Synchronization programs are only as reliable as the products on which they are built. FACTREL® Injection (gonadorelin injection) and LUTALYSE® Injection (dinoprost injection) is a product combination approved by the Food and Drug Administration (FDA) for use with each other to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows.

- The flexible labels provide the option to prescribe Zoetis products in a manner consistent with many reproduction management strategies, plus flexible dosage with FACTREL allows convenience and adaptability to protocol needs.
- You can feel confident prescribing and using products that you have trusted for years, backed by industry-leading field service and expertise.
- Since its launch more than 30 years ago, LUTALYSE has been the most widely used prostaglandin in the dairy industry.¹
- Backed by data with more than 12,000 combined cows studied in competitive trials which demonstrate that FTAI with FACTREL and LUTALYSE provide an effective method of synchronizing estrus.²-⁴

**FLEXIBLE LABEL**

With a flexible FTAI label, the FDA approval helps ensure you, your clients and their herds are able to choose from several proven estrous synchronization schedules. You can meet with the individual needs of each operation with the example protocols shown on the right. And all with a NEW more convenient larger size FACTREL vial.

**COMMOTTED TO HELPING YOU**

We understand the challenges of today’s dairies and are committed to helping you and your clients overcome them. With this approval, you can use FACTREL and LUTALYSE in many of the synchronization programs recommended by the Dairy Cattle Reproduction Council.

**IMPORTANT SAFETY INFORMATION FOR FACTREL:** FACTREL is for use in cattle only. See full prescribing information, attached.

**IMPORTANT SAFETY INFORMATION for LUTALYSE:** Women of childbearing age and persons with respiratory problems should exercise extreme caution when handling LUTALYSE. LUTALYSE is readily absorbed through the skin and may cause abortion or bronchospasms, therefore spillage on the skin should be washed off immediately with soap and water. Aseptic techniques should be used to reduce the possibility of post-injection clostridial injections. Do not administer LUTALYSE in pregnant cattle unless cessation of pregnancy is desired. See full Prescribing Information, attached.

¹ MDI MAT ending June 2011. u7
² Data on File, Study Report No. 13PETREPRO01-08D, Zoetis Inc.
⁴ Poock S, Lucy M. Conception rate for postpartum dairy cows treated with different gonadorelin (GnRH) products for first or resynchronized timed AI. Presented at 2015 Midwest ADSA/ASAS Meeting, Des Moines, IA, March 16-18, 2015.

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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 C₂₉H₃₄N₂O₁₂. The corresponding values for gonadorelin hydrochloride are 1219 (1 HCl) expressed as C₂₉H₃₄N₂O₁₂HCl, or 1255 (2 HCl) expressed as C₂₉H₃₄N₂O₁₂H₂Cl.

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.

DOSEAGE

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 at 48 hours after LUTALYSE</td>
</tr>
<tr>
<td>Day 10 (Thursday)</td>
<td>FTAI at 24 hours after 2nd FACTREL</td>
<td>FTAI at 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 follicle 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.

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 Zoetics 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

Distributed by: Zoetis Inc.
Kalamazoo, MI 49007

NADA 139-237, Approved by FDA
Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION
LUTALYSE® Injection (5 mg dinoprost/mL) is a sterile solution containing the naturally occurring prostaglandin F2 alpha (dinoprost) as the tromethamine salt. Each mL contains dinoprost tromethamine equivalent to 5 mg dinoprost: also, benzyl alcohol, 16.5 mg added as preservative. When reconstituted, pH was adjusted with sodium hydroxide and/or hydrochloric acid. Dinoprost tromethamine is a white or slightly off-white crystalline powder that is readily soluble in water at room temperature in concentrations to at least 200 mg/mL.

INDICATIONS FOR USE
Cattle: LUTALYSE Injection is indicated as a luteolytic agent. LUTALYSE Injection is effective only in those cattle having a corpus luteum, i.e., those which ovulated at least 5 days prior to treatment. Future reproductive performance of animals that are not cycling will be unaffected by injection of LUTALYSE Injection.

