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

Zoetis
Florham Park, NJ 07932

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 prostaglandin3,4 that cattle producers and veterinarians have trusted for more than 35 years. Dinoprost, the active ingredient of LUTALYSE®, is the naturally occurring prostaglandin F₂α (PGF₂α) 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 tromethamine injection).
**Recommended Indications for LUTALYSE HighCon Injection**

- For estrus synchronization in beef cows, beef heifers, and replacement dairy heifers
- For unobserved (silent) estrus in lactating dairy cows with a corpus luteum
- For treatment of pyometra (chronic endometritis) in cattle
- For abortion in beef cows, beef heifers, and replacement dairy heifers
- For use with FACTREL® 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

**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
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**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)® and Beef Quality Assurance (BQA)® 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 Tolerance**

**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. 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

<table>
<thead>
<tr>
<th>Dose volume (25 mg/hd)</th>
<th>IM route</th>
<th>SC route</th>
<th>Max. doses per bottle</th>
<th>Approved species</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUTALYSE HighCon</td>
<td>2 mL</td>
<td>✔️</td>
<td>✔️</td>
<td>125 (250-mL btl.)</td>
</tr>
<tr>
<td>LUTALYSE</td>
<td>5 mL</td>
<td>✔️</td>
<td>—</td>
<td>20 (100-mL btl.)</td>
</tr>
</tbody>
</table>
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 2-mL IM of **LutaLyse HighCon** to be 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 tromethamine) 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.

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**SC Dosing: Bioavailability and Injection Site Tolerance**

**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. 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 (PGFm, the primary metabolite of PGF2α) 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 PGFm bioavailability were maximum plasma concentration (Cmax) and area under the plasma concentration vs time curve from time of injection to the limit of quantification of the assay (AUClast). These variables were
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 Cmax and AUClast 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, flexible, FDA-approved prostaglandin option for breeding management.

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.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LUTALYSE (5 mL IM; LS means)</th>
<th>LUTALYSE HighCon (2 mL SC; LS means)</th>
<th>Ratio (LUTALYSE HighCon / LUTALYSE)</th>
<th>90% CI (80%-164%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>41.26</td>
<td>55.12</td>
<td>1.34</td>
<td>120.42 – 148.20</td>
</tr>
<tr>
<td>AUClast (h*ng/mL)</td>
<td>66.85</td>
<td>65.81</td>
<td>0.98</td>
<td>94.20 – 102.87</td>
</tr>
</tbody>
</table>

Cmax = maximum plasma concentration (PGF₂α)
AUClast = area under the plasma concentration vs time curve from time of injection to the limit of quantification of the assay

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*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.

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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.
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
3. Animalytix ruminant segments and equine MAT ending Jan 2015.
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 postpartum 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 estrus 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.

DOSEAGE AND ADMINISTRATION
As with any multi-dose vial, practice aseptic techniques in withdrawing each dose to decrease the possibility of post-injection bacterial infections. Adequately clean and disinfect the vial stopper prior to entry with a sterile needle and syringe. Use only sterile needles, and use each needle only once. No vial stopper should be entered more than 20 times.

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:

<table>
<thead>
<tr>
<th>Day 0 (Monday)</th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 (the following Monday)</td>
<td>LUTALYSE HighCon</td>
<td>LUTALYSE HighCon</td>
<td>LUTALYSE HighCon</td>
</tr>
<tr>
<td>Day 9 (Wednesday)</td>
<td>2nd FACTREL + FTAI after 48 hours</td>
<td>2nd FACTREL 48 hours after LUTALYSE HighCon</td>
<td>2nd FACTREL 56 hours after LUTALYSE HighCon</td>
</tr>
<tr>
<td>Day 10 (Thursday)</td>
<td>FTAI 24 hours after 2nd FACTREL</td>
<td>FTAI 18 hours after 2nd FACTREL</td>
<td></td>
</tr>
</tbody>
</table>

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 postpartum 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 bronchospasms. 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 PGE2 and PGG2, 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 PGG2a, 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 LUD 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 PGEs and PGFs, 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 (1H PGF2 alpha) in the rat and in the rabbit was similar. Although quantitative differences were observed, qualitatively similar metabolites were produced. A study demonstrated that equilibrium doses of 1H PGF2 alpha and 1H 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 1H PGF2 alpha rapidly distributed into 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 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.

