WORKING TOGETHER FOR REPRODUCTIVE SUCCESS.

Lutalyse® Injection (dinoprost tromethamine injection)  
Lutalyse® HighCon Injection (dinoprost tromethamine injection)  
Factrel® Injection (prostaglandin injection)  
Bovi-Shield GOLD FP

DAIRY WELLNESS MAKES A DIFFERENCE™
Keeping a dairy's breeding program in high gear requires a daily commitment to following protocols and investing the necessary time to make it work. If any one part of a program begins to slip, cows won’t become pregnant, and the dairy will find itself in a difficult position.

Establishing a pregnancy is a step-by-step process that begins in the previous lactation. Fresh cows are uniquely challenged by the stress of calving and a suppressed immune system at a time in which their energy intake cannot keep up with demands. The result is a negative energy balance and greater risk of metabolic and reproductive diseases such as metritis. Transition cow management is critical — rations must be properly balanced and available with adequate feedbunk space to prepare cows for calving, as well as provide the nutrients they need to improve their energy status. Without a return to a positive energy balance, fresh cows will not return to healthy reproductive cyclicity, causing delays in rebreeding.

Even after cows return to healthy cycling, additional factors will impact their reproductive efficiency.

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<td>Cows that have lower genetic values for traits like Daughter Pregnancy Rate (DPR) have a reduced chance to get pregnant than those that are higher for the same trait.</td>
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Getting cows pregnant is complex and requires a multifaceted approach. It takes the full commitment of dairy staff and resources to maintain an efficient and successful reproductive program.
Reproductive success is measured by confirmed pregnancies and delivering live, newborn calves. Zoetis works with dairy managers, their vets and their advisers to develop solutions that help get cows prepared for breeding. Backed by years of proven success, Zoetis products are a leading choice of dairy producers across the country and can help improve the efficiency of a reproductive program.

More than just leading technologies, Zoetis provides expertise on capturing the most value from your investment. The team of technical experts supporting Zoetis products works with you to effectively incorporate each solution into the dairy’s reproductive program. This ensures you are maximizing reproductive efficiency and capturing an effective return on investment. And more important, ensures that the reproductive program is designed to get cows bred and protect the growing fetus from reproductive disease.

Superior products backed by industry-leading expertise. That’s the Zoetis reproductive solution.
Exclusive synchronization approval.

Zoetis is dedicated to helping customers improve their businesses by bringing reproductive solutions to market. This includes more than just new products, but also investing in research that leads to the development of label indications for existing products.

Producers can take their reproductive success to a higher level with an exclusive approval for the concurrent use of LUTALYSE® Injection (dinoprost tromethamine injection) or LUTALYSE HighCon Injection (dinoprost tromethamine injection) and EAZI-BREED™ CIDR® Cattle Insert. LUTALYSE and LUTALYSE HighCon are the only prostaglandin products approved for use in synchronization protocols with EAZI-BREED CIDR. A synchronization program, using leading products from Zoetis, can improve the efficiency and success of breeding programs.

**LACTATING DAIRY COWS**

- Day 0: Administer EAZI-BREED CIDR
- Day 7: Administer LUTALYSE or LUTALYSE HighCon
- Day 9: Remove EAZI-BREED CIDR
- Day 12: Observe heat and breed

**DAIRY HEIFERS**

- Day 0: Administer EAZI-BREED CIDR
- Day 6: Administer LUTALYSE or LUTALYSE HighCon
- Day 7: Remove EAZI-BREED CIDR
- Day 10: Observe estrus and breed 12 hours later

These approved directions for concurrent use of LUTALYSE or LUTALYSE HighCon and EAZI-BREED CIDR are another example of how Zoetis — the world leader in dairy reproduction research and support — continues to develop new ways to get even better results from its line of reproductive solutions.
LUTALYSE® Injection (dinoprost tromethamine injection) is the most widely used prostaglandin in the dairy industry.¹

- LUTALYSE® Injection along with LUTALYSE HighCon Injection (dinoprost tromethamine injection) are the only prostaglandins approved to be used with EAZI-BREED™ CIDR® Cattle Insert
- Approved for use with FACTREL® Injection (gonadorelin injection) to synchronize estrous to allow for fixed-time Al
- 5 mL dose; available in 30 mL and 100 mL vials

LUTALYSE® HighCon is a high-concentration formula of LUTALYSE Injection for greater convenience and flexibility in artificial insemination synchronization programs.