• For estrus synchronization in beef cattle and non-lactating dairy heifers.
• For unobserved (silent) estrus in lactating dairy cows with a corpus luteum.
• For treatment of pyometra (chronic endometritis) in cattle.
• For abortion of feedlot and other non-lactating cattle.
• For use with FACTREL (gonadorelin injection) injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows.
• For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in lactating dairy cows.
• For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in suckled beef cows and replacement beef and dairy heifers, advancement of first postpartum estrus in suckled beef cows, and advancement of first pubertal estrus in beef heifers.

Mares: LUTALYSE Injection is indicated as a luteolytic agent. LUTALYSE Injection is effective only in those mares having a corpus luteum, i.e., those which ovulated at least 7 days prior to treatment. Future reproductive performance of animals that are not cycling will be unaffected by injection of LUTALYSE Injection.

• For estrus synchronization in estrous cycling mares.
• For difficult-to-breed mares (clinically anestrous mares that have a corpus luteum). A thorough examination is recommended to confirm the presence of a corpus luteum.
• For estrus synchronization in estrous cycling mares that are not cycling for 4 to 8 days following injection of a luteolytic agent.
• For estrus synchronization in mares that are not cycling due to previous treatment with equine chorionic gonadotropin (eCG).
• For estrus synchronization in mares that are not cycling due to previous treatment with a prostaglandin.
• For estrus synchronization in mares that are not cycling due to previous treatment with an equine anti-mullerian hormone (eAMH) injection.
• For estrus synchronization in mares that are not cycling due to previous treatment with an injectable GnRH analog (e.g., gonaclone).

DOSAGE AND ADMINISTRATION
As with any multi-dose vial, practice aseptic techniques in withdrawing each dose to decrease the possibility of post-injection bacterial infections. Adequately clean and disinfect the vial stopper prior to entry with a sterile needle and syringe. Use only sterile needles, and use each needle only once. No vial stoppers should be entered more than 20 times. For this reason, the 100 mL bottle only should be used for cattle. The 30 mL bottle may be used for cattle, swine, or mares.

Cattle:
1. For Estrus Synchronization in Beef Cattle and Non-Lactating Dairy Heifers. LUTALYSE Injection is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum. Administer a dose of 5 mL LUTALYSE Injection during diestrus (4 or more days after ovulation) to return to estrus within 14 to 21 days. Cattle that do not become pregnant to breeding at estrus on days 1 to 5 after injection will be expected to return to estrus in about 18 to 24 days.

2. For Unobserved (Silent) Estrus in Lactating Dairy Cows with a Corpus Luteum. Inject a dose of 5 mL LUTALYSE Injection (25 mg dinoprost) intramuscularly. Breed cows as they are detected in estrus. If estrus has not been observed by 80 hours after injection, breed at 80 hours. If the cow returns to estrus, breed at the usual time relative to estrus. With the two injections can be bred after the second injection either at the usual time relative to detected estrus or at 80 hours after the second injection of LUTALYSE Injection. Estrus is expected to occur 1 to 5 days after injection if a corpus luteum was present. Cattle that do not become pregnant to breeding at estrus on days 1 to 5 after injection will be expected to return to estrus in about 18 to 24 days.

Mares:
1. For Parturition Induction in Swine: For intramuscular use for parturition induction in swine. LUTALYSE Injection is indicated for parturition induction in swine when injected within 3 days of normal predicted farrowing. The response to treatment varies with individual animals with a mean interval from administration of 2 mL LUTALYSE Injection (10 mg dinoprost) to parturition of approximately 30 hours. This can be employed to control the time of farrowing in sows and gilts in late gestation.

Management Considerations: Several factors must be considered for the successful use of LUTALYSE Injection for parturition induction in swine. The producer must be able to determine a relatively specific time (treatment earlier than 3 days prior to normal predicted farrowing may result in increased piglet mortality). It is important that adequate records be maintained on (1) the average length of gestation period for the animals on a specific location, and (2) the breeding and projected farrowing dates for the animals. This information is essential to determine the appropriate time for administration of LUTALYSE Injection.

2. Difficult-to-Breed Mares: For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in suckled beef cows and replacement beef and dairy heifers, advancement of first postpartum estrus in suckled beef cows, and advancement of first pubertal estrus in beef heifers:

• Administer one EAZI-BREED CIDR Cattle Insert per animal for 7 days (for example, if administered on a Monday remove the following Monday).

