FACTREL® Injection (gonadorelin injection) is an available form of gonadotropin-releasing hormone (GnRH), which causes the secretion of LH and FSH. Naturally occurring hormones cause ovulation of the dominant follicles present in the ovary.

- FACTREL is indicated for the treatment of ovarian follicular cysts that can reduce reproductive efficiency in cattle, therefore, treatment helps reduce the number of days to next estrus.
- FACTREL (a GnRH product) has an FDA-approved label to use in conjunction with LUTALYSE® Injection (dinoprost injection) to synchronize estrous cycles to allow for a fixed-time artificial insemination (FTAI) in lactating dairy cattle.
- 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.  
  1-3
- Improves breeding efficiency when used as part of a FTAI protocol.
- FACTREL offers the only flexible dosage treatment option to meet needs of individual operations and animals.

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 Data on File, Study Report No. 13PETREPRO01-08D, Zoetis Inc.
3 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 C₃₀H₄₂N₂O₁₃. The corresponding values for gonadorelin hydrochloride are 1219 (1 HCl) expressed as C₃₀H₄₂N₂O₁₃HCl, or 1255 (2 HCl) expressed as C₃₀H₄₂N₂O₁₃·2HCl.

**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.

**INDICATIONS FOR USE**

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 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 + FTAI at 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.

**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

Distributed by:
Zoetis Inc.
Kalamazoo, MI 49007

Revised: May 2015 40004714A&P
Lutalyse® Injection
(dinoprost injection)
5 mg dinoprostone/mL as dinoprost tromethamine

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

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

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

1. For estrus synchronization in beef cattle and non-lactating dairy heifers
2. For unobserved (silent) estrus in lactating dairy cows with a corpus luteum
3. For treatment of pyometra (chronic endometritis) in cattle
4. For abortion of feedlot and other non-lactating cattle
5. For use with FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows
6. For use with EA2-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in lactating dairy cows
7. For use with EA2-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
8. For use with EA-2-BREED CIDR® Cattle Insert for use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert
9. For estrus synchronization in beef cattle and non-lactating dairy heifers
10. For treatment of pyometra (chronic endometritis) in cattle

Mares:
1. For estrus synchronization in beef cattle and non-lactating dairy heifers.
2. For unobserved (silent) estrus in lactating dairy cows with a corpus luteum.
3. For controlling the timing of estrus of estrous cycling mares.
4. For difficult-to-breed mares (clinically anestrous mares that have a corpus luteum)
5. For controlling estrus in estrous cycling mares.
6. For estrus synchronization in beef cattle and non-lactating dairy heifers
7. For use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in lactating dairy cows
8. For use with EA-2-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
9. For use with EA2-BREED™ CIDR® Cattle Insert for use with EAZI-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert
10. For estrus synchronization in beef cattle and non-lactating dairy heifers

DOSAGE AND ADMINISTRATION
As with any multi-dose vial, practice aseptic techniques in withdrawing each dose to decrease the chance of infection. LUTALYSE Injection is for intramuscular injection only. LUTALYSE Injection may be administered at any time during estrus, but is most effective when administered at about 12 to 24 hours after the last detection of estrus, or when estrus is not detected within 48 hours. LUTALYSE Injection is indicated for its luteolytic effect in mares. Administer a single dose of 5 mL LUTALYSE Injection intramuscularly either once or twice at a 10 to 12 day interval. With the single injection, cattle should be bred at the usual time relative to estrus. With the two injections cattle can be bred after the second injection either at the usual time relative to detected estrus or at about 60 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.

For Unobserved (Silent) Estrus in Lactating Dairy Cows with a Corpus Luteum. Inject a dose of 5 mL LUTALYSE Injection (25 mg dinoprostone) intramuscularly. Breed cows as they are detected in estrus. If estrus has not been observed by 80 hours after injection, breed at 80 hours. If the cow returns to estrus, breed at the usual time relative to estrus.

