A 14-day continuous intra-amniotic infusion study in rats at 20 mg PGF 2α per kg body weight indicated prostaglandin F2 α (PGF 2α) induced metritis, especially at later stages of gestation.

**Cattle:** In cattle, evaluation was made of clinical observations, clinical chemistry, hematology, urinalysis, organ weights, and gross pathological findings. Following treatment of cattle 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 hematologic or clinical chemistry parameters measured. Clinically, a slight transient increase in heart rate was detected. Racial temperatures were normal. No observable behavior or clinical signs were noted. There was no evidence of toxicological effects. Thus, dinoprost had a safety factor of 25.

Rectal administration during the conduct of the study. Injection Site Safety Summary: Eight non-lactating, non-pregnant, multiparous cows were injected with LUTALYSE HighCon Injection (12.5 mg dinoprost/mL) by intramuscular or subcutaneous injection. Breed cows with a corpus luteum. Inject a dose of 2 mL LUTALYSE HighCon Injection to the approved IM administration of 25 mg of LUTALYSE HighCon Injection to the TS administration of 25 mg of LUTALYSE HighCon Injection. Therefore, the effectiveness studies conducted with LUTALYSE HighCon Injection support the effectiveness of LUTALYSE HighCon Injection.

**Treatment for Protrusion of the Uterus (endometritis) in Cattle:** In studies conducted with LUTALYSE HighCon 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 40 mm or less based on palpation per rectum at 14 and 28 days. Host cattle that recovered in response to LUTALYSE HighCon 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 Induction of 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 treatment group less than 100 days of gestation ranged between 26 and 84%. More or less of the pregnant cattle were less than 150 days of gestation. The abortion rates following injection of LUTALYSE HighCon Injection increased with increasing doses up to about 25 mg. As examples, the abortion rates, over 7 feedlots of LUTALYSE HighCon Injection for abortion varies considerably with the stage of gestation.

**Injection Site Safety:** Eight non-lactating, non-pregnant cows were injected with 15 mg dinoprost per kg body weight. Similarly administered 15 mg dinoprost per kg body weight indicated prostaglandins such bone changes were not observed in monkeys. A 14-day continuous intravenous infusion study in rats at 25 mg PGF 2α per kg body weight indicated prostaglandins about 25 mg. As examples, the abortion rates, over 7 feedlots indicated that the first day of gestation should not lead to complications at abortion. However, induction of parturition or abortion with any exogenous compound may precipitate dystocia, fetal or maternal death or abortion, especially at later stages of gestation.

**LUTALYSE HighCon 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 prostan glandin 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 5 days prior to treatment.

- For estrus synchronization in beef cows, beef heifers and replacement dairy heifers.
- For unsolicited (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 a full description of the studies conducted for the use of FACTREL® 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) except during brief periods 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. Kamalamos, MI 49007 Made in Spain Revised: August 2015 P1207-669US/06-15
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 Frelin® (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows: Administer 2 to 4 mL FACREL Injection (100-200 mg 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 to 24 hours after the second dose of FACTREL Injection.

The above framework is designed immediately above:

- Observe animals for signs of estrus on Days 2 to 5 after removal of the EAZI-BREED CIDR Cattle Insert and any mammalian estrus syndrome to allow abortion in estrus following normal herd practices.
- 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 after 2nd abortion.

- Administer one dose of 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 at the time of removal of the EAZI-BREED CIDR Cattle Insert.

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.

Residue Warnings: No milk discard or preslaughter 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 cystidial 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 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 agents 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 prostaglandin for 6 weeks postpartum may 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 Zoetsis Inc. at 1-888-965-8471. For additional information about adverse drug experience, dial the Animal Health Hotline at 1-888-FDA-VETS or visit our website at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

TABLE 1: Relative Bioavailability Results for LUTALYSE HighCon Injection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Product/Route</th>
<th>LSMean</th>
<th>Ratio (%)</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LUTALYSE Injection (IM)</td>
<td>41.26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>LUTALYSE Injection (SC)</td>
<td>50.80</td>
<td>1.23</td>
<td>110.99</td>
<td>136.60</td>
</tr>
<tr>
<td>AUC0→∞ (hr*ng/mL)</td>
<td>LUTALYSE HighCon Injection (SC)</td>
<td>55.12</td>
<td>1.34</td>
<td>120.42</td>
<td>148.20</td>
</tr>
<tr>
<td>AUC0→∞ (hr*ng/mL)</td>
<td>LUTALYSE HighCon Injection (SC)</td>
<td>65.81</td>
<td>0.98</td>
<td>94.20</td>
<td>102.87</td>
</tr>
<tr>
<td>Cmax - maximum plasma concentration</td>
<td></td>
<td>67.25</td>
<td>1.00</td>
<td>96.26</td>
<td>105.12</td>
</tr>
<tr>
<td>AUC0→∞ - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay</td>
<td></td>
<td>65.81</td>
<td>0.98</td>
<td>94.20</td>
<td>102.87</td>
</tr>
</tbody>
</table>

TARGET ANIMAL SAFETY

Laboratory Animals: Dinoprost was non-toxic in rats when administered orally at 1.25, 3.2, 10.0 and 20.0 mg dinoprost/kg/day from day 6-15 of gestation 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-toxic 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 0.5 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.
3. For Treatment of Pyometra (chronic endometritis) in Cattle: inject a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramammary 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 intramammary or subcutaneous injection. Cattle that abort will abort within 35 days of injection.

