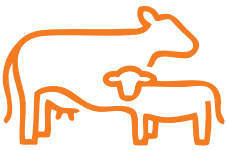
zoetis

TECHNICAL BULLETIN

July 2024



FACTREL® Injection (gonadorelin injection) and LUTALYSE® Injection (dinoprost tromethamine injection) achieved equivalent conception risk as compared with other on-farm fixed-time artificial insemination protocols in lactating dairy cows.

Zoetis
Parsippany, NJ 07054

KEY POINTS

- Fixed-time artificial insemination (FTAI) is an important, successful and widely accepted practice to improve pregnancy rates (PRs) on dairy operations.
- Zoetis' pivotal efficacy trials for an approved FTAI label showed pregnancies per fixed-time artificial insemination (P/FTAI), commonly referred to as conception risk (CR), for cows in six commercial dairies were significantly improved using FACTREL® Injection (*gonadorelin injection*) (2 mL dose, 27.3%) compared with the control group (17.1%, *P*=0.001).[1] This was an increase of 59.6%.
- In the largest FTAI noninferiority study to date with 5,827 animals, first service CR was compared utilizing different gonadotropin-releasing hormone (GnRH) products in FTAI. CR for FACTREL (37.6%) was not different (*P*=0.65) from the current farm protocol (39.0%). FACTREL was noninferior to current farm protocols utilizing gonadorelin diacetate tetrahydrate.[2]
- In an independent noninferiority FTAI study of 2,620 cows from 40 Canadian herds, first service CR was 40.4% for FACTREL and 41.0% for Fertiline® (*GnRH acetate*, Vétoquinol, Lavaltrie, Quebec, Canada); FACTREL was noninferior to Fertiline.[3] Another independent study with 3,938 cows showed CR of FACTREL was noninferior to Cystorelin® (*gonadorelin diacetate tetrahydrate injection*) in FTAI (36% vs. 37%, respectively).[4]
- Using FACTREL (2 mL dose) and LUTALYSE® Injection (*dinoprost injection*) in combination provides a Food and Drug Administration (FDA)-approved method of synchronizing estrus and achieving equivalent CRs and PRs in thousands of dairy cows in widespread locations utilizing a variety of FTAI programs.
- With more than 12,000 combined cows studied, producers can have confidence that FACTREL is effective and can be successfully utilized in their FTAI programs in combination with LUTALYSE, when administered according to label.

INTRODUCTION

Estrous synchronization followed by FTAI has been widely used to manage and improve PRs in commercial dairy operations. The professional literature describes Ovsynch programs consisting of GnRH injection, followed by prostaglandin F2 (PGF_2) administration seven days later, followed by a second injection of GnRH approximately 48 to 56 hours later, with FTAI either 24 or 16 hours later.[5-8] Typically, both doses of GnRH are 100 µg because that dose, used to treat ovarian cysts, was once the only FDA-approved dose in cattle.

Zoetis conducted a pivotal efficacy study to establish the effectiveness of FACTREL® and LUTALYSE® (dinoprost tromethamine injection) for synchronizing estrous cycles to facilitate FTAI in lactating dairy cows and to determine the appropriate dose of FACTREL. This large, multisite study was conducted under commercial production conditions using a variety of Ovsynch regimens and three FACTREL treatments. In addition, two large noninferiority studies in commercial dairies compared CR outcomes from FTAI regimens using FACTREL or other GnRH products, and a third study compared CR in cows administered FACTREL or Cystorelin®.

MATERIALS AND METHODS

Pivotal Efficacy Study of FACTREL vs. Placebo[1]

A total of 1,142 Holstein, Jersey or crossbred cows from six commercial dairies (New York, Michigan, Minnesota, Florida, Colorado and California) were enrolled at >32 and <140 days post-calving. Cows were clinically normal and had a body condition score of >2 and <4 at enrollment. They were randomly assigned to one of four groups: Control — 5 mL LUTALYSE administered on Day 7 with FTAI 72 + 2 hours later; or doses of 100, 150, or 200 µg (2, 3 or 4 mL) FACTREL, administered accordingly:

Day 0: first dose of FACTREL

Day 7: 5 mL LUTALYSE

Day 9: second dose of FACTREL at either 48 ± 2 hours after LUTALYSE with FTAI 24 + 2 hours later (Day 10) or 56 ± 2 hours after LUTALYSE with FTAI 17 ± 2 hours later (Day 10).