• Administer 5 mL LUTALYSE Injection (equivalent to 5 mg/mL dinoprost) 1 day prior to EAZI-BREED CIDR Cattle Insert removal, on Day 6 of the 7 day administration period.

• Observe animals for signs of estrus on Days 1 to 3 after removal of the EAZI-BREED CIDR Cattle Insert and inseminate animals about 12 hours after onset of estrus.

WARMING 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. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at https://www.fda.gov/animal-veterinary/adverse-drug-experience-reporting.

Residue Warnings: No milk discard or preslaughter drug withdrawal period is required for labeled uses in cattle. No preslaughter drug withdrawal period is required for labeled uses in swine. Use of this product in excess of the approved dose may result in drug residues. Do not use in horses intended for human consumption.

Animal Safety Warnings: Severe localized cuticular 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 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 these drugs should not be administered concurrently. Do not administer to pregnant cattle, unless abortion is desired. Cattle administered a prostegin would be expected to have a reduced response to LUTALYSE Injection. Do not administer to sows and/or gilts prior to 3 days of normal parturition.
predicted farrowing as an increased number of stillbirths and postnatal mortality may result. In mares, LUTALYSE injection is ineffective when administered prior to day 5 after ovulation. Mare pregnancy status should be determined prior to treatment since LUTALYSE injection has been reported to induce abortion and parturition when sufficient doses were administered. Mares should not be treated if they suffer from either acute or subacute disorders of the vascular system, gastrointestinal tract, respiratory system, or reproductive tract.

ADVERSE REACTIONS

Cattle: Limited salivation has been reported in some instances.

Swine: The most frequently observed side effects were erythema and pruritus, slight incoordination, nesting behavior, itching, urination, defecation, abdominal muscle spasms, tail movements, hyperpnea or dyspnea, decreased respiratory rate, and diarrhea. Other reactions seen have been increase in heart rate, increase in respiratory rate, some abdominal discomfort, locomotor incoordination, and lying down. These effects are usually seen within 15 minutes of injection and disappear within one hour. Mares usually continue to eat during the period of expression of side effects. One anaphylactic reaction of several hundred mares treated with LUTALYSE Injection was reported but was not confirmed.

Contact Information: To report adverse reactions call Zoetis Inc. at 1-888-963-8471.

CLINICAL PHARMACOLOGY

General Biologic Activity: Prostaglandins occur in nearly all mammalian tissues. Prostaglandins, especially PGE's and PGF's, have been shown, in certain species, to 1) increase at time of parturition in amniotic fluid, maternal placenta, myometrium, and blood, 2) stimulate myometrial activity, and 3) to induce either abortion or parturition. Prostaglandins, especially PGF2α, have been shown to increase in the uterus and blood to levels similar to levels achieved by exogenous administration which suggests that these prostaglandins could be capable of either initiating or augmenting the maternal response of parturition or abortion. However, these prostaglandins could also induce bone deposition. However, such bone changes were not observed in the 10 mg dose group.

Mares: The most frequently observed side effects are sweating and decreased rectal temperature. However, these side effects are transient in all cases observed and have not been detrimental to the animal. Other reactions seen have been increase in heart rate, increase in respiratory rate, some abdominal discomfort, locomotor incoordination, and lying down. These effects are usually seen within 15 minutes of injection and disappear within one hour. Mares usually continue to eat during the period of expression of side effects. One anaphylactic reaction of several hundred mares treated with LUTALYSE Injection was reported but was not confirmed.

TARGET ANIMAL SAFETY

Laboratory Animals: Dinoprost was non-toxic, when administered orally at 1.25, 3.0, 10.0 and 20.0 mg dinoprost/kg/day from day 6-15 of gestation. The abortion rates following injection of LUTALYSE Injection increased with increasing doses of dinoprost up to 25 mg/kg/day. The abortions occurred within 14 days after injection of LUTALYSE Injection. The abortion rates following injection of LUTALYSE Injection increased with increasing doses of dinoprost up to 25 mg/kg/day. The abortions occurred within 14 days after injection of LUTALYSE Injection.