5. For use with Frelin (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 mg 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**
- 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
- Day 10 (Thursday): FTAI 24 hours after 2nd FACTREL

**Example 2**
- Day 0 (Monday): 1st FACTREL 1st FACTREL 1st FACTREL
- Day 7 (the following Monday): LUTALYSE HighCon LUTALYSE HighCon LUTALYSE HighCon
- Day 14: FTAI 14 days after LUTALYSE HighCon

**Example 3**
- Day 0 (Monday): 1st FACTREL 1st FACTREL 1st FACTREL
- Day 7 (the following Monday): LUTALYSE HighCon LUTALYSE HighCon LUTALYSE HighCon
- Day 13: FTAI 56 hours after LUTALYSE HighCon

6. For use with EAZI-BREED™ CIDR® (progesterone intravaginal implant) 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 the removal is on the following Monday).
- Administer a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) by intramammary 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 3 after removal of the EAZI-BREED CIDR Cattle Insert and record the day of estrus and the age of pregnant animals.

- Administer one EAZI-BREED CIDR Cattle Insert per animal for 7 days (for example if administered on a Monday the removal is 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 may 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 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 cutisiodial 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 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 IUI 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 PGF2α and PGFα, 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 triluminal dinoprost (14 PGF2α 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 14 PGF2α alpha Tham and 14 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 radioactivity of 14 PGF2α alpha had rapidly distributed in tissues and dissipated in tissues with almost the same rate as it did in the serum. The half-life of the drug in bovine blood has been reported to be on the order of minutes. A complete study on the distribution of 14 PGF2 alpha Tham in the tissue of rats was well correlated with the work carried on the monkey. 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 transformation, binding or other systems need to 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 Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax.
A 14-day continuous intravenous infusion study in rats at 20 mg FGF.2 per kg body weight indicated prostaglandins of the F series 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 pathology. Observations following treatment of with various doses up to 250 mg dinoprost administered twice intramuscularly at a 10 day interval or doses of 25 mg dinoprost every 10 days. There was no unequivocal effect of dinoprost on the hematology or clinical chemistry parameters measured. Clinically, a slight transient increase in heart rate was detected. Rectal temperature was elevated about 1.5˚ F through the 6th hour.

Unequivocal effect of dinoprost on the hematology or with various doses up to 250 mg dinoprost administered similarly administered 15 mg dinoprost per kg body weight indicated prostaglandins A 14-day continuous intravenous infusion study in rats at precipitate dystocia, fetal death, retained placenta and/or safe dose), based on studies conducted with cattle. At observations or general health observations related to drug site observations were conducted on all animals once on the neck on Day 0 and the second injection was administered on the right neck on Day 10. Clinical observations were injected with LUTALYSE HighCon (12.5 mg dinoprost/mL) (see \textit{CLINICAL PHARMACOLOGY}, \textit{Relative Bioavailability Study}). This study demonstrated the equivalence of the dose administration of 25 mg of LUTALYSE HighCon to the IM administration of 25 mg of dinoprost. Therefore, the effectiveness studies conducted with LUTALYSE HighCon 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 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 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 \textsuperscript{*} (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.

\textbf{HOW SUPPLIED} LUTALYSE HighCon Injection is available in 20, 100 and 250 mL vials.

\textbf{STORAGE, HANDLING AND DISPOSAL} Store below 25°C (77°F) and protected from freezing. Exposed to 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.

\textbf{NADA} #141-442, Approved by FDA

\section*{Lutalyse\textsuperscript{*} HighCon Injection (dinoprost tromethamine injection)}

\subsection*{12.5 mg dinoprost/mL as dinoprost tromethamine}

For use in cattle only.

\textbf{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.

\textbf{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, benzoic 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.

\textbf{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 5 days prior to treatment.

For estrus synchronization in beef cows, beef heifers and replacement dairy heifers.

- For use with FACTREL \textsuperscript{*} (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.

\textbf{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:

- \textbf{For cattle} must be ready and they must have a corpus luteum and be healthy;
- \textbf{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;
- \textbf{Physical facilities} must be adequate to allow cattle handling without being detrimental to the animal;
- \textbf{Estrus} must be detected accurately if timed AI is not employed;
- \textbf{Semen} of high fertility must be used;
- \textbf{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.

\textbf{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. Thoroughly clean and disinfect the 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. \textbf{For Prenatal Synchronization of Estrus in Beef Heifers and Replacement Dairy Heifers.} LUTALYSE HighCon Injection is used to control the timing of estrus in insemination. Estrus cycles occurring that cattle have a corpus luteum. Inject a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) intramuscularly or intravenously, either by twice at 10 to 12 day interval. With the single injection, cattle should be bred at the usual time relative to estrus. With the two injection regimen, can be continued after the second injection occurs or 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 of 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. \textbf{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.