- The choice between intramuscular administration and the first and only FDA-approved subcutaneous administration
- 2-mL dose; available in 20 mL, 100 mL and 250 mL vials.

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

IMPORTANT SAFETY INFORMATION FOR FACTREL: Factrel is for use in cattle only. See full Prescribing Information, attached.
Successful breeding just got easier with EAZI-BREED® CIDR® Cattle Insert. EAZI-BREED CIDR can improve the timing and efficiency of a dairy breeding program.

EAZI-BREED CIDR helps to improve the effectiveness of reproduction programs by tightening estrous synchronization so groups of cows and heifers come into heat and can be bred in a narrow window. Groups of cows also can be synchronized to return to estrus after insemination for potential rebreeding in a desired time frame. Use of EAZI-BREED CIDR can result in several improvements to a reproduction program.

- More cows and heifers become pregnant earlier, resulting in higher pregnancy rates
- Easier and more accurate heat detection
- More focused heat detection and easier AI breeding within a narrower window of time
- Heifers freshening at a younger and consistent age
- Accurate breeding and calving dates of cows and heifers
- Improved efficiencies in labor management

FOR BEST RESULTS WITH EAZI-BREED CIDR

1. Wear protective gloves
2. Wash the applicator between uses
3. Fit the body of the insert into the applicator with the tail along the slot
4. Apply a generous amount of lubricant to the tip of the insert
5. Shift the tail to one side and clean the vulva
6. Make sure the insert is on the underside of the applicator, curling down, to ensure that the tail will be hidden from other cows
Ovarian follicular cysts reduce reproductive efficiency. FACTREL® Injection (gonadorelin injection) is indicated for the treatment of ovarian follicular cysts in cattle. Use of FACTREL Injection can reduce the number of days to return to estrus as part of a healthy reproductive cycle.

FACTREL Injection is an available form of gonadotropin-releasing hormone (GnRH), which causes the secretion of LH and FSH. These two naturally occurring hormones cause the ovulation of the dominant follicle present on the ovary.

- Approved for use with LUTALYSE® Injection (dinoprost tromethamine injection) or LUTALYSE HighCon Injection to synchronize estrous cycles to allow for fixed-time AI in lactating dairy cows
- Reduced infertility from ovarian cysts
- Number of days to next estrus is reduced
- Better utilization of AI genetics when cows are prepared for insemination through resolution of follicular cysts

**IMPORTANT SAFETY INFORMATION FOR FACTREL:** Factrel is for use in cattle only. See full Prescribing Information, attached.

**IMPORTANT SAFETY INFORMATION FOR LUTALYSE/LUTALYSE HIGHCON:**
Women of childbearing age and persons with respiratory problems should exercise extreme caution when handling Lutalyse/Lutalyse HighCon. Lutalyse/Lutalyse HighCon are readily absorbed through the skin and may cause abortion and/or bronchospasms, therefore spillage on the skin should be washed off immediately with soap and water. Aseptic technique should be used to reduce the possibility of post-injection clostridial infections. Do not administer Lutalyse/Lutalyse HighCon in pregnant cattle unless cessation of pregnancy is desired. See full Prescribing Information, attached.
You invest heavily to ensure the reproductive success of your herd. Insure that investment with the most comprehensive reproductive protection on the market. BOVI-SHIELD GOLD FP® 5 L5 HB helps provide comprehensive coverage against five viral pathogens and Lepto hardjo-bovis, giving you the peace of mind in knowing your herd’s future is protected.

No other cattle vaccine offers protection like BOVI-SHIELD GOLD FP 5 L5 HB — a viral combination vaccine with comprehensive reproductive protection.

- Helps prevent IBR abortion
- Prevents BVD Types 1 and 2 persistent infection
- Prevents Lepto hardjo-bovis infection
- Prevents Lepto hardjo-bovis urinary shedding and kidney colonization
- Single-dose protection — IBR, PI3, BRSV and BVD Types 1 and 2

BOVI-SHIELD GOLD FP 5 L5 HB is convenient and flexible for producers and available in varying sizes to give more management options.

