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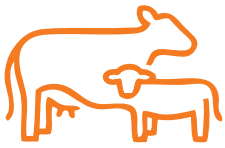

LUTALYSE® *HighCon* Injection for Heifers and Cows: Low Dose Volume with Flexible Routes of Administration

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LUTALYSE HighCon® represents a new, prostaglandin choice, providing the same reliable performance of LUTALYSE® in a concentrated, low-dose 2-mL formulation for on-label SC or IM administration.

Summary

- LUTALYSE® *HighCon* Injection (*dinoprost tromethamine injection*) is a new, more concentrated, **cattle-only** formulation of LUTALYSE® Injection, approved for the same bovine indications and total dosage (25 mg dinoprost/hd) but with notable distinctions:
  - LUTALYSE *HighCon* is dosed at only 2 mL/head (instead of 5 mL of LUTALYSE), allowing for faster administration, more doses per bottle, and less product in each injection site.
  - LUTALYSE *HighCon* is the *first and only* prostaglandin FDA-approved for subcutaneous (SC) administration, in addition to the intramuscular (IM) route (helps minimize injection site irritation, blemishes, and muscle damage compared to IM route).
- ***IM research:*** Based on formulation characteristics and injection site safety[1], FDA deemed 2 mL IM of LUTALYSE *HighCon* bioequivalent to 5 mL IM of original LUTALYSE.
- ***SC research:*** A pharmacokinetics study assessed the relative bioavailability of 2 mL of LUTALYSE *HighCon* administered SC compared to 5 mL of LUTALYSE administered IM.[2]
  - Outcomes confirmed that SC LUTALYSE *HighCon* was therapeutically equivalent to IM LUTALYSE, and injection site assessments showed SC dosing was well tolerated.
- LUTALYSE *HighCon* offers producers and veterinarians a new, route-flexible, FDA-approved prostaglandin option for breeding management of heifers and cows.

Progressive dairy producers have long recognized that breeding management programs help optimize the productivity, efficiency, and profit potential of their operations. For several decades the strategic use of prostaglandin has been a key component of breeding management, supporting estrus synchronization, fixed-time artificial insemination (FTAI), and other strategies.

LUTALYSE® Injection (*dinoprost injection*) is the most-researched, most-recommended, and most-used prostaglandin[3,4] that cattle producers and veterinarians have trusted for more than 35 years. Dinoprost, the active ingredient of LUTALYSE, is the naturally occurring prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) that can help producers control breeding, improve pregnancy rates, reduce reproductive culls, reduce time necessary for heat detection, and make more efficient use of labor.

LUTALYSE® *HighCon* Injection

In an effort to continue technological advancement in breeding management, Zoetis scientists have developed, researched, and earned FDA approval for a more concentrated LUTALYSE formulation: new LUTALYSE® *HighCon* Injection *(dinoprost*

Approved Indications for LUTALYSE *HighCon* Injection
(identical to original LUTALYSE)

- 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® Injection (*gonadorelin injection*) to synchronize estrous cycles to allow 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

Recommendations for Administering Injectable Animal Health Products[5-7]
(SC preferred over IM)

- Whenever possible, choose products formulated and labeled for injection SC rather than IM. Products cleared for SC, IV, or oral administration are recommended.
- IM administration of all compounds (including sterile saline) can cause unacceptable tissue consequences. IM injections must be eliminated; whenever possible, avoid IM use.
- Products labeled for SC administration should be administered in front of the shoulder, preferably in the neck region; products labeled for IM use should be given in the neck region.
- Products with a low dose volume are recommended.

tromethamine injection). This novel product was developed to help optimize user convenience and flexibility when implementing the many breeding strategies that involve use of a prostaglandin.

LUTALYSE *HighCon* is a ready-to-use injectable solution containing 12.5 mg of dinoprost tromethamine per mL, and is approved for the exact same cattle indications and dose rate (25 mg dinoprost/hd) as the original LUTALYSE (see sidebar). While LUTALYSE *HighCon* delivers the same benefits of LUTALYSE, the new product offers 3 notable distinctions:

- High-concentration formulation, so only a ***2-mL dose volume*** is needed to deliver 25 mg of dinoprost instead of the 5-mL dose volume needed with LUTALYSE. Allows for faster administration, more doses per bottle, and less volume in each injection site.
- The *first and only* prostaglandin approved for ***subcutaneous*** (SC) administration, in addition to the intramuscular (IM) route. Provides producers and veterinarians flexible dose-route options consistent with strict Dairy Animal Care and Quality Assurance (DACQA)[5] and Beef Quality Assurance (BQA)[6,7] standards (i.e., SC administration plus the lower dose volume helps minimize injection site irritation, blemishes, and muscle damage compared to the IM route).
- Available in 3 bottle sizes to best suit herd and management needs. A large 250-mL vial offers the maximum number of doses (125) in a single bottle, while the smaller, lighter-weight 20-mL and 100-mL vials are easy to handle during administration.

