FACTREL Injection (gonadorelin injection)  

50 mcg gonadorelin per mL (as gonadorelin hydrochloride) Solution for Intramuscular Injection.

For use in cattle only

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 C₅₅H₇₅N₁₇O₁₃2HCl.

**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.

**INDICATIONS FOR USE**

For the treatment of ovarian follicular cysts in cattle. The treatment effect of FACTREL Injection when used in cattle with ovarian follicular cysts is a reduction in the number of days to first estrus.

For use with LUTALYSE® (dinoprost tromethamine) Sterile Solution to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows.

**DOSE**

For the treatment of ovarian follicular cysts in cattle: Administer 2 mL of FACTREL Injection as a single intramuscular injection.

For use with LUTALYSE® (dinoprost tromethamine) Sterile Solution to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows: Administer 2 to 4 mL.

**FACTREL INJECTION**

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) Sterile Solution 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</td>
</tr>
<tr>
<td>Day 10 (Thursday)</td>
<td>FTAI at 24 hours after 2nd FACTREL</td>
<td>FTAI at 56 hours after LUTALYSE</td>
</tr>
</tbody>
</table>

Doses of FACTREL Injection greater than 2 mL have not been shown to provide additional benefit on pregnancy rate to FTAI.

**SAFETY AND TOXICITY**

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 cause 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 prominent 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.

No withdrawal period or milk discard time is required when used according to labeling.

**EFFECTIVENESS**

For the treatment of ovarian follicular cysts in cattle:

The treatment effect of FACTREL Injection when used in cattle with ovarian follicular cysts 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) Sterile Solution 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 Sterile Solution 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 Sterile Solution (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 Sterile Solution and FTAI was conducted 24 or 17 hours later, respectively. For control cows FTAI was performed 72 hours after the LUTALYSE Sterile Solution dose was administered. All treatment groups had significantly greater pregnancy rates to FTAI than cows administered LUTALYSE Sterile Solution 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. No benefit on pregnancy rate to FTAI was demonstrated with increasing dose of FACTREL Injection from 2 to 4 mL.

**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 Sterile Solution 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 multi-dose vials (box of one).

**STORAGE CONDITIONS**

Store at refrigerator temperature 2° to 8°C (36° to 46°F).

NADA 139-237, Approved by FDA

Zoetis

Distributed by: Zoetis Inc.

Kalamazoo, MI 49007

4310I

Revised: March 2013 13950800
LUTALYSE
dinoprost tromethamine injection

**Sterile Solution**

**CAUTION**
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**For Intramuscular Use Only**

**Description**: LUTALYSE Sterile Solution is a luteolytic agent used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum. This product is especially useful for the induction of estrus or at about 80 hours after the second injection of LUTALYSE. Estrus is expected to occur 1 to 5 days after injection. With the two injections, cattle can be bred after the second injection either at the usual time relative to estrus.

**Precautions**: Do not administer intravenously (I.V.) as this route may potentiate adverse reactions. Other reactions seen have been reported, including: anaphylactic shock, transient pruritus, transient respiratory distress, laryngospasm, and coughing. No milk discard or preslaughter drug withdrawal period is required for labeled uses in cattle. No Metabolic and Physiological Effects: To date, no metabolic, toxicologic, pharmacokinetic, or reproductive effects have been reported in animals after injection of this product. It has been reported to cause increase in blood pressure, heart rate, respiration rate, and some abdominal discomfort, locomotor incoordination, and smooth muscle stimulation in certain species.

**Usage**: This product contains the naturally occurring prostaglandin F2 alpha (dinoprost) as the tromethamine salt. Each mL contains dinoprost tromethamine, USP, 2 mg. Dinoprost tromethamine is a white, slightly hygroscopic, crystalline powder that is readily soluble in water at room temperature in concentrations to at least 200 mg/mL.

**General Biologic Activity**: Prostaglandins occur in nearly all mammalian tissues. Prostaglandins, especially PGE's and PGF's (prostaglandins of the E and F series, respectively), have been demonstrated to play an important role in the control of ovulation, placentation, myometrium, and blood. They also stimulate mammary gland secretion of milk and induce the termination of pregnancy by eliciting the release of the corpus luteum and by altering the myometrial contractility of the uterus. They are produced, stored, and released in response to many physiological and pathological circumstances. Dinoprost tromethamine is a luteolytic agent for use in cattle at 25 mg (5 mL) of dinoprost tromethamine administered intramuscularly either once or twice at a 10 to 12 day interval.