- L5: 5-way leptospirosis, including Lepto hardjo-bovis
- Approved for IM or SC administration
- 50-, 10- and 5-dose vials

Upgrade to the next level of reproductive protection with BOVI-SHIELD GOLD FP 5 L5 HB.

**LABEL INDICATIONS:** Do not use in pregnant cattle (abortions can result) unless they were vaccinated, according to label directions, with any BOVI-SHIELD GOLD FP or PREGGUARD GOLD FP vaccine prebreeding initially and within 12 months thereafter. Do not use in calves nursing pregnant cows unless their dams were vaccinated within the past 12 months as described above. **To help ensure safety in pregnant cattle, heifers must receive at least 2 doses of any BOVI-SHIELD GOLD FP or PREGGUARD GOLD FP vaccine with the second dose administered approximately 30 days prebreeding.**
A good reproduction program maintains the size and productivity of the milking herd. A great program becomes a profit driver for the dairy. Producers who aggressively manage their reproduction program ensure the full productivity of their herd is realized and create opportunities for extra farm revenues.

Successful reproduction requires absolute commitment by all involved:
1. **Dedicated and consistent efforts**
   - Dedicated heat detection and monitoring
   - Accurate execution of synchronization protocols
   - Proper and sanitary administration of product

2. **Well-researched tools**
   - Avoid products and programs that lack scientific basis
   - Choose reproduction tools that have a proven track record of success
   - Use only well-researched synchronization programs

3. **Proper AI techniques**
   - Producers and breeders need to monitor breeding practices closely
   - Proper semen thawing and handling
   - Insemination at optimal time
   - Proper semen placement

4. **Early and timely pregnancy diagnosis**
   - Open cows must be identified quickly
   - Ultrasound or blood test for early detection (30-40 days post-breeding)
   - Routine follow-up at 45-68 days post-breeding

5. **Proper nutrition and management**
   - Stressors that reduce fertility should be reduced or eliminated
   - Properly balanced transition ration
   - Comfortable housing
   - Heat abatement during summer

6. **Up-to-date disease protection**
   - Vaccinations must safeguard reproduction
   - Herd vaccination program should help protect against reproductive diseases that decrease fertility and increase risk of abortions
   - Vaccines should have a duration of immunity through the management period

7. **Emphasize faster genetic improvement**
   - Speed up genetic progress
   - Choose bulls with high overall profitability indexes, such as Dairy Wellness Profit Index™ (DWP$™) and Net Merit (NM$), which emphasize DPR.
   - Establish genomic selection strategies using CLARIFIDE® or CLARIFIDE® Plus with your calves and heifers to make the most of female selection, which is the other half of the genes impacting reproduction; you can emphasize the same important profitability index of DWP$ or NM$.
Delays in rebreeding cost time and money.

A delay in rebreeding will increase the number of days a cow is open. And the cost for days open adds up in a number of ways — increased breeding costs, a greater risk of culling, higher replacement costs and reduced milk production.

Leading researchers are now determining the average costs of an increase in days open. While the calculations are estimates, the dollars are very real.

University of Florida experts estimate the cost per extra day open to be $3.19 to $5.41 per cow. A major determinant of cost was availability of replacement heifers.  

Delays in rebreeding are estimated to cost as much as $3 per extra day open, according to research from the University of Pennsylvania School of Veterinary Medicine, which focused on quantifying the net present value of a dairy cow.

Reproductive performance drives the profit engine of a dairy. Ensuring that cows are rebred in a timely manner is a critical part of ensuring the future profitability of a dairy herd.
Replacement heifers represent the best genetics, on average, in a herd and are an important part of its future makeup. Ensuring they are bred and freshening for the first time between 22 and 24 months of age is crucial to future production. Since gestation is a fixed length, first service conception risk and age at first breeding will be the biggest drivers of reproductive efficiency.

Improving heifer reproduction will rely on moving heifers into a breeding pen on a routine basis when they reach age and/or growth targets. Examinations to confirm pregnant females should be conducted just as often to allow pregnant females to be moved out of the pen. This means that if heifers are moved into the breeding pen on a weekly basis, pregnancy checks should be conducted weekly as well.