Three sites elected to use the earlier timing for the second administration of FACTREL and three sites elected the later administration.

Cows were observed for estrus and abnormal clinical signs at least once daily from Day 1 to the end of the study. Cows in estrus after Day 12 were assumed to be not pregnant and could be inseminated. Final pregnancy diagnosis was conducted 42 to 65 days after breeding. The primary efficacy variable was the P/FTAI, herein referred to as Conception Risk (CR), defined as:

$$CR = \frac{\text{number pregnant at final pregnancy diagnosis}}{\text{number of animals inseminated at FTAI – animals removed from analysis}} \times 100$$

CR was analyzed as a binary variable using a generalized linear mixed model with a binomial error distribution and a logit link function. The statistical model included fixed effects for treatment and random effects of site, site by treatment, enrollment cohort within site and residual. Parity was included as a covariate, and treatment differences were analyzed using site-by-treatment interactions. Within-herd treatment protocols were the same for approximately equal numbers of animals per treatment group. Least squares means, standard errors and 95% confidence intervals were constructed, and effectiveness was determined as statistically significant using a two-tailed test and a *P* value of ≤0.05.

Zoetis Noninferiority Study of FACTREL® vs. Current Farm Protocol[2]

Primiparous or multiparous Holstein dairy cows from eight herds in five states (Arizona, California, Michigan, Idaho, Wisconsin) were recruited into this comparison of FACTREL with other GnRH products (Cystorelin®, Merial, Duluth, GA or Fertagyl® (*gonadorelin*), Merck Animal Health, Summit, NJ) used in a variety of FTAI programs (PG-3-G-Ovsynch[9], Presynch-Ovsynch[10], Double Ovsynch[11]). All GnRH doses were 2 mL. Participating dairies ranged in size from 2,200 to 5,300 lactating cows, with 305 Mature Equivalent (ME) ranging from 24,032 lb. to 27,068 lb. Inclusion criteria included a body condition score of ≥3[12], healthy at start of Ovsynch, no Eazi-Breed™ CIDR® Cattle Insert use and insemination exactly as scheduled. LUTALYSE was the only prostaglandin used; all doses were 5 mL, providing 25 mg PGF_2 per dose. Pregnancy diagnosis was made by rectal palpation or ultrasound 42 to 55 days after insemination. The primary outcome measured was CR following first insemination.

Logistic regression models were used to compare the upper limit treatment difference of the 95% confidence intervals. FACTREL would be considered noninferior if this difference was <7%. The primary outcome was based on pregnancy diagnosis following first insemination (P = pregnant or O = open). Since the primary outcome represented a binomial distribution, results were analyzed using the PROC GLIMMIX procedure of SAS with a logit link function. The final statistical model included fixed effects due to parity group (1 or ≥2), treatment (FACTREL or current farm protocol) and the treatment by parity group interaction; random model effects included first breeding month within herd and parity group, and the herd-by-parity group by treatment interaction. The 305ME milk, computed from Week 10 milk yield, was tested as a covariate but was found to be without effect on the model.

Noninferiority Study of FACTREL vs. Fertiline®[3]

Commercial dairy herds from two veterinary clinics in Québec recruited cows for a study of a Double Ovsynch protocol using FACTREL or Fertiline, a product approved for use in Canada for treatment of cows with cystic ovaries. This noninferiority study was based on not finding a difference of >7% between first service CR. All cows >33 days in milk (DIM) were randomly assigned to receive either FACTREL or Fertiline for their GnRH injections. Reproductive performance at first service and peripartum health events of all cows were recorded over a 14-month period. Cows were examined for pregnancy diagnosis by transrectal palpation or ultrasound.

Logistic regression models were used to compare CR of the two GnRH products accounting for the random effect of herd. Predictors of CR and their interaction with the GnRH variable ($P<0.10$) were tested as fixed effects: parity (primiparous vs. multiparous), breeding season and recording of retained placenta or metritis. The reduced model was obtained after deleting all variables that did not qualitatively change the odds ratio.

RESULTS

Pivotal Efficacy Study of FACTREL® vs. Placebo[1]

Fifty-two cows were removed from the study because of protocol deviations or injury, illness, culling or death. Their data were included up to the day of removal. A third of the remaining cows (307/1,090, 33.9%) were first parity, and 66.1% (720/1,090) were second parity. Figure 1 depicts the CR for the four study groups. All the doses of FACTREL resulted in significantly greater CR than treatment without FACTREL. There were no significant differences between FACTREL treatment groups for CR, and none of the pair-wise comparisons between groups approached significance. Parity had no significant effect on CR. No abnormal clinical signs were attributed to treatment.

