

Date of Approval: June 28, 2013

# CORRECTED FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 139-237

FACTREL Injection

Gonadorelin Injection

Lactating Dairy Cows

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

Sponsored by:

Zoetis Inc.

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## General Information

A. File Number

NADA 139-237

B. Sponsor

Zoetis Inc.  
333 Portage St.  
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

FACTREL Injection

D. Established Name

Gonadorelin injection

E. Pharmacological Category

Peptide hormone

F. Dosage Form:

Injectable solution

G. Amount of Active Ingredient

50 mcg gonadorelin per mL (as gonadorelin hydrochloride)

H. How Supplied

20 mL vial

I. Dispensing Status

Rx

J. Dosage Regimen

For use with LUTALYSE (dinoprost tromethamine) Sterile Solution to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows: Administer 2 to 4 mL FACTREL Injection (100 – 200 mcg gonadorelin) per cow as an intramuscular injection in a treatment regimen with the following framework:

- Administer the first dose of FACTREL Injection (2 – 4 mL) at Day 0.
- Administer LUTALYSE (25 mg dinoprost, as dinoprost tromethamine) Sterile Solution by intramuscular injection 6 to 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.

#### K. Route of Administration

Intramuscular injection

#### L. Species/Class

Lactating dairy cows

#### M. Indication

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

#### N. Effect of Supplement

This supplement provides for addition of a new indication for use with LUTALYSE (dinoprost tromethamine) Sterile Solution to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows.

### II. EFFECTIVENESS

#### A. Dosage Characterization

This supplemental approval does not change the previously approved dosage for treatment of cystic ovaries. The Freedom of Information (FOI) Summary for the original approval of NADA 139-237 dated November 11, 1989, contains dosage characterization information for treatment of cystic ovaries in cattle.

Most studies in the published literature for gonadorelin-prostaglandin reproductive synchrony/ FTAI regimens in cattle use a 100 mcg dose of gonadorelin diacetate tetrahydrate (Fricke et al. 1998, Gumen et al. 2003, Jordan et al. 2002, Momcilovic et al. 1998, Pursley et al. 1995, Pursley et al. 1997, Stevenson et al. 1999, Stevenson et al. 1996). Very few studies compare the effectiveness of other salts of gonadorelin in these synchrony/FTAI regimens. Given this, and the uncertainty with respect to an appropriate dose of FACTREL Injection (gonadorelin injection as gonadorelin hydrochloride or HCl) to elicit ovulation and induce a surge of luteinizing hormone (Souza et al. 2009, Cline 2002), the sponsor conducted a multi-center dose titration and confirmation study to identify appropriate dose(s) of FACTREL Injection for use in gonadorelin-prostaglandin reproductive synchrony/FTAI regimens (see Section II.B below). Data from that study supported a range of 100 – 200 mcg gonadorelin (2 – 4 mL FACTREL Injection) as effective in FTAI regimens.

The sponsor's multi-center study (Section II.B) formed the primary basis to establish the effectiveness of FACTREL Injection and LUTALYSE (dinoprost tromethamine) Sterile Solution "for synchronizing estrous cycles to allow FTAI in lactating dairy cows." In addition, published literature was used to provide for

additional flexibility to the timing of events reflected on the FACTREL labeling for the use of the sponsor's products in estrous synchrony/FTAI regimens. Gonadorelin-prostaglandin estrous synchrony/FTAI regimens generally rely on the temporal treatment with an initial gonadorelin (G1) injection, a prostaglandin (P) injection, and a final gonadorelin (G2) injection, followed by FTAI. The timing of events in these regimens is based upon published research results (dairy and beef cattle) combined with the known biology of the bovine estrous cycle. Although the majority of published reports used the diacetate tetrahydrate salt of gonadorelin, the sponsor's product (FACTREL Injection, gonadorelin HCl) represents a different salt of the same active moiety, and thus has the same biological action. Therefore, use of the published literature to support more flexible timing of events relative to the sponsor's application is appropriate. Below is a brief summary of information related to this, and its use for the current application.

*Timing from G1 to P:* The purpose of administering the initial gonadorelin (G1) is to initiate a new wave of follicular development (Pursley et al. 1995, Pursley et al. 1997, Schmitt et al. 1996, Thatcher et al. 1989, Twagiramungu et al. 1995). The conventional interval between G1 and P is 7 days. Pregnancy rate to FTAI is similar when the interval between G1 and P is 6 or 7 days (Martinez et al. 2002). The maximum duration between G1 and P is influenced by the typical duration of an ovarian follicular wave, which is 7 to 9 days (Fortune et al. 2001, Ginther et al. 2001). Durations beyond this timeframe may nullify the positive effect of inducing a new follicular wave and new dominant follicle. This supports a maximum interval of 8 days between G1 and P to assure ovulation of the dominant follicle that emerged following G1. This supports the directions for use statement "Administer LUTALYSE (25 mg dinoprost, as dinoprost tromethamine) Sterile Solution by intramuscular injection 6 to 8 days after the first dose of FACTREL Injection".