**TARGET ANIMAL SAFETY**

An interesting observation in the above study was that the radioactive dose of 1H PGF2 alpha rapidly distributed into 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 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.

**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 (1.25 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 Cmax and AUC to demonstrate therapeutic equivalence.

The pivotal relative bioavailability study was a randomized, non-replicated, three treatment, three period, six sequence crossover design 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 PGF2α (metabolite) concentrations. PGF2α 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 2. The Cmax and AUClast 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.

**Injection Site Safety Summary:** Eight non-lactating, non-pregnant dairy cows were injected with saline and eight animals were injected with LUTALYSE HighCon (1.25 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 1. This hardness was probably a result of text article administration. No hardness was noted on the left neck on the previous day. No abnormal skin appearance was noted in any animal during this study. Swelling with a volume of 3.53 ml 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 (1.25 mg dinoprost/mL) to the approved IM administration of 25 mg of LUTALYSE Injection (5 mg dinoprost/mL). 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 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. Most cattle that recovered in response to LUTALYSE Injection recovered within 10 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% 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, on average, for cattle at 25 mg dose titration doses were 22%, 50%, 71%, 90% and 78% for cattle at 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.

**zotexis**

Distributed by: Zoetis Inc.
Kalamazoo, MI 49007

Made in Spain

Revised: August 2015

P1207-669US/06-15A&P
Caution:
5 mg dinoprost/mL as dinoprost tromethamine
(Lutalyse® Injection)
be used for cattle. The 30 mL bottle may be used for cattle, swine, or mares.

**INDICATIONS FOR USE**
- 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

**DOSAGE AND ADMINISTRATION**

**LUTALYSE Injection.**

- **For estrus synchronization in beef cattle and non-lactating dairy heifers**
  - Day 0 (Monday): 1st FACTREL
  - Day 1 (Tuesday): 2nd FACTREL + LUTALYSE
  - Day 9 (Wednesday): 2nd FACTREL + LUTALYSE
  - Day 10 (Thursday): LUTALYSE

- **For use with EZAI-BRED™ CIRD® (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 postnatal estrus in beef heifers**

- **For estrus synchronization in beef cattle and non-lactating dairy heifers**
  - Day 0 (Monday): 1st FACTREL
  - Day 1 (Tuesday): 2nd FACTREL + LUTALYSE
  - Day 9 (Wednesday): 2nd FACTREL + LUTALYSE
  - Day 10 (Thursday): LUTALYSE

**User Safety:**
- Caution: Drug residues may occur unless abortion is desired. Cattle administered a progestin would be expected to have a reduced
  - Lactating dairy cows:
  - For estrus synchronization in lactating dairy cows with a corpus luteum
  - For use with FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow 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ぎ in gestation.**

**WARRIORS AND PRECAUTIONS**

**User Safety:**
- Not for human use. Keep out of the reach of children. Women of childbearing age, asthmatics, and persons with bronchial and other respiratory problems should exercise extreme caution when handling this product. In the early stages, women may be unaware of their pregnancies. Dinoprost tromethamine is readily absorbed through the skin and can cause abortion and/or bronchospasms. Accidental spillage on the skin should be washed off immediately with soap and water.
- To report suspected adverse events, for technical assistance or to obtain a copy of the Material Safety Data Sheet (MSDS) contact Zoetis Inc. at 1-888-963-8471.