Zoetis Noninferiority Study of FACTREL vs. Current Farm Protocol[2]

A total of 5,827 animals were enrolled, including 1,741 (30%) primiparous and 4,086 (70%) multiparous cows; 2,909 received FACTREL and 2,918 received other GnRH products in the first service FTAI protocols. Synchronization start dates ranged from 29 to 61 DIM, with days between the start of presynchronization and insemination ranging from 20 to 38. The final statistical model showed that neither lactation group (P=0.32) nor lactation group by treatment interaction (P=0.77) was significant. The least squares mean for first service CR among cows treated with FACTREL was 37.6% (n=2,902), and among cows treated with gonadorelin diacetate tetrahydrate was 39.0% ((n=2,918), Figure 2). Thus, the difference between treatments was 1.4% (upper and lower 95% confidence intervals of -3.9% to 6.9%). On the basis of these results, first service CRs were not different between treatments (P=0.65), and FACTREL is noninferior to gonadorelin diacetate tetrahydrate.

Noninferiority Study of FACTREL vs. Fertiline®[3]

A total of 2,620 cows from 40 herds were recruited into this study (mean = 65 ±46.2 cows/herd) and the average parity of these cows was 2.4 (±1.48).[3] The Double Ovsynch protocol started on average at 38 DIM (±4.6). The first service CR was 40.4% (n=1,328) for FACTREL and 41.0% (n=1,292) for Fertiline (Figure 3). Results were similar for each practice site. Interactions were not significant and the odds ratio of GnRH was similar in the complete and reduced models. Therefore, in the logistic regression model accounting for the effect of herd clustering, the odds ratio of GnRH variable was 0.98 (using FACTREL® as referent; 95% confidence interval: 0.84-1.16; P=0.84). Conception risk was significantly higher (P<0.01) in primiparous cows (48.7%; n=850) compared with multiparous cows (36.9%; n=1,770).