Research has found that administering LUTALYSE® Injection (dinoprost tromethamine injection) on the day heifers are moved to the breeding pen, and then again 10 to 12 days later for animals not yet inseminated, can improve breeding success. The new, high concentration formula of LUTALYSE is LUTALYSE HighCon Injection (dinoprost tromethamine injection).

For heifers not inseminated during their first 28 days in the breeding pen, EAZI-BREED® CIDR® Cattle Insert should be used for timed breeding. This will ensure all heifers are inseminated within 36 days of arrival into the AI pen.

**MONITORING PERFORMANCE**

Performance should be monitored on an ongoing basis using these measurements: pregnancy rate, insemination risk, conception risk and the distribution of age at first insemination. Measurement of progress should be evaluated after each pregnancy check.
There are many factors affecting fertility in dairy cattle. Some are within your control while others aren’t. The team of experts from Zoetis can help you make sense of the complicated reproductive puzzle and provide reproductive solutions to improve breeding success.

The complete line of reproductive solutions from Zoetis includes the most researched and trusted products in the marketplace. Backed by a team of reproduction specialists, these solutions can help any dairy improve the success and profitability of its milking herd.

Let Zoetis work together with you for reproductive success.
**Lutalyse® Injection**

(dinoprost tromethamine injection)

5 mg dinoprost/mL as dinoprost tromethamine

**INDICATIONS FOR USE**

- For use with FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination.
- For treatment of pyometra (chronic endometritis) in cattle having a corpus luteum, i.e., those which ovulated at least five days prior to treatment.

**DESCRIPTION**

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.

- For estrus synchronization in beef cows, beef heifers and replacement dairy heifers
- For unobserved (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 use with EAZI-BREED™ CIDR® (progesterone intravaginal implant) Cattle: Cattle for synchronization of estrus in lactating dairy cows
- For use with EAZI-BREED™ CIDR® (progesterone intravaginal implant) Cattle: Cattle 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.

**Swinie**

- For parturition induction in swine

**Mares**

- For controlling the timing of estrus in estrus cycling mares
- For difficult-to-breed mares (clinically anestrous mares that have a corpus luteum)

**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 Injection. Some of these factors are:

- Cattle must be ready to breed—they must have a corpus luteum and be healthy;
- 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;
- Physical facilities must be adequate to allow cattle handling without being detrimental to the animal;
- Estrus must be detected accurately if timed AI is not employed;
- Semen of high fertility must be used;
- Females 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 unless other management deficiencies are remedied first. Cattle expressing estrus following LUTALYSE Injection are receptive to breeding by a bull. Using bulls to breed large numbers of cattle in heath following LUTALYSE Injection will require proper management of bulls and cattle.

**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 disinfected the vial 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. For this reason, the 100 mL bottle should only be used for cattle. The 30 mL bottle may be used for cattle, swine, or mares.

**Cattle**

- 1. For Estrus Synchronization in Beef Cows, Beef Heifers and Replacement Dairy Heifers:
  - LUTALYSE Injection is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum. Inject a dose of 5 mL LUTALYSE Injection (25 mg dinoprost) intramuscularly either once or twice at a 1 to 2 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 80 hours after the second injection of LUTALYSE Injection. Estrus is expected to occur 1 to 2 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.
- 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.
- 3. For Treatment of Pyometra (chronic endometritis) in Cattle:
  - Inject a dose of 5 mL LUTALYSE Injection (25 mg dinoprost) intramuscularly.
- 4. For Abortion in Beef Cows, Beef Heifers and Replacement Dairy Heifers:
  - LUTALYSE 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 25 mg dinoprost (5 mL) intramuscularly.
  - Cattle that abort will abort within 35 days of injection.
- 5. For use with FACTREL® (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 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) at 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.

**WARMING CHARACTERISTICS**

- **Swine**
  - 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 by 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 product must be administered at a relatively specific time (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 each animal. This information is essential to ensure the appropriate time for administration of LUTALYSE Injection.