Management Considerations:
Factors contributing to success and failure of reproduction management, and these factors are important also when time of breeding is to be regulated with LUTALYSE Injection. Some of these factors are:

1. Cattle must be ready to breed—they must have a corpus luteum and be healthy.
2. Nutritional status must be adequate to allow the animal to have a functional corpus luteum.
3. Physical facilities must be adequate to allow cattle handling without being detrimental to the animal.
4. Estrus must be detected accurately if timed Al is not employed.
5. Semen must be inseminated properly.

A successful breeding program can employ LUTALYSE Injection effectively, but a poorly managed breeding program will continue to be poor when LUTALYSE Injection is employed. The success of LUTALYSE Injection usage depends on the management of the breeding program, and the factors important to the success of the breeding program. Management Considerations:

1. Controlling Time of Estrus of Estrous Cycling Mares:
2. Difficult-to-Breed Mares:
3. Extended Mares:

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 birth defects in domestic animals. 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/vets.

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 food use.

Animal Safety Warnings:

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 the use of drugs that inhibit prostaglandin synthesis should be avoided. Do not administer to pregnant cattle, unless abortion is desired. Cattle administered a progestin would be expected to have a reduced response to LUTALYSE Injection. Do not administer to sows and/or gilts prior to 3 days of normal gestation.

Below are three examples of treatment regimens for FTAI that fit within the dosage regimen framework described immediately above.

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</tr>
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</tr>
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<td>FTAI</td>
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</tr>
<tr>
<td>24 hours after LUTALYSE</td>
<td>18 hours after 2nd FACTREL</td>
<td></td>
</tr>
</tbody>
</table>

6. For use with EA2-BREED™ CIDR® (progesterone intravaginal insert) Cattle Insert for Synchronization of Estrus in Lactating Dairy Cows:

- Administer one EA2-BREED CIDR Cattle Insert per animal and remove 7 days later (for example if administered on a Monday remove the following Monday).
- Administer 5 mL LUTALYSE Injection at the time of removal of the EA2-BREED CIDR Cattle Insert.
- Observe animals for signs of estrus on Days 2 to 5 after removal of the EA2-BREED CIDR Cattle Insert and inseminate animals found in estrus following normal herd practices.

7. For use with EA2-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 EA2-BREED CIDR Cattle Insert per animal for 7 days (for example, if administered on a Monday remove on the following Monday).
- Inject 5 mL LUTALYSE Injection (equivalent to 5 mg/mL dinoprostone) 1 day prior to EA2-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 EA2-BREED CIDR Cattle Insert and inseminate animals about 12 hours after onset of estrus.
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 (18 mares). Neither heart rate nor respiratory rates were significantly altered (P > 0.05) when compared to contemporary control values. Sweating was observed for 0 of 9, 2 of 9, 7 of 9, 9 of 9, and 8 of 9 mares injected with 0.25, 1.0, 2.5, 3.0, 5.0, or 10.0 mg dinoprost tromethamine, respectively. Sweating was temporary in all cases and was mild for doses of 3.0 mg or less but was extensive (beads of sweat over the entire body and dripping) for the 10 mg dose. Sweating after the 5.0 mg dose was intermediate between that seen for mares treated with 3.0 and 10.0 mg. Sweating began within 15 minutes after injection and ceased by 45 to 60 minutes after injection. Rectal temperature was decreased during the interval 0.5 until 1.0, 3 to 4, or 5 hours after injection for 0.25 mg, 1.0, 2.5, and 3.0, or 5.0 and 10.0 mg dose groups, respectively. Average rectal temperature during the period of gestation 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 on 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 use with FACTREL® (gonadorelin injection) Injection to synchronize estrus 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 estrus, for an average of 58 days and treated during the breeding season, behavioral estrus was detected in 81 percent at an average time of 3.7 days after injection with 5 mg LUTALYSE Injection; ovulation occurred an average of 7.0 days after treatment. Of those mares bred, 59% were pregnant following an average of 1.4 services during that estrus.

HOW SUPPLIED

LUTALYSE Injection is available in 30 and 100 mL vials.

STORAGE, HANDLING, AND DISPOSAL

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

NADA 108-901, Approved by FDA

Zoetis

Distributed by: Zoetis Inc.
Kalamazoo, MI 49007

Revised: August 2014

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