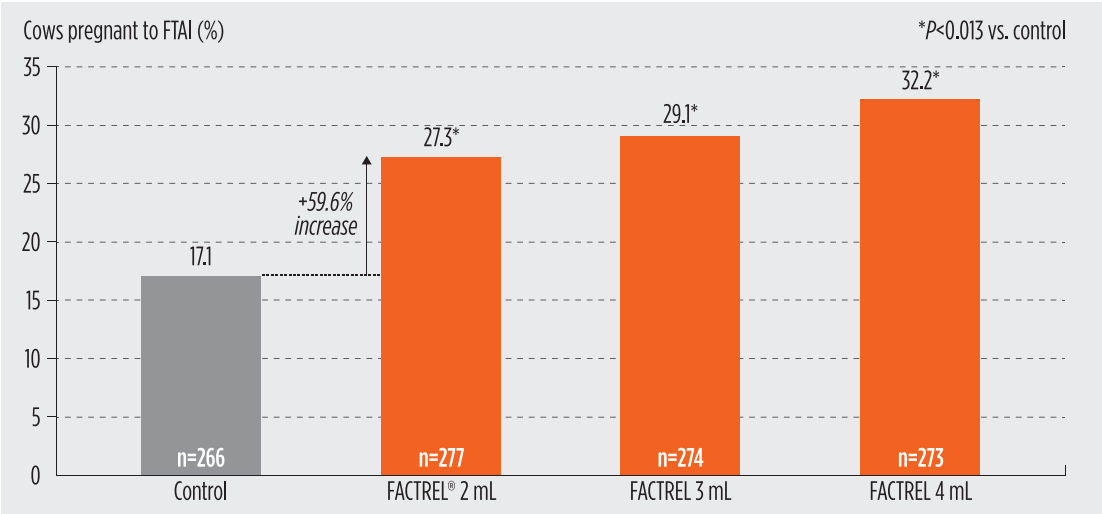


Figure 1. Conception Risk (%) in a Pivotal Efficacy Study of FACTREL vs. Placebo

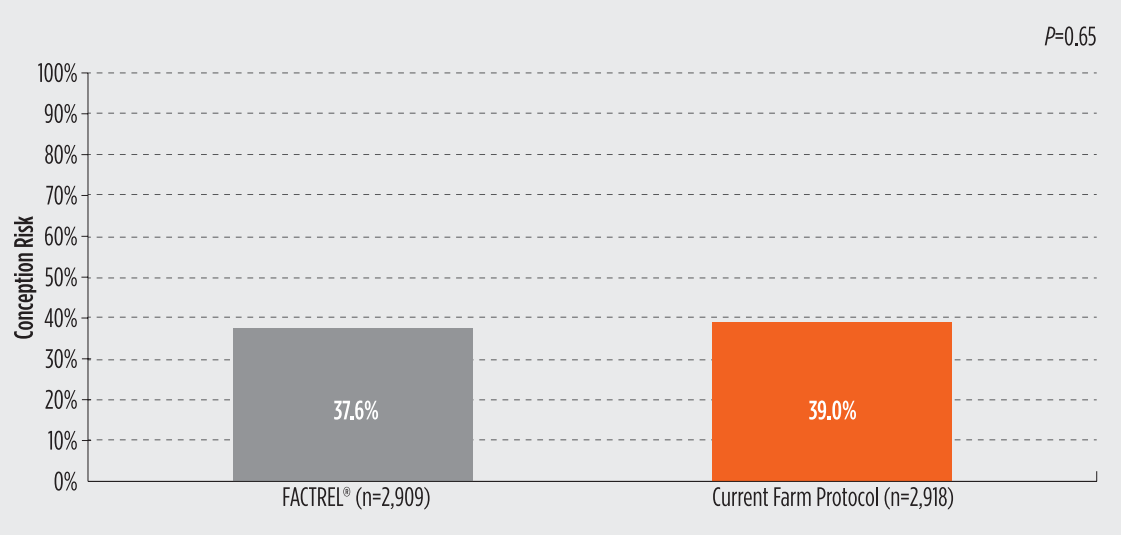


Figure 2. First Service Conception Risk in Fixed Time Insemination Programs Using FACTREL® or Current Farm Protocol

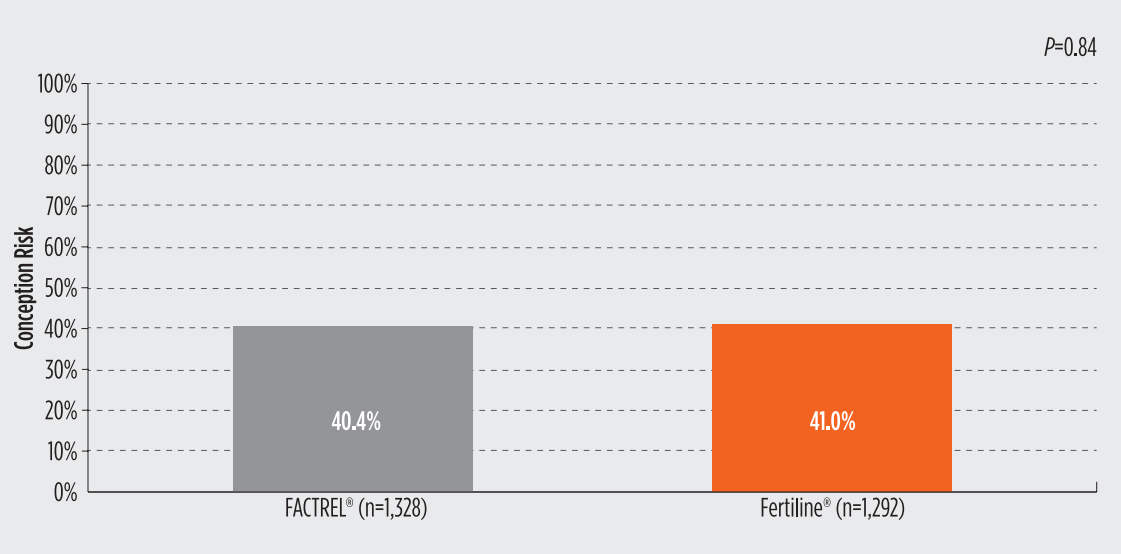


Figure 3. First Service Conception Risk in a Double Ovsynch Program Using FACTREL or Fertiline®

DISCUSSION

Timed artificial insemination after synchronization of ovulation has become one of the most commonly used reproductive technologies developed in the last 40 years.[11] Indeed, Wiltbank and Pursley estimated that 9% of U.S. dairy herds used estrous synchronization/FTAI protocols in 1998, but that 58% of farms used these protocols in 2008. Wiltbank and Pursley provide an excellent historical review of the development of Ovsynch protocols for cattle, which use exogenous prostaglandin (PGF_2) to induce luteolysis, and GnRH to stimulate surges of luteinizing hormone (LH) to induce ovulation. By itself, Ovsynch was shown to have no effect on fertility in dairy cows (CR or pregnancies/cows bred) compared with traditional breeding programs based on observing estrus. However, Ovsynch is effective for reducing average days open in dairy herds because it ensures that all cows on protocol are inseminated, and therefore have an increased probability of becoming pregnant.