*Timing from P to G2:* The conventional interval between P and G2 is 2 to 3 days (e.g., 48 to 72 hours). In dairy cows, pregnancy rates were similar between cows given G1 and P and bred by AI on detected estrus compared to cows given G1, P, then G2 30 to 36 hours after P, and bred by FTAI (Pursley et al. 1997). Intervals shorter than 30 hours do not appear to maintain the same level of effectiveness (Rantala et al. 2009, Schmitt et al. 1996). An interval greater than 72 hours is not supported by the scientific literature. The purpose of treating cows with G2 is to induce a pre-ovulatory surge in LH in a predictable manner, such that ovulation in groups of animals occurs in a sufficiently narrow time-frame to allow FTAI. Given that dairy cows displayed an LH surge at an average of 71 hours after P (Louis et al. 1974), an interval between P and G2 greater than 72 hours is unlikely to provide any benefit as the LH surge may already have occurred. These data support the directions for use statement "Administer a second dose of FACTREL Injection (2 - 4 mL) 30 to 72 hours after the LUTALYSE injection".

*Timing from G2 to FTAI:* The interval between G2 and FTAI varies for different estrous synchronization regimens. Pursley et al. (1998) demonstrated that pregnancy rate did not differ among cows bred to FTAI 0, 8, 16, or 24 hours after G2, but was reduced in cows bred to FTAI 32 hours after G2. The dose confirmation field study reported below performed FTAI 17 ( $\pm 2$ ) to 24 ( $\pm 2$ ) hours after G2. Results from this field study combined with the data from Pursley et al. (1998) support use of FTAI 0 to 24 hours after G2. In addition, producers may opt to inseminate cows based on detected estrus following P. Some cows may express estrus prior to the G2 or predetermined time for FTAI. Several published studies demonstrated that the pregnancy rate in dairy cows to AI based on detected estrus

after P was similar to pregnancy rates obtained after a full GPG regimen and FTAI were conducted (Pursley et al., 1997, Santos et al. 2004). These results support the use of AI based on detected estrus after P, without use of G2. Taken together, these data support the directions for use statement "Perform FTAI 0 to 24 hours after the second dose of FACTREL Injection, or inseminate cows on detected estrus using standard herd practices."

Thus, the information generated in the sponsor's multi-center study (Section II.B) in combination with published literature supports the following labeling directions for use:

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) Sterile Solution by intramuscular injection 6-8 days after the first dose of FACTREL Injection.
- Administer a second dose of FACTREL Injection (2-4 mL) 30-72 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.

#### 1. Literature Cited

Cline, M.A.. (2002). Efficacy of synthetic gonadotropin releasing hormone analogs for control of ovulation during estrus synchronization protocols. Master's Thesis. Virginia Polytechnic Institute. Blacksburg, VA.

Fortune, J.E., Rivera, G.M., Evans, A.C., Turzillo, A.M. (2001). Differentiation of dominant versus subordinate follicles in cattle. *Biology of Reproduction*. 65: 648-654.

Fricke, P. M., J.N. Guenther, and M.C. Wiltbank. (1998). Efficacy of decreasing the dose of GnRH used in a protocol for synchronization of ovulation and timed AI in lactating dairy cows. *Theriogenology*. 50: 1275-1284.

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Momcilovic, D., Archbald, L.F., Walters, A., Tran, T., Kelbert, D., Risco, C., & Thatcher W.W. (1998). Reproductive performance of lactating dairy cows treated with gonadotrophin-releasing hormone (GnRH) and/or prostaglandin F2a (PGF2a) for synchronization of estrus and ovulation. *Theriogenology*. 50: 1131-1139.

Pursley, J.R., Mee, M.O., & Wiltbank, M.C. (1995). Synchronization of ovulation in dairy cows using PGF2a and GnRH. *Theriogenology*. 44: 915-923.

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Santos, J.E.P., Juchem, S.O., Cerri, R.L.A., Galyao, K.N., Chebel, R.C., Thatcher, W.W., Dei, C.S., Bilby, C.R. (2004). Effect of bST and reproductive management on reproductive performance of Holstein dairy cows. *J. Dairy Sci.* 87: 868-881.

Schmitt, E.J., Diaz, T., Drost, M., Thatcher, W.W. (1996). Use of a gonadotropin-releasing hormone agonist or human chorionic gonadotropin