Mares: Dinoprost tromethamine was administered to adult mares (weighing 320 to 485 kg; 2 to 20 years old), at the rates of 0, 100, 200, 400, and 800 mg per mare per day for 8 days. Route of administration for each dose group was both intramuscularly (2 mares) and subcutaneously (2 mares). Mares were observed for the development of uterine contractions in all treated groups for clinical (reduced sensitivity to pain; locomotor incoordination; hypergastromotility) and hematological, biochemical (elevated cholesterol, total bilirubin, LDH, and glucose), and hematology (decreased eosinophils; increased hemoglobin, hematocrit, and erythrocytes) measurements. The effects in the 100 mg dose group, 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 show any adverse effects following termination of the side effects.

Mares treated with either 400 mg or 800 mg exhibited more profound symptoms. The excessive hyperstimulation of the gastrointestinal tract caused a protracted diarrhea, slight electrolyte imbalance (decreased sodium and potassium), dehydration, gastrointestinal irritation, and slight liver malfunction (elevated SGOT, SGPT at 800 mg only). Heart rate was increased but pH of the urine was decreased. Other measurements evaluated in the study remained within normal limits. No mortality occurred in any of the groups. No apparent differences were observed between the intramuscular and subcutaneous routes of administration. Luteolytic doses of dinoprost tromethamine are on the order of 5 to 10 mg administered on one day, therefore, LUTALYSE Injection was demonstrated to have a wide margin of safety. Thus, the 100 mg dose gave a safety margin of 10 to 20X for a single injection or 80 to 160X for the daily injections.

Additional studies investigated the effects in the mare of single intramuscular doses of 0.25, 1.0, 2.5, 3.0, 5.0, and 10.0 mg dinoprost tromethamine. Heart rate, respiration rate, rectal temperature, and sweating were measured at 0, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, and 6.0 hr. after injection. Neither heart rate nor respiration rates were significantly altered (P > 0.05) when compared to control. Rectal temperature was decreased during the interval 0.5 until 1.0, 1.5, 2.0, 3.5, 4.0, and 5.0 hr. after injection. Slight sweating was observed in the 200 mg group and at 1.0, 3.0, 25, 5.0, and 10.0 mg dose groups, respectively. Average rectal temperature during the periods of decreased temperature was on the order of 97.5 to 99.6, with the greatest decreases observed in the 10 mg dose group.

EFFECTIVENESS

Cattle: For Treatment of Pyometra (chronic endometritis) in Cattle: In studies conducted with LUTALYSE Injection, pyometra was defined as presence of a corpus luteum in the ovary and uterine horns containing fluid but not a conceptus based on palpation per rectum. Return to normal was defined as evacuation of fluid and return of the uterine horn size to 40mm or less based on palpation per rectum at 14 and 28 days. Most cattle that recovered in response to LUTALYSE Injection recovered within 14 days after injection. After 14 days, recovery rate of treated cattle was no different than that of non-treated cattle.

Reduce the dose of Feedlot and Other Non-Lactating Cattle: Commercial cattle were palpated per rectum for pregnancy in six feedlots. The percent of pregnant cattle in each feedlot 10 days after conception 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 10%, 59%, 71%, 90%, and 78% in cattle dosed with 0.0 mg, 0.25 mg, 1.0 mg, 2.5 mg, and 10.0 mg dinoprost/kg/day, respectively. The statistical predicted relative abortion rate based on the dose titration data, was about 93% for the 5 mg (25 mg/kg) LUTALYSE injection dose for cattle injected up to 100 days of gestation.

For use with FACTREL® (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows: For a full description of the studies conducted for the use of FACTREL Injection and LUTALYSE Injection, please refer to the labeling for FACTREL Injection.

Mares: For Difficult-to-Breed Mares: In one study with 122 Standardbred and Thoroughbred mares in clinical anestrus for an average of 58 days and treated during the breeding season, behavioral estrus was detected in 81 percent at an average time of 3.7 days after injection with 5 mg LUTALYSE Injection; ovulation occurred an average of 7.0 days after treatment. Of those mares bred, 59% were pregnant following an average of 1.4 services during that estrus.

HOW SUPPLIED

LUTALYSE Injection is available in 30 and 100 mL vials.

STORAGE, HANDLING, AND DISPOSAL

Store at controlled room temperature 20° to 25°C (68° to 77°F). Protect from freezing.

Zoetis

Distributed by: Zoetis Inc., Kalamazoo, MI 49007

Revised: August 2014

NDA 108-901, Approved by FDA