Subsequently, researchers recognized that not all cows enrolled into Ovsynch are at a stage of the estrous cycle that is responsive to the initial GnRH treatment. As a consequence, several presynchronization programs were developed, with the goal of "priming" cows for Ovsynch to thereby increase conception. The overall impact of presynchronization is to improve fertility of cows during the Ovsynch phase, which substantially improves conception per insemination compared with using Ovsynch programs alone.[11]

FACTREL®, which contains GnRH hydrochloride (HCl) as the active ingredient, is one of four GnRH products approved for use in Ovsynch protocols in dairy cows (FDA, 2013; NADA 139-237); in the case of FACTREL, LUTALYSE and LUTALYSE High Con prostaglandin to be used in combination. Pivotal trials supporting the use of FACTREL for estrous synchronization were reported by Chenault et al.,[1] who showed improvements in CR compared with a negative control when Ovsynch48 or Ovsynch56 protocols were implemented at FACTREL doses of 2 mL (100 µg gonadorelin), 3 mL (150 µg gonadorelin), and 4 mL (200 µg gonadorelin). The improvement in pregnancies per FTAI in the FACTREL groups was expected, as the control group regimen would fail to synchronize ovulation in cows during the first five to seven days of the estrous cycle, and ovulation in many of the cows responding to the PGF_2 injection would occur outside the window of optimum fertility for FTAI at 72 hours.

Previous studies of GnRH products reported a reduced ovulation rate in response to 100 µg of FACTREL, which contains the HCl salt of GnRH, compared with the same doses of the diacetate tetrahydrate form of GnRH (Cystorelin®, Fertagyl,[12-13] among others). Whereas Souza et al. attributed the treatment-related effect on ovulation to reduced LH concentrations in response to FACTREL, they showed no significant treatment differences among the products evaluated on time to peak LH concentration, peak LH concentration or area under the LH concentration by time curve in cows treated with 100 µg GnRH. Even among GnRH products in the form of the diacetate tetrahydrate salt, ovulation rates ranged from 73.6% to 85.0% of cows treated, which suggests inherent variability in responses. Release of LH from the anterior pituitary is very pulsatile in nature, and other factors, such as progesterone level, also affect LH secretion.[14]

Contradicting the implications of data reported by Souza et al.[13] that decreased ovulation rates will yield decreased CR, Cline[15] evaluated CR in beef cows to Ovsynch protocols that utilized either FACTREL or Cystorelin®, and showed a tendency for a greater proportion of cows treated with FACTREL to be pregnant at 45 days post-insemination than cows treated with Cystorelin. Cline also showed that neither peak LH concentration nor area under the LH concentration by time curve was different in beef cows treated with Cystorelin or FACTREL. Martinez et al.[16] also evaluated LH responses to GnRH products and showed that mean LH concentrations were higher among nonlactating Holstein cows treated with Cystorelin than those treated with FACTREL®. However, they also showed that peak LH concentrations were higher among cows treated with Cystorelin than those treated with a different product containing the same salt of GnRH, Fertagyl®. Taken together, it seems plausible that treatment differences in various studies may simply represent spurious observations, or biological variation in stage of cycle, and unlikely that GnRH products containing the same active ingredient administered at the same dose would, in fact, cause differential responses in LH profiles. Giordano et al.[14] pointed out that many factors impact responsiveness to GnRH experimentally, including the type and physiological conditions of the animals used, variations among GnRH products,

GnRH doses administered, LH assay methods, parameters used to compare LH secretions and steroid milieu at the time of GnRH treatment. Giordano et al. further showed that magnitude of LH secretion in response to GnRH treatments in cattle is mitigated in part by circulating concentrations of progesterone present at the time of GnRH injection.

