at an interval of 10 days.

EFFECTIVENESS

The requirement for substantial evidence of effectiveness was fulfilled by a pharmacokinetic study comparing the relative bioavailability of the SC administration of 25 mg of LUTALYSE HighCon Injection (12.5 mg dinoprost/mL) to the approved IM administration of 25 mg of LUTALYSE Injection (5 mg dinoprost/mL) (see **CLINICAL PHARMACOLOGY, Relative Bioavailability Study**). This study demonstrated the equivalence of the SC administration of 25 mg of LUTALYSE HighCon to the IM administration of 25 mg of LUTALYSE Injection. Therefore, the effectiveness studies conducted with LUTALYSE Injection support the effectiveness of LUTALYSE HighCon Injection.

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.

HOW SUPPLIED

LUTALYSE HighCon Injection is available in 20, 100 and 250 mL vials.

STORAGE, HANDLING AND DISPOSAL

Store below 25°C (77°F), with brief excursions between 0°C and 40°C (32°F and 104°F). Use contents within 12 weeks of first vial puncture. Stopper may be punctured a maximum of 20 times.

Approved by FDA under NADA # 141-442

zoetis

Distributed by:
Zoetis Inc., Kalamazoo, MI 49007

Revised: September 2021

40034683A&P