**Mares:**

- LUTALYSE Injection is indicated for its luteolytic effect in mares. Administer a single intramuscular injection of 1 mg per 100 lbs (45.5 kg) body weight which is usually 1 mL to 2 mL LUTALYSE Injection. This luteolytic effect can be utilized to control the timing of estrus in estrus cycling and clinically anestrous mares that have a corpus luteum in the following circumstances:
  - 1. Controlling Time of Estrus of Estrous Cycling Mares:
    - Mares treated with LUTALYSE Injection during diestrus (4 or more days after ovulation) will return to estrus within 2 to 4 days in most cases and ovulate 8 to 12 days after treatment. This procedure may be utilized as an aid to scheduling the use of stallions.
  - 2. Difficult-to-Breed Mares:
    - In extended diestrus there is failure to exhibit regular estrus cycles which is different from true anestrus. Many mares described as anestrus during the breeding season have serum progesterone levels consistent with the presence of a functional corpus luteum. A proportion of “barren”, maiden, and lactating mares do not exhibit regular estrus cycles and may be in extended diestrus. Fertilization and abortion, early fetal death and resorption, or as a result of “pseudopregnancy” , there may be serum progesterone levels consistent with a functional corpus luteum. Treatment of such mares with LUTALYSE Injection usually results in regression of the corpus luteum followed by estrus and/or ovulation. Treatment of “anestrus” mares which abort subsequent to 36 days of pregnancy may not result in return to estrus due to presence of functional endometrial cups.

**WARNINGS AND PRECAUTIONS**

**User Safety:** Not for human use. Keep out of the reach of children. Women of childbearing age, anesthetics, 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 Safety Data Sheet (SDS) 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.

**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 cutaneous 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 whether localized or diffuse. Do not administer intravenously (IV) as this route may potentiate adverse reactions. Non-steroidal anti-inflammatory drugs may inhibit proglandin synthesis; therefore this class of drugs should not be administered concurrently. Do not administer to pregnant cattle, unless abortion is desired. Cattle administered a progestin would be expected to have a reduced response to LUTALYSE Injection. Do not administer to sows and/or gilts prior to day 3 of gestation 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, increased vocalization, salivation, and at the 100 mg (10%) dose only, possible vomiting. These side effects are transitory, lasting from 10 minutes to 3 hours, and were not detrimental to the health of the animal.

Mares: The most frequently observed side effects are sweating and decreased rectal temperature. However, these 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 respiration 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 PGF2α and PGI2, 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 1) increase the uterus and blood levels similar to levels achieved by exogenous dinoprost, 2) to cause premature closure of the uterine vessels (sheep), 3) to be related to IUD induced luteal regression (sheep), and 4) to 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 PGI2, 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 tritiated labeled dinoprost (1H PGF2α) 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 1H PGF2α alpha Tham and 1H PGF2α 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 radioactive dose of 1H PGF2α alpha rapidly distributed in tissues and dissipated in tissues with almost the same curve as it did in the serum. The half-life of dinoprost in bovine blood has been reported to be on the order of minutes. A complete study on the distribution of decline of 1H PGF2α alpha Tham in the tissue of rats was well correlated with the work done in the cow. 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, transport, excretion, binding or other systems need to be established by the body to metabolize injected dinoprost.

TARGET ANIMAL SAFETY

Laboratory Animals: Dinoprost was not teratogenic in rats when administered orally at 1.25, 3.2, 10.0 and 20.0 mg dinoprost/kg/day from day 6th-15th of gestation or when administered subcutaneously at 0.5 and 1.0 mg/kg/day on gestation days 6, 7, 8 and 9, 10 and 11 or 12, 13 and 14 or 15, 16 and 17 or orally at doses of 0.01, 0.1 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.

A 14-day continuous intravenous infusion study in rats at 20 mg PGF2α per kg body weight indicated prostaglandins of the F series could induce bone depositions. However, such bone changes were not observed in monkeys similarly treated with LUTALYSE Injection at 15 mg dinoprost per kg body weight for 14 days.