The most important measure of the relative utility of different GnRH products in Ovsynch protocols is the ability of cows to conceive following treatment and insemination. To this end, data reported herein by Zoetis, as well as two comparable studies conducted without Zoetis participation, all appear to show that CR is similar, regardless of the GnRH product utilized. Table 1 summarizes first service CR data from the largest Zoetis noninferiority study, as well as those from other publications.

The third study by Poock and Lucy supports the conclusion that GnRH products induce equivalent effect. Their study of 3,938 Holsteins compared CR in cows subjected to a FTAI protocol using FACTREL® or Cystorelin®;[4] this study yielded pregnancy outcomes on approximately 1,975 cows per treatment group. Again treatment differences were not significant (P>0.10). This result is consistent with the two noninferiority studies described here, which compared FTAI outcomes (CR) in thousands of animals that received FACTREL, Fertiline® or current farm protocol. In these studies which included more than 12,000 cows, there was no difference in CR between cows treated with FACTREL and all other salt versions of gonadorelin, regardless of the FTAI protocol used.

Synchronization protocols aid in reproductive management by allowing dairy producers to synchronize estrus and ovulation, improve insemination rates and improve CR to first service FTAI compared with breeding practices that depend on heat detection.[17] Using FACTREL and LUTALYSE® in combination provided an FDA-approved method of synchronizing estrus and achieving consistent CRs in thousands of dairy cows in widespread locations utilizing a variety of FTAI programs.

TABLE 1. CONCEPTION RISK (%) REPORTED IN PUBLISHED STUDIES

Investigator(s)	Total Observations (n)	Conception Risk (%)		Comparator Salt
		FACTREL	Comparator Gonadorelin Salt	
Zoetis, 2015[2]	5,827	37.6	39.0	Diacetate tetrahydrate
Caldwell et al., 2014[3]	2,620	40.4	41.0	Acetate
Poock and Lucy, 2015[4]	3,938	36.0	37.0	Diacetate tetrahydrate

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 and/or bronchiospasms, 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 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. Please see full Prescribing Information, attached.

REFERENCES

[1] Chenault JR, Meeuwse DM, LaGrow C, et al. Evaluation of gonadotropin-releasing hormone hydrogen chloride at 3 doses with prostaglandin F2 for fixed-time artificial insemination in dairy cows. *J Dairy Sci* 2014;97:2816-2821.

[2] Data on File, Study Report No. 13PETREPRO01-08D, Zoetis Inc.

[3] Caldwell V, Tison N, Martineau R, Dubuc J, Des Côteaux L. Non-inferiority randomized field clinical trial of two GnRH commercial products used in a systematic double-ovsynch protocol at first breeding in dairy cows. Proc Am Assoc Bov Pract Conf 2014.

[4] Poock S, Lucy M. Conception rate for postpartum dairy cows treated with different gonadorelin (GnRH) products for first or resynchronized timed AI. Presented at 2015 Midwest ADSA/ASAS Meeting, Des Moines, IA, March 16-18, 2015.

[5] Pursley JR, Mee MO, Wiltbank MC. Synchronization of ovulation in dairy cows using PGF2 and GnRH. *Theriogenology* 1995;44:915-923.

[6] Schmitt E, Diaz J-PT, Drost M, Thatcher WW. Use of gonadotropin-releasing hormone agonist or human chorionic gonadotropin for timed insemination in cattle. *J Anim Sci* 1996;74:1084-1091.

[7] Stevenson JS, Kobayashi Y, Shipka MP, Rauchholz KC. Altering conception of dairy cattle by gonadotropin-releasing hormone preceding luteolysis induced by prostaglandin F2 . *J Dairy Sci* 1996;79:402-410.

[8] Stevenson JS, Kobayashi Y, Thompson KE. Reproductive performance of dairy cows in various programmed breeding systems including ovsynch and combinations of gonadotropin-releasing hormone and prostaglandin F2 . *J Dairy Sci* 1999;82:506-515.

[9] Stevenson JS, Pulley SL, Mellieon HI. Prostaglandin F2 and gonadotropin-releasing hormone administration improve progesterone status, luteal number, and proportion of ovular and anovular dairy cows with corpora lutea before a timed artificial insemination program. *J Dairy Sci* 2011;95:1831-1844.

[10] Moriera F, Orlandi C, Risco CA, et al. Effects of presynchronization and bovine somatotropin on pregnancy rates to a timed artificial insemination protocol in lactating dairy cows. *J Dairy Sci* 2001;84:1646-1659.