**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 at the rate of the approved dose may result in drug residues. Do not use in horses intended for human consumption.
- Animal Safety Warnings:
  - Severe localized cutaneous reactions associated with injection of LUTALYSE Injection have been reported. In rare instances, such reactions have resulted in death. Injectable drug residues may occur 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 gifts prior to 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 gestation. Inject a dose of 25 mg dinoprost (5 mL) intramuscularly. Cattle that abort will abort within 72 hours of the fixed-time LUTALYSE injection.
  - For use with FACTREL® (gonadorelin injection) Injection to synchronize estrous cycles to allow 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 gestation. Inject a dose of 25 mg dinoprost (5 mL) intramuscularly. Cattle that abort will abort within 72 hours of the fixed-time LUTALYSE injection.
- 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 species 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.
  - Cattle 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.
  - Cows on detectedestrus using standard herd practices.
  - Administration of LUTALYSE Injection during diestrus (4 or more days after ovulation) will return to estrus within 2 to 4 days in most cases and ovulate 6 to 12 days after treatment. This procedure may be utilized as an aid to scheduling the use of the estrous cycle.
predicted farrowing as an increased number of stillbirths and postnatal mortality may result. In mares, LUTALYSE Injection in a single injection when adminstered 4 to 5 days prior to ovulation. Mares pregnant 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, nestling behavior, itching, urination, defecation, abdominal muscle spasms, tail movements, hyperperspiration or dyspnea, increased vocalization, salivation, and at the 100 (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 noted included increased facial and head movements, increased respiratory rate, palpitations, increased urination, increased rectal temperature, and sweating. These reactions 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.

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 amnion fluid, 2) relax placental vessels, 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 capable of crossing from the uterine lumen to the maternal lymph 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 calcium levels 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 (H3 PGF2α) 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 H3 PGF2α Tham and H3 PGF2α free acid administrated 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 H3 PGF2α alpha rapidly distributed in tissues and dissipated in tissues with almost the same curve as it did in the serum. The half-life of dinoprost in bovine blood has been reported to be on the order of minutes. A complete study on the distribution of decline of 3H PGF2α Tham in the tissue of rats was well correlated with the half-life of dinoprost in bovine blood has been reported to be on the order of minutes. A complete study on the distribution of decline of 3H PGF2α Tham in the tissue of rats was well correlated with the half-life of dinoprost in bovine blood has been reported to be on the order of minutes.

CLINICAL PHARMACOLOGY

EFFECTIVENESS

Mares:

Dinoprost tromethamine was administered to adult mares (weighing 330 to 485 kg; 2 to 20 years old), at the rates of 0.0, 100, 200, 400, and 800 mg per mare per day for 10 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; hypergastronomility; 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 treatment. 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 900 mg). Heart rate was increased but pH of the urine was decreased. Other measurements evaluated in this 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 daily injections. Additional studies investigated the effects in the mare of single intramuscular doses of 0, 25.0, 1.0, 2.5, 3.0, 5.0, and 10.0 mg dinoprost tromethamine. Heart rate, respiration rate, rectal temperature, and sweating were measured at 0.25, 0.5, 0.75, 1.0, 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 control and normal values. Sweating was observed for 9, 2, 9, 7, 9, 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 dropping) 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 doses, respectively. Average rectal temperature during the periods of decreased temperature was on the order of 97.4 to 98.1, with the greatest decreases observed in the 10 mg dose group.

Additional studies administered for the use of FACTREL Injection and LUTALYSE Injection, please refer to the labeling for FACTREL Injection.

LACTATION

Mares: For Difficult-to-Breed Mares: In one study with 122 Standardbred and Thoroughbred mares in clinical anestrous 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.

STOREAGE, 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.

of the side effects.

Revised: August 2014
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-NH2 with identical physiological activities. The molecular weight of gonadorelin is 1182 with a molecular formula of C55H75N17O13. The corresponding values for gonadorelin hydrochloride are 1219 (1 HCl) expressed as C55H75N17O13HCl, or 1255 (2 HCl) expressed as C55H75N17O13 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:

<table>
<thead>
<tr>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 (Monday)</td>
<td>1st FACTREL</td>
<td>1st FACTREL</td>
</tr>
<tr>
<td>Day 7 (the following Monday)</td>
<td>LUTALYSE</td>
<td>LUTALYSE</td>
</tr>
<tr>
<td>Day 9 (Wednesday)</td>
<td>2nd FACTREL + FTAI at 48 hours after LUTALYSE</td>
<td>2nd FACTREL 48 hours after LUTALYSE</td>
</tr>
<tr>
<td>Day 10 (Thursday)</td>
<td>FTAI 24 hours after 2nd FACTREL</td>
<td>FTAI 18 hours after 2nd FACTREL</td>
</tr>
</tbody>
</table>

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

zooetis
Zoetis Inc.
Kalamazoo, MI 49007

Revised: May 2015

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