Cattle: In cattle, evaluation was made of clinical observations, clinical chemistry, histology, urinalysis, organ weights, and gross plus microscopic measurements following treatment with various doses up to 250 mg dinoprost administered twice intramuscularly at a 10 day interval or doses of 25 mg dinoprost daily for 10 days. There was no unequivocal effect of dinoprost on the hematological, clinical chemistry parameters measured. Clinically, a slight transitory increase in heart rate was detected. Rectal temperature was elevated about 1.5° F through the 6th hour after injection with 250 mg dinoprost, but had returned to baseline at 24 hours after injection. No dinoprost associated gross lesions were detected. There was no evidence of toxicological effects. Thus, dinoprost had a safety factor of at least 10X on injection (25 mg luteolytic dose vs. 250 mg safe dose), based on studies conducted with cattle. At luteolytic doses of dinoprost had no effect on pregnancy. If given to a pregnant cow, it may cause abortion; the dose required for abortion varies considerably with the stage of gestation, induction of abortion in feedlot cattle at stage of gestation up to 100 days of gestation did not result in dystocia, retained placenta or death of heifers in the field studies. The smallness of the fetus at this early stage of gestation should not lead to complications at abortion. However, induction of parturition or abortion with any exogenous compound may precipitate dystocia, fetal death, retained placenta and/or metritis, especially at later stages of gestation.

Swine: In pigs, evaluation was made of clinical observations, food consumption, clinical pathologic determinations, body weight changes, urinalysis, organ weights, and gross and microscopic observations following treatment with single doses of 10, 30, 50 and 100 mg dinoprost administrated intramuscularly. The results indicated no treatment related effects from dinoprost treatment that were deleterious to the health of the animals or to their offspring.

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). Changes were detected in all treated groups for clinical (reduced sensitivity to pain; locomotor incoordination; hypoglycemia; sweating; hyperthermia; labored respiration), blood chemistry (elevated cholesterol, total bilirubin, LDH, and glucose), and histopathology (decreased eosinophils; increased hemoglobin, hematocrit, and erythrocytes) measurements. The effects in the 100 mg dose, 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 sustain 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 8 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 0.25, 0.5, 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 contemporary control values. Sweating was observed for 0 of 9, 2 of 7, 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 more extensive (beads of sweat over the entire body and dripping from the muzzle) for the 5.0 mg dose group. 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 8 daily injections.
3. For Treatment of Pyometra (chronic endometritis) in Cattle.

No vial stopper should be entered more than 20 times. To entry with a sterile needle and syringe. Use only sterile needles, and use each needle only once. Possibility of post-injection bacterial infections. Adequately clean and disinfect the vial stopper prior injection of LUTALYSE HighCon Injection.

Future reproductive performance of animals that are not cycling will be unaffected by LUTALYSE HighCon Injection are receptive to breeding by a bull. Using bulls to breed large numbers managed breeding program will continue to be poor when LUTALYSE HighCon Injection is employed. A successful breeding program can employ LUTALYSE HighCon Injection effectively, but a poorly

e. Semen of high fertility must be used;

b. Nutritional status must be adequate as this has a direct effect on conception and the important also when time of breeding is to be regulated with LUTALYSE HighCon Injection. Some of these factors are:

a. Cattle must be ready to breed—they must have a corpus luteum and be healthy;

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:

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.

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 stopper should be entered more than 20 times.

1. For Estrus Synchronization in Beef Cows, Beef Heifers and Replacement Dairy Heifers. LUTALYSE HighCon Injection is used to control the timing of estrus and ovulation in estrous cycling cattle that have a corpus luteum. Inject a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) intramuscularly or subcutaneously either once or 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 injections cattle can be bred after the second injection either at 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 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.

2. For Unobserved (Slient) 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 first estrus.

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 FACTREL* (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:

<table>
<thead>
<tr>
<th>Example</th>
<th>Day 0 (Monday)</th>
<th>Day 7 (the following Monday)</th>
<th>Day 9 (Wednesday)</th>
<th>Day 10 (Thursday)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example 1</td>
<td>1st FACTREL</td>
<td>LUTALYSE HighCon</td>
<td>2nd FACTREL + FTAI after 48 hours</td>
<td>FTAI 24 hours after 2nd FACTREL</td>
</tr>
<tr>
<td>Example 2</td>
<td>1st FACTREL</td>
<td>LUTALYSE HighCon</td>
<td>2nd FACTREL</td>
<td>FTAI 18 hours after 2nd FACTREL</td>
</tr>
<tr>
<td>Example 3</td>
<td>1st FACTREL</td>
<td>LUTALYSE HighCon</td>
<td>2nd FACTREL</td>
<td>FTAI</td>
</tr>
</tbody>
</table>

6. For use with EAZI-BREED™ CIDR* (progesterone intravaginal insert) 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 remove 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.
- Observe animals for signs of estrus on Days 2 to 5 after removal of the EAZI-BREED CIDR Cattle Insert and inseminate animals found in estrus following normal herd practices.