[11] Wiltbank MC, Pursely JR. The cow as an induced ovulator: timed AI after synchronization of ovulation. *Theriogenology* 2014;81:170-185.

[12] Wildman EE, Jones GM, Wagner PE, et al. A dairy cow body condition scoring system and its relationship to selected production characteristics. *J Dairy Sci* 1982;65:495-501.

[13] Souza AH, Cunha AP, Silva EPB, et al. Comparison of gonadorelin products in lactating dairy cows: efficacy based on induction of ovulation of an accessory follicle and circulating luteinizing hormone profiles. *Theriogenology* 2009; 72:271-279.

[14] Giordano JO, Fricke PM, Guenther JN, et al. Effect of progesterone on magnitude of the luteinizing hormone surge induced by two different doses of gonadotropin-releasing hormone in lactating cows. *J Dairy Sci* 2012; 95:3781-3793.

[15] Cline MA. *Efficacy of synthetic gonadotropin releasing hormone analogs for control of ovulation during estrus synchronization protocols*. MS Thesis; Virginia Tech: 2002.

[16] Martinez MF, Mapletoft RJ, Kastelic P, Carruthers T. The effects of 3 gonadorelin products on luteinizing hormone release, ovulation, and follicular wave emergence. *Can Vet J* 2003;44:125-131.

[17] Lucy MC, Chebel RC, Fricke PM, Dalton JC, Poock SE. Dairy Cow Synchronization Protocols. Available at: http://www.dcrcouncil.org/media/Public/2013%20English%20Dairy%20Cow%20Protocol.pdf. Accessed May 13, 2014.

Approved by FDA under NADA # 139-237

Factrel® Injection

(gonadorelin injection)

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

For use in cattle only

CAUTION

Federal 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-NH_2 with identical physiological activities. The molecular weight of gonadorelin is 1182 with a molecular formula of $C_{55}H_{75}N_{17}O_{13}$. The corresponding values for gonadorelin hydrochloride are 1219 (1 HCl) expressed as $C_{55}H_{75}N_{17}O_{13}HCl$, or 1255 (2 HCl) expressed as $C_{55}H_{75}N_{17}O_{13}$ 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.

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:

	Example 1	Example 2	Example 3
Day 0 (Monday)	1st FACTREL	1st FACTREL	1st FACTREL
Day 7 (the following Monday)	LUTALYSE	LUTALYSE	LUTALYSE
Day 9 (Wednesday)	2nd FACTREL + FTAI at 48 hours after LUTALYSE	2nd FACTREL 48 hours after LUTALYSE	2nd FACTREL 56 hours after LUTALYSE
Day 10 (Thursday)		FTAI 24 hours after 2nd FACTREL	FTAI 18 hours after 2nd FACTREL

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.

WARNINGS AND PRECAUTIONS

For use in animals only. Not for human use. Keep out of reach of children.

RESIDUE WARNINGS

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

EFFECTIVENESS

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.

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 injection) Injection 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 Injection 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 Injection (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 Injection and FTAI was conducted 24 or 17 hours later, respectively. For control cows FTAI was performed 72 hours after the LUTALYSE Injection dose was administered. All treatment groups had significantly greater pregnancy rates to FTAI than cows administered LUTALYSE Injection 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.

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.

CONTACT INFORMATION

For a copy of the Safety Data Sheet or to report adverse reactions, call 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 www.fda.gov/reportanimalae.

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), with excursions permitted to 25°C (77°F). Use contents within 1 month of first vial puncture.

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zoetis

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Zoetis Inc.
Kalamazoo, MI 49007

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Prescribing Information for Use in Cattle

Lutalyse® Injection

(dinoprost tromethamine injection)

5 mg dinoprost/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 dinoprost/mL) is a sterile solution containing the naturally occurring prostaglandin F_2 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 and water for injection.

When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid. Dinoprost tromethamine is a white or slightly off-white crystalline powder that is readily soluble in water at room temperature in concentrations to at least 200 mg/mL.

INDICATIONS FOR USE
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.