**DINOPROST**: A dinoprost metabolite has been shown in laboratory animals. The metabolism of tritium labeled dinoprost (3H PGF2 alpha) in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar results were obtained. The metabolites are primarily the glucuronic acid conjugate of 15,16 and 17 or orally at doses of 0.01, 0.1 and 1.0 mg/kg/day on days 6-18 or 15,16 and 17 of gestation. A slight and marked embryo lethal effect was observed in dams given 1.0 and 5.0 mg/kg/day respectively. This was due to the expected luteolytic properties of the drug. A 14-day intravenous intramuscular study in rats at 20 mg/kg/day for 7 days did not induce bone deposition. However, such bone changes were not observed in monkeys similarly administered LUTALYSE Sterile Solution at 15 mg PGF2 α per kg body weight. A slight and marked embryo lethal effect was observed in dams given 1.0 and 5.0 mg/kg/day respectively. This was due to the expected luteolytic properties of the drug. A 14-day intravenous intramuscular study in rats at 20 mg/kg/day for 7 days did not induce bone deposition. However, such bone changes were not observed in monkeys similarly administered LUTALYSE Sterile Solution at 15 mg PGF2 α per kg body weight.

**Residue Warnings**: As with all parenteral products careful aseptic techniques should be used to decrease the possibility of post-injection bacterial contamination. A sterile medication and aseptic technique are essential for the prevention of local and systemic infection. Treatment of “anestrus” mares which abort subsequent to 36 days of pregnancy may result not in estrus due to presence of functional endometrial cups.

**Warning**: User Safety: Not for human use. Women of childbearing age, asthmatics, and persons with bronchial and other respiratory problems should be aware of their pregnancies. Dinoprost tromethamine is readily absorbed through the skin and can cause abortion. 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. No Metabolic and Physiological Effects: To date, no metabolic, toxicologic, pharmacokinetic, or reproductive effects have been reported in animals after injection of this product. It has been reported to cause increase in blood pressure, heart rate, respiration rate, and some abdominal discomfort, locomotor incoordination, and smooth muscle stimulation in certain species.

**Animal Safety Warnings**: Severe localized ophthalmic reactions associated with injection of LUTALYSE have been reported. **Handling**: Store at controlled room temperature 20° to 25°C (68° to 77°F). Protect from freezing.

**How Supplied**: LUTALYSE Sterile Solution is available in 30 and 100 mL vials.

**Usage**: This product contains the naturally occurring prostaglandin F2 alpha (dinoprost) as the tromethamine salt. Each mL contains dinoprost tromethamine, USP, 2 mg. Dinoprost tromethamine is a white, slightly hygroscopic, crystalline powder that is readily soluble in water at room temperature in concentrations to at least 200 mg/mL.

**General Biologic Activity**: Prostaglandins occur in nearly all mammalian tissues. Prostaglandins, especially PGE's and PGF's (prostaglandins of the E and F series, respectively), have been demonstrated to play an important role in the control of ovulation, placentation, myometrium, and blood. They also stimulate mammary gland secretion of milk and induce the termination of pregnancy by eliciting the release of the corpus luteum and by altering the myometrial contractility of the uterus. They are produced, stored, and released in response to many physiological and pathological circumstances. Dinoprost tromethamine is a luteolytic agent for use in cattle at 25 mg (5 mL) of dinoprost tromethamine administered intramuscularly either once or twice at a 10 to 12 day interval.

**DINOPROST**: A dinoprost metabolite has been shown in laboratory animals. The metabolism of tritium labeled dinoprost (3H PGF2 alpha) in the rat and in the monkey was similar. Although quantitative differences were observed, qualitatively similar results were obtained. The metabolites are primarily the glucuronic acid conjugate of 15,16 and 17 or orally at doses of 0.01, 0.1 and 1.0 mg/kg/day on days 6-18 or 15,16 and 17 of gestation. A slight and marked embryo lethal effect was observed in dams given 1.0 and 5.0 mg/kg/day respectively. This was due to the expected luteolytic properties of the drug. A 14-day intravenous intramuscular study in rats at 20 mg/kg/day for 7 days did not induce bone deposition. However, such bone changes were not observed in monkeys similarly administered LUTALYSE Sterile Solution at 15 mg PGF2 α per kg body weight. A slight and marked embryo lethal effect was observed in dams given 1.0 and 5.0 mg/kg/day respectively. This was due to the expected luteolytic properties of the drug. A 14-day intravenous intramuscular study in rats at 20 mg/kg/day for 7 days did not induce bone deposition. However, such bone changes were not observed in monkeys similarly administered LUTALYSE Sterile Solution at 15 mg PGF2 α per kg body weight.

**Residue Warnings**: As with all parenteral products careful aseptic techniques should be used to decrease the possibility of post-injection bacterial contamination. A sterile medication and aseptic technique are essential for the prevention of local and systemic infection. Treatment of “anestrus” mares which abort subsequent to 36 days of pregnancy may result not in estrus due to presence of functional endometrial cups.

**Warning**: User Safety: Not for human use. Women of childbearing age, asthmatics, and persons with bronchial and other respiratory problems should be aware of their pregnancies. Dinoprost tromethamine is readily absorbed through the skin and can cause abortion. 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. No Metabolic and Physiological Effects: To date, no metabolic, toxicologic, pharmacokinetic, or reproductive effects have been reported in animals after injection of this product. It has been reported to cause increase in blood pressure, heart rate, respiration rate, and some abdominal discomfort, locomotor incoordination, and smooth muscle stimulation in certain species.

**Animal Safety Warnings**: Severe localized ophthalmic reactions associated with injection of LUTALYSE have been reported.