7. 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 perubtal 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 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 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 drug withdrawal period is required for labeled uses in cattle. Use of this product in excess of the approved dose may result in drug residues.

Animal Safety Warnings: Severe localized clostridial 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 whether localized or diffuse. Do not administer intravenously (IV) as this route may potentiate adverse reactions. Non-steroidal anti-inflammatory drugs may inhibit prostaglandin synthesis; therefore this class of drugs should not be administered concurrently. Do not administer to pregnant cattle, unless abortion is desired. Cattle administered a progestin would be expected to have a reduced response to LUTALYSE Injection.

ADVERSE REACTIONS

Limited salivation has been reported in some instances.

Contact Information: To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS) 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/AnimalVetinary/SafetyHealth.

CLINICAL PHARMACOLOGY

General Biologic Activity: Prostaglandins occur in nearly all mammalian tissues. Prostaglandins, especially PGE2 and PGF2α, 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 1) increase
An interesting observation in the above study was that the radioactive dose of 3H PGF2 alpha rapidly intravenously to rats demonstrated no significant differences in blood concentration of dinoprost. A slight and marked embryo lethal effect was observed in dams given 1.0 and 5.0 mg orally at doses of 0.01, 0.1 and 1.0 mg dinoprost/kg/day on days 6-18 or 5.0 mg/kg/day on days 8-18 on gestation days 6, 7 and 8, 9 or 10 and 11 or 12, 13 and 14, or 15 and 16, or 17 or orally at doses of 0.01, 0.1 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 lutetiolic properties of the drug.

Changes were not observed in monkeys similarly administered 15 mg dinoprost per kg body weight for 14 days.

Cattle: In cattle, evaluation was made of clinical observations, clinical chemistry, hematology, urinalysis, organ weights, and gross plus microscopic measurements following treatment with various doses up to 250 mg dinoprost administered twice intramuscularly at a 10 day interval or doses of 25 mg administered daily for 10 days. There was no unequivocal effect of dinoprost on the hematology or clinical chemistry parameters measured. Clinically, a slight transitory increase in heart rate was detected. Rectal temperature was elevated about 1.5˚ F through the 6th hour after treatment. There were no abnormalities associated with the stage of gestation. Induction of abortion in feedlot cattle at stages of gestation up to 100 days of gestation did not result in dystocia, retained placenta or death of heifers in the field studies. The smallness of the fetus at this early stage of gestation should not lead to complications at abortion. However, induction of parturition or abortion with any exogenous compound may precipitate dystocia, fetal death, retained placenta and/or metritis, especially at latter stages of gestation.

**Injection Site Safety Summary:** Eight non-lactating, non-pregnant dairy cows were injected with saline and eight animals were injected with LUTALYSE HighCon (12.5 mg dinoprost/mL @ 25 mg/animal) twice, at an interval of ten days. The first injection was administered in the left neck on Day 0 and the second injection was administered in the right neck on Day 10. Clinical observations were conducted on Days -14, -1, 0, 1, 2, 10, and 11, and injection site observations were conducted on all animals once on Days -14, -1, and once daily from Day 0 until Day 11. Animals were euthanized on Day 11. There were no abnormal clinical observations or general health observations related to drug administration during the course of the study. Injection site observations revealed no findings of erythema, heat, or sensitivity. No hardness was noted at the injection sites in any control animal post treatment administration. In the treated group, two animals had hardness noted on the right neck on Day 11. This hardness was probably a result of test article administration at that site on the previous day. No abnormal skin appearance was noted in any animal during this study. Swelling with a volume of 3.33 cm was observed on Day 11 in the right neck in one treated animal. At necropsy discoloration (variations of dark red, tan, gray, or yellow mottled) in the subcutaneous tissue was observed at all dinoprost injection sites. More discolored subcutaneous tissue was present at the Day 10 injection sites compared to the Day 0 injection sites. There was no discoloration observed in the deep muscle tissue. In summary, this study demonstrated that subcutaneous injection of LUTALYSE HighCon was well tolerated when injected subcutaneously into dairy cows at a dose of 25 mg dinoprost/cow twice at an interval of 10 days.

