**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 P gland F 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.

- **For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in lactating dairy cows and replacement beef and dairy heifers, advancement of first postpartum estrus in suckled beef cows, and advancement of first postpartal estrus in beef heifers:**
  - Administer one EA-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 intramammary or subcutaneous injection. Cattle that abort will abort within 35 days of injection.

6. For use with EA-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for Synchronization of Estrus in Lactating Dairy Cows:

- Administer a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramammary or subcutaneous injection at the time of removal of the EA-BREED CIDR Cattle Insert.
- **Observe animals for signs of estrus on Days 2 to 5 after removal of the EA-BREED CIDR Cattle Insert.**

7. For use with EA-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 postpartal estrus in beef heifers:

- **Observe animals for signs of estrus on Days 1 to 3 after removal of the EA-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 while 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 bronchospms. Aximal 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 cutisbons associated with injection of LUTALYSE Injection have been reported. In rare instances, such infections have resulted in death. Aggressive antibiotic therapy should be employed at the first sign of infection at the injection site whether localized or diffuse. Do not administer intravenously (IV) as this route may potentiate adverse reactions. Non-steroidal anti-inflammatory drugs may inhibit prostaglandin synthesis therefore this class of drugs should not be administered concurrently. Do not administer to pregnant cattle, unless abortion is desired. Cattle administered a progestin would be expected to have a reduced response to LUTALYSE Injection.

**Adverse Reactions**

Limited salivation has been reported in some instances.

**Contact Information**

For a copy of the Safety Data Sheet or to report adverse reactions, call Zoetis Co. Inc. at 1-888-963-8471. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.
Similar. Although quantitative differences were observed, and 3H PGF2 alpha free acid administered intravenously to rats at 60 and 10 minutes prior to dose administration, and at 5, 10, 15, 20, 30, 75 minutes, and at 2, 3, 4, 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 PGF2αs. The results of the relative bioavailability study are summarized in Table 1. The Cmax and AUC0-t 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 Injection vs LUTALYSE High Con

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Product/ Route</th>
<th>LSMean</th>
<th>Ratio T/R</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL) Injection</td>
<td>LUTALYSE</td>
<td>50.80</td>
<td>1.23</td>
<td>110.99</td>
<td>136.60</td>
</tr>
<tr>
<td></td>
<td>LUTALYSE High Con Injection</td>
<td>55.12</td>
<td>1.34</td>
<td>120.42</td>
<td>148.20</td>
</tr>
<tr>
<td>AUC0-t (hr*ng/mL) Injection</td>
<td>LUTALYSE</td>
<td>65.81</td>
<td>1.00</td>
<td>96.26</td>
<td>105.12</td>
</tr>
<tr>
<td></td>
<td>LUTALYSE High Con Injection</td>
<td>66.85</td>
<td>0.97</td>
<td>94.20</td>
<td>102.87</td>
</tr>
</tbody>
</table>

A 14-day continuous intravascular infusion study in rats at 20 mg PGF2α per kg body weight indicated prostaglandin 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 examinations 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. A slight transient increase in the rectal temperature was observed during the conduct of the study. 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 pregnancy, 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 fetal abnormalities. 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 the dose required to precipitate dystocia, fetal death, retained placenta and/or metritis, especially at latter stages of gestation.

Injection Site Safety Summary: In pregnant and non-pregnant dairy cows, intramammary instillation of dinoprost was evaluated. No abnormal skin appearance was noted in any animal. No sensory sensitivity. No hardness was noted at the injection sites during the conduct of the study. Injection site reactions were observed at the left horn on Day 0 and the second injection was administered in the right horn 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 at the end of gestation. All clinical observations or general health observations related to drug administration during the course of the study. Injection site observations recorded no findings of erythema, heat, or soreness. 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 horn 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. Swellings with a volume of 3.53 cm³ was observed on Day 11 in the right horn in one treated animal. At necropsy decoloration (violations of dark red, tan, gray, or yellow) and atrophy were 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. No discoloration was 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). 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: Intramuscular injections of LUTALYSE Injection were administered once at 10 days. No abnormal skin appearance was noted in any animal. No sensory sensitivity. No hardness was noted at the injection sites during the conduct of the study. Injection site reactions were observed at the left horn on Day 0 and the second injection was administered in the right horn 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 at the end of gestation. All clinical observations or general health observations related to drug administration during the course of the study. Injection site observations recorded no findings of erythema, heat, or soreness. 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 horn 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. Swellings with a volume of 3.53 cm³ was observed on Day 11 in the right horn in one treated animal. At necropsy decoloration (violations of dark red, tan, gray, or yellow) and atrophy were 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. No discoloration was 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.