LUTALYSE *HighCon* is approved for use *only* in dairy and beef cattle (no other species on the label; not approved for mares or swine like LUTALYSE), with no meat or milk withdrawal.

The following information is a summary of bioavailability and injection site research conducted by Zoetis in support of LUTALYSE *HighCon* approval by FDA.

IM Dosing: Bioequivalence and Injection Site Toleration

IM Bioequivalence

The efficacy and safety of IM dinoprost was established when FDA approved LUTALYSE Injection in 1979, and much additional research has been conducted over the intervening 35+ years. As a result of this large body of knowledge and research data, FDA granted Zoetis a waiver from the requirement to demonstrate *in vivo* IM bioequivalence of LUTALYSE *HighCon* Injection to original IM LUTALYSE.

This waiver was based on the fact that LUTALYSE *HighCon* is the same dosage form as LUTALYSE (injectable solution), used via the same route (IM), used at the same dosage (25 mg dinoprost/hd), and contains the same inactive ingredients in the same concentrations. Also, no serious adverse effects were reported at IM injection sites when the higher drug concentration was administered (see following study).

IM Experiment Design

A study investigated the injection site tolerance of LUTALYSE *HighCon* when administered IM to dairy cows.[1] The study involved 8 open, non-lactating Holstein cows ranging in weight from 1221 to 1808 lb. Each cow received the same treatment: a **2-mL IM** injection with LUTALYSE *HighCon* (standard dose of 25 mg dinoprost/hd) in the left neck (day 0). Ten days later, each animal received another identical 2-mL IM dose in the right neck (day 10), thus providing a total of 16 IM sites for evaluation.

Throughout the study (days -1 through day 11), all cows were monitored daily for injection site reactions and received daily

	Dose volume (25 mg/hd)	IM route	SC route	Max. doses per bottle	Approved species
LUTALYSE *HighCon*	**2** mL	✔	✔	125 (250-mL btl.)	Cattle
LUTALYSE	5 mL	✔	—	20 (100-mL btl.)	Cattle, swine, mares

physical examinations by a veterinarian. Injection sites were evaluated for the presence of redness, heat, sensitivity, firmness, necrosis, scaling, erosion, and drainage by visual observation and palpation. The volume of any swelling was calculated for each injection site over time. All animals were euthanized on day 11 and injection sites were examined for gross pathology (external skin surface, SC tissue, surface of the neck musculature, and deep interior of the neck musculature). If gross pathology was noted, samples were collected for histopathological evaluation.

IM Results

No abnormal general-health or clinical observations related to IM administration of LUTALYSE *HighCon* were reported. No redness, heat, sensitivity, necrosis, drainage, scaling, or erosion was noted at any of the 16 IM injection sites. Transient firmness in the neck was observed at 7 sites.

Mild swelling and mild to moderate hemorrhage were the most common findings observed at the IM injection sites, both grossly and microscopically. Minor swelling was noted in 6 animals on the left neck, resolving by day 9; and 3 animals had swelling on the right neck at 1 day after the second injection. Resultant maximal swelling volume was considered small relative to the target animal and, therefore, acceptable for IM injection. Some gross pathology was observed, altered tissue corresponding to both injections on day 0 and day 10. Areas of altered tissue were characterized by discoloration (dark red, tan, or tan and white mottled) and correlated microscopically with minimal to mild hemorrhage at most sites. Mild to moderate hemorrhage was observed at 6 sites examined microscopically.

IM Conclusions

Based on formulation characteristics and injection site tolerance, FDA deemed a 2-mL IM dose of LUTALYSE *HighCon* bioequivalent to a 5-mL IM dose of original LUTALYSE.

The injection site safety study demonstrated that IM injection with 2 mL (25 mg dinoprost/hd) of LUTALYSE *HighCon* was well tolerated in cattle. Mild swelling and mild to moderate hemorrhage were the most common findings observed at the injection sites, typical of IM injection.

SC Dosing: Bioavailability and Injection Site Toleration

SC Experiment Design

A pharmacokinetic research study assessed the relative bioavailability of **SC** injection with new LUTALYSE *HighCon* Injection compared to **IM** dosing with conventional LUTALYSE Injection.[2] The study involved 24 estrous-cycling, non-lactating Holstein heifers (≥ 550 lb) housed under typical dairy conditions and fed a total mixed ration appropriate for dairy heifers (feed and water ad libitum).