**EFFECTIVENESS**

The effectiveness data for LUTALYSE Injection at doses of 25 and 35 mg IM were used to support an adjustment Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for Cmax and AUC to demonstrate therapeutic equivalence. The pivotal relative bioavailability study was a randomized, non-replicated, three treatment, three period, six sequence crossover study in 24 cows (4 cows per sequence). Each cow received a single dose of 25 mg dinoprost administered as 5 mL of LUTALYSE Injection SC, or 2 mL of LUTALYSE HighCon SC, with a washout period of 48 hours between doses. Plasma samples were collected at 60 and 10 minutes prior to dose administration, and at 5, 10, 15, 20, 30, 75 minutes, and at 2, 3, 4.5, 6, 7.5, and 12 hours after each dose. Samples were analyzed by UPLC-MS/MS for PGF2α (dinoprost) and PGFm (metabolite) concentrations. PGMf was chosen as the analyte of interest because its concentrations are reflective of exogenously administered dinoprost (after subtraction of endogenous concentrations), and it has a longer half-life and therefore less blood level fluctuations than PGF2α. The results of the relative bioavailability study are summarized in Table 1. The Cmax and AUC of LUTALYSE HighCon were within the adjusted 90% Confidence Intervals. Therefore, the SC administration of 25 mg of LUTALYSE HighCon Injection was considered to be equivalent to the IM administration of 25 mg of LUTALYSE Injection.

### Table 1: Relative Bioavailability Results for LUTALYSE HighCon Injection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Product/ Route</th>
<th>LSMean</th>
<th>Ratio T/R</th>
<th>Lower 90% CI</th>
<th>Upper 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/mL)</td>
<td>LUTALYSE Injection (IM)*</td>
<td>41.26</td>
<td>1.00</td>
<td>36.1</td>
<td>47.2</td>
</tr>
<tr>
<td></td>
<td>LUTALYSE Injection (SC)</td>
<td>50.80</td>
<td>1.23</td>
<td>48.0</td>
<td>54.0</td>
</tr>
<tr>
<td></td>
<td>LUTALYSE HighCon Injection (SC)</td>
<td>55.12</td>
<td>1.34</td>
<td>51.7</td>
<td>59.0</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;2-12&lt;/sub&gt; (hr·mg/mL)</td>
<td>LUTALYSE Injection (IM)*</td>
<td>66.85</td>
<td>1.00</td>
<td>60.6</td>
<td>73.8</td>
</tr>
<tr>
<td></td>
<td>LUTALYSE Injection (SC)</td>
<td>67.25</td>
<td>1.00</td>
<td>61.5</td>
<td>73.7</td>
</tr>
<tr>
<td></td>
<td>LUTALYSE HighCon Injection (SC)</td>
<td>65.81</td>
<td>0.98</td>
<td>62.4</td>
<td>69.5</td>
</tr>
</tbody>
</table>

Cmax - maximum plasma concentration
AUC<sub>2-12</sub> - the area under the plasma concentration vs. time curve from time of injection to the limit of quantification of the assay
* Reference product and route of administration
† Geometric means

**TARGET ANIMAL SAFETY**

**Laboratory Animals:** Dinoprost was not teratogenic in rats when administered orally at 1.25, 3.0, 10.0 and 20.0 mg dinoprost/kg/day from day 6-15th of gestation or when administered subcutaneously at 0.5 and 1.0 mg/kg/day on gestation days 6, 7 and 8 or 9, 10 or 11 and 12, 13 and 14. Dinoprost was non-teratogenic in the rabbit when administered with albu-minum solution 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 or 14, or 15, 16 and 17 or orally at doses of 0.01, 0.1 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 lutetiolic properties of the drug.

A 14-day continuous intravenous infusion study in rats at 20 mg PGF2α per kg body weight indicated prostaglandins of the F series could induce bone deposition. However, such bone
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 C55H75N17O13. The corresponding values for gonadorelin hydrochloride are 1219 (1 HCl) expressed as C55H76N17O13HCl, or 1255 (2 HCl) expressed as C55H79N17O15 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. 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:

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.

DOSAGE

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 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>

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.

MATERIAL SAFETY DATA SHEET

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.

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1 Animaliix ruminant segments and equine MAT ending Jan 2017.