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

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:

a. Cattle must be ready to breed—they must have a corpus luteum and be healthy;
b. Nutritional status must be adequate as this has a direct effect on conception and the initiation of estrus in heifers or return of estrous cycles in cows following calving;
c. Physical facilities must be adequate to allow cattle handling without being detrimental to the animal;
d. Estrus must be detected accurately if timed AI is not employed;
e. Semen of high fertility must be used;
f. 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 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 heat 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 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. 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 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 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 (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) 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:

	Example 1	Example 2	Example 3
Day 0 (Monday)	1st FACTREL	1st FACTREL	1st FACTREL
Day 7 (the following Monday)	LUTALYSE	LUTALYSE	LUTALYSE
Day 9 (Wednesday)	2nd FACTREL + FTAI at 48 hours after LUTALYSE	2nd FACTREL at 48 hours after LUTALYSE	2nd FACTREL 56 hours after LUTALYSE
Day 10 (Thursday)		FTAI 24 hours after 2nd FACTREL	FTAI 18 hours after 2nd FACTREL

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 5 mL LUTALYSE 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 pubertal estrus in beef heifers:

- Administer one EAZI-BREED CIDR Cattle Insert per animal for 7 days (for example, if administered on a Monday remove on the following Monday).
- Inject 5 mL LUTALYSE Injection (equivalent to 5 mg/mL dinoprost) 1 day prior to EAZI-BREED CIDR Cattle Insert removal, on Day 6 of the 7 day administration period.
- Observe animals for signs of estrus on Days 1 to 3 after removal of the EAZI-BREED CIDR Cattle Insert and inseminate animals about 12 hours after onset of estrus.

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 bronchiospasms. 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
Cattle: Limited salivation has been reported in some instances.

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CLINICAL PHARMACOLOGY
General Biologic Activity: Prostaglandins occur in nearly all mammalian tissues. Prostaglandins, especially PGE's and PGF's, have been shown, in certain species, to 1) increase at time of parturition in amniotic fluid, maternal placenta, myometrium, and blood, 2) stimulate myometrial activity, and 3) to induce either abortion or parturition. Prostaglandins, especially $PGF_2\alpha$, have been shown to 1) increase in the uterus and blood to levels similar to levels achieved by exogenous administration which elicited luteolysis, 2) be capable of crossing from the uterine vein to the ovarian artery (sheep), 3) be related to IUD induced luteal regression (sheep), and 4) be capable of regressing the corpus luteum of most mammalian species studied to date. Prostaglandins have been reported to result in release of pituitary tropic hormones. Data suggest prostaglandins, especially PGE's and PGF's, may be involved in the process of ovulation and gamete transport. Also $PGF_2\alpha$ 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 tritium labeled dinoprost (^3H PGF_2 alpha) in the rat and in the monkey was similar.

Although quantitative differences were observed, qualitatively similar metabolites were produced.

A study demonstrated that equimolar doses of ^3H PGF_2 alpha Tham and ^3H PGF_2 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 ^3H PGF_2 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 ^3H PGF_2 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, excretory, binding or other systems need be established by the body to metabolize injected dinoprost.

TARGET ANIMAL SAFETY
Laboratory Animals: Dinoprost was non-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 and 8 or 9, 10 and 11 or 12, 13 and 14. Dinoprost was non-teratogenic in the rabbit when administered either subcutaneously at doses of 0.5 and 1.0 mg dinoprost/kg/day on gestation days 6, 7 and 8 or 9, 10 and 11 or 12, 13 and 14 or 15, 16 and 17 or orally at doses of 0.01, 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 $PGF_2\alpha$ per kg body weight indicated prostaglandins of the F series could induce bone deposition. However, such bone changes were not observed in monkeys similarly administered LUTALYSE Injection at 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 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, dinoprost had no effect on progeny. 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 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.

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

For Abortion in Beef Cows, Beef Heifers and Replacement Dairy Heifers: Commercial cattle were palpated per rectum for pregnancy in six feedlots. The percent of pregnant cattle in each feedlot less than 100 days of gestation ranged between 26 and 84; 80% or more of the pregnant cattle were less than 150 days of gestation. The abortion rates following injection of LUTALYSE Injection increased with increasing doses up to about 25 mg. As examples, the abortion rates, over 7 feedlots on the dose titration study, were 22%, 50%, 71%, 90% and 78% for cattle up to 100 days of gestation when injected IM with LUTALYSE Injection doses of 0,1 (5 mg), 2 (10 mg), 4 (20 mg) and 8 (40 mg) mL, respectively. The statistical predicted relative abortion rate based on the dose titration data, was about 93% for the 5 mL (25 mg) LUTALYSE Injection dose for cattle injected up to 100 days of gestation.

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

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).
Use contents within 12 weeks of first vial puncture. Protect from freezing.

Approved by FDA under NADA # 108-901

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