Heifers were subjected to an estrous synchronization program and injected with 25 mg dinoprost tromethamine as:

- **5 mL IM** of LUTALYSE Injection (5 mg dinoprost/mL);
- **2 mL SC** of LUTALYSE *HighCon* Injection (12.5 mg dinoprost/mL).

All animals received both of these treatments in a crossover design (48 to 96 hours between doses). Injections were administered in the lateral region of the neck in distinct sites.

Multiple blood samples were obtained after each dinoprost injection to allow for pharmacokinetic evaluation of the 2 treatment forms/routes. Plasma samples were collected at 60 and 10 minutes before each dinoprost 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. Plasma samples were assessed for prostaglandin F metabolite (PGF_m, the primary metabolite of $PGF_{2\alpha}$) using a validated ultra-performance liquid chromatography-mass spectrometry/mass spectrometry (UPLC-MS/MS) method. General health observations were conducted at least once daily and injection sites were observed for reactions at approximately 3, 12, and 24 hours post-administration, all by technicians masked to treatment assignments.

Pharmacokinetic variables used to evaluate relative PGF_m bioavailability were maximum plasma concentration (C_{max}) and area under the plasma concentration vs time curve from time of injection to the limit of quantification of the assay (AUC_{last}). These variables were

LUTALYSE® HighCon is the first and only prostaglandin approved for SC administration, in accordance with DACQA and BQA recommendations.[5-7]

FDA deemed 2 mL IM of LUTALYSE® HighCon to be bioequivalent to 5 mL IM of LUTALYSE.® IM injection of LUTALYSE® HighCon was well tolerated.[1]

Table 1 – Relative bioavailability results for SC injection with LUTALYSE *HighCon*.

Parameter	LUTALYSE (5 mL IM; LS means)	LUTALYSE *HighCon* (2 mL SC; LS means)	Ratio (LUTALYSE *HighCon* / LUTALYSE)	90% CI (80%-164%)
C_{max} (ng/mL)	41.26	55.12	1.34	120.42 – 148.20
AUC_{last} (h•ng/mL)	66.85	65.81	0.98	94.20 – 102.87

C_{max} = maximum plasma concentration (PGF_m)

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

Pharmacokinetic data confirmed that SC dosing of LUTALYSE® HighCon (just 2 mL) was therapeutically equivalent to an IM 5-mL dose of LUTALYSE,® and SC administration was well tolerated.[2]

LUTALYSE® HighCon offers producers and veterinarians a new, flexible, FDA-approved prostaglandin option for breeding management.

calculated for each dose in each individual animal (corrected for baseline levels) and statistically analyzed by appropriate standard methods, including logarithmic transformation. Back-transformed least squares (LS) means and 90% confidence intervals (CI) were reported. The criteria to demonstrate therapeutic equivalence between the 2 treatments were an adjusted test/reference ratio of 1.4 (LS means ratio of LUTALYSE *HighCon*/LUTALYSE) and 90% equivalence limits of 80%-164% for both C_{max} and AUC_{last}.*

SC Results

Relevant pharmacokinetic outcomes for the 2 treatment groups are summarized in Table 1. Both groups achieved high maximum blood concentrations in excess of 40 ng/mL, though average C_{max} in cattle treated SC with 2 mL of LUTALYSE *HighCon* was 34% higher than that of animals treated IM with 5 mL of LUTALYSE. Results of the AUC_{last} calculations demonstrated comparable overall drug distribution profile for the 2 products/routes. Notably, the 90% CI about the ratio of the 2 products for both C_{max} and AUC_{last} were contained within the limits of 80% to 164% (previously established to define the lower and upper bounds of dinoprost efficacy). Because the C_{max} and AUC_{last} achieved by 2 mL of LUTALYSE *HighCon* administered SC were within the adjusted test/reference ratio and 90% CI, therapeutic equivalence was demonstrated to 5 mL of LUTALYSE administered IM.

Minor swelling was observed at only 2 of the 24 injection sites (8%) where 2 mL of LUTALYSE *HighCon* was administered SC. Swelling was fully resolved by 24 hours after dose administration. No other reactions were observed in SC- or IM-treated heifers, and no other treatment-related adverse reactions were reported. Thus, the use of LUTALYSE *HighCon* via the SC route was well tolerated and deemed safe for cattle.

SC Conclusions

Based on the comparison of C_{max} and AUC_{last} between the 2 treatment groups, 2 mL (25 mg) of LUTALYSE *HighCon* administered to cattle by SC injection was shown to be therapeutically equivalent to a 5-mL (25 mg) IM injection of LUTALYSE. In addition, SC administration of LUTALYSE *HighCon* was well tolerated, with only minor swelling observed at 8% of 24 SC injection sites.

Conclusions

Research has confirmed that a 2-mL dose of LUTALYSE *HighCon*, whether administered SC or IM, is bioequivalent to a 5-mL IM dose of original LUTALYSE. In addition, injection site tolerance studies demonstrated that SC or IM dosing of LUTALYSE *HighCon* is well tolerated by treated cattle.

LUTALYSE *HighCon* offers producers and veterinarians a new, route-flexible, FDA-approved prostaglandin option for breeding management of heifers and cows. LUTALYSE *HighCon* delivers the same proven performance of LUTALYSE but in a convenient high-concentration formulation that reduces dose volume (only 2 mL), provides more doses per bottle (up to 125), and uniquely allows for administration by the much preferred SC route.

*The test/reference ratio was based on dosing data for original LUTALYSE that established a safe and effective upper dose of 35 mg dinoprost, yielding a test/reference ratio of 35/25, or 1.4. Both an upper and lower bound for comparability was established; the lower bound defined a minimal effective concentration, while the upper bound avoided potential negative feedback loops that could impact effectiveness.

IMPORTANT SAFETY INFORMATION FOR LUTALYSE/LUTALYSE *HIGHCON*: Women of childbearing age and persons with respiratory problems should exercise extreme caution when handling LUTALYSE/LUTALYSE *HighCon*. LUTALYSE/LUTALYSE *HighCon* are 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. Aseptic technique should be used to reduce the possibility of post-injection clostridial infections. Do not administer LUTALYSE/LUTALYSE *HighCon* in pregnant cattle unless cessation of pregnancy is desired. See full Prescribing Information, attached.

IMPORTANT SAFETY INFORMATION FOR FACTREL: FACTREL is for use in cattle only. See full Prescribing Information, attached.

IMPORTANT SAFETY INFORMATION FOR EAZI-BREED CIDR: Avoid contact with skin by wearing protective gloves when handling EAZI-BREED CIDR inserts. Do not use in heifers of insufficient size or age for breeding or in cattle with abnormal, immature, or infected genital tracts. Do not use inserts more than once.

References

1. Data on file, Study Report No. 1433N-60-10-849, Zoetis Inc.
2. Data on file, Study Report No. A431N-US-13-179, Zoetis Inc.
3. Animalytix ruminant segments and equine MAT ending Jan 2015.
4. Based on a literature search of *J Anim Sci, J Dairy Sci,* and *Theriogenology*, 1994-2011.
5. Dairy animal care and quality assurance (DACQA). National Dairy Herd Information Association, 2010. www.bqa.org/CMDocs/bqa/DairyBQAManual.pdf, accessed Aug 2015.
6. Smith GC, Tatum JD, Belk KE. Beef quality assurance – past, present, future. *Range Beef Cow Symposium*; 1997, paper 138. http://digitalcommons.unl.edu/rangebeefcowsymp/138, accessed Aug 2015.
7. George MH, Ames RA, Glock RG, et al. Incidence, severity, amount of tissue affected and effects on histology, chemistry and tenderness of injection-site lesions in beef calves administered a control compound or one of seven chemical compounds. Report to the National Cattlemen's Beef Association, Englewood, CO. 1996:1-46.

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: 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.

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.
NADA #141-442, Approved by FDA

zoetis

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Made in Spain
Revised: August 2015

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.

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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

NADA 139-237, Approved by FDA

Factrel® Injection

(gonadorelin injection)

50 mcg gonadorelin per mL (as gonadorelin hydrochloride) Solution for Intramuscular Injection.

For use in cattle only

CAUTION

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

DESCRIPTION

FACTREL Injection is a sterile solution containing 50 micrograms of synthetic gonadorelin (as hydrochloride) per mL in aqueous formulation containing 0.6% sodium chloride and 2% benzyl alcohol (as a preservative).

Gonadorelin is the gonadotropin releasing hormone (GnRH) which is produced by the hypothalamus and causes the release of the gonadotropin luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary.

FACTREL Injection has the identical amino acid sequence as endogenous gonadorelin; 5-oxo Pro-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2 with identical physiological activities. The molecular weight of gonadorelin is 1182 with a molecular formula of $C_{55}H_{75}N_{17}O_{13}$. The corresponding values for gonadorelin hydrochloride are 1219 (1 HCl) expressed as $C_{55}H_{75}N_{17}O_{13}HCl$, or 1255 (2 HCl) expressed as $C_{55}H_{75}N_{17}O_{13}$ 2HCl.

INDICATIONS FOR USE

For the treatment of ovarian follicular cysts in lactating dairy cows, beef cows, and replacement dairy and beef heifers. The treatment effect of FACTREL Injection when used in lactating dairy cows, beef cows, and replacement dairy and beef heifers is a reduction in the number of days to first estrus.

For use with LUTALYSE® (dinoprost tromethamine injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows.

DOSAGE

For the treatment of ovarian follicular cysts in lactating dairy cows, beef cows, and replacement dairy and beef heifers: Administer 2 mL of FACTREL Injection as a single intramuscular injection.

For use with LUTALYSE (dinoprost tromethamine 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) 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

MECHANISM OF ACTION

Follicular cysts are enlarged non-ovulatory follicles resulting from a malfunction of the neuroendocrine mechanism controlling follicular maturation and ovulation. Exogenous administration of agents possessing luteinizing hormone (LH) activity, such as pituitary extracts or human chorionic gonadotropin, often causes ovulation or regression of follicular cysts. FACTREL Injection induces release of endogenous luteinizing hormone (LH) to produce this same effect.

Gonadorelin, through release of LH has been demonstrated to induce ovulation of dominant ovarian follicles present on the bovine ovary during the estrous cycle. Administration of FACTREL Injection has the same effect.

WARNINGS AND PRECAUTIONS

For use in animals only. Not for human use. Keep out of reach of children.

RESIDUE WARNINGS

No withdrawal period or milk discard time is required when used according to labeling.

EFFECTIVENESS

For the treatment of ovarian follicular cysts in lactating dairy cows, beef cows, and replacement dairy and beef heifers:

The treatment effect of FACTREL Injection when used in lactating dairy cows, beef cows, and replacement dairy and beef heifers is a reduction in the number of days to first estrus.

There were no significant differences in days from treatment to conception, frequency of cows conceiving at first or subsequent heats, or conception rates among treated or non-treated control animals, when FACTREL Injection was used alone for treatment of cystic ovaries.

For use with LUTALYSE (dinoprost tromethamine injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows:

A field study was conducted to compare control (0 mL FACTREL Injection) to two doses of 2, 3 or 4 mL FACTREL Injection (100-200 mcg gonadorelin) for use with LUTALYSE Injection to synchronize estrous cycles to allow FTAI in lactating dairy cows under field conditions. Cows were examined prior to study start and only clinically normal cows were enrolled. A total of 1142 cows were enrolled at 6 commercial dairies. Cows were assigned randomly in blocks of 4 cows to each of 4 treatment groups consisting of:

Day 0: 2, 3 or 4 mL dose of FACTREL Injection or no injection (Control)
Day 7: 5 mL LUTALYSE Injection (all treatment groups)
Day 9: 2, 3 or 4 mL dose of FACTREL Injection or no injection (Control)
Day 10: Fixed-time artificial insemination

On Day 9 the second dose of FACTREL Injection (cows received the same dose as for first treatment) was given either 48 or 56 hours after the dose of LUTALYSE Injection and FTAI was conducted 24 or 17 hours later, respectively. For control cows FTAI was performed 72 hours after the LUTALYSE Injection dose was administered. All treatment groups had significantly greater pregnancy rates to FTAI than cows administered LUTALYSE Injection alone, and were 17.1, 27.3, 29.1 and 32.2% for cows receiving 0 (Control), 2, 3 or 4 mL FACTREL Injection, respectively.

SAFETY AND TOXICITY

In cows the intramuscular administration of up to 12.5 times maximum recommended dosage (2,500 mcg/day) of FACTREL Injection for 3 days did not affect any physiological or clinical parameter. Likewise, single intramuscular doses of 500 mcg did not interfere with pregnancy. No evidence of irritation at injection site was found in any animal.

A total of 1142 cows were enrolled in the previously noted field study that evaluated the effectiveness of two doses of 2, 3 or 4 mL of FACTREL Injection for use with LUTALYSE Injection to synchronize estrous cycles to allow FTAI in lactating dairy cows. Cows were observed daily for abnormal clinical signs. Over the course of the study there were 148 adverse health events documented in 118 cows. These adverse health events were common conditions in dairy cows (mastitis, lameness and pneumonia) and are not considered related to treatment.

ADVERSE REACTIONS

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.

HOW SUPPLIED

FACTREL Injection (gonadorelin injection), 50 mcg/mL is available in 20 mL and 50 mL multi-dose vials (box of one).

STORAGE CONDITIONS

Store at refrigerator temperature 2° to 8°C (36° to 46°F). Use contents within 1 month of first vial puncture.

NADA 139-237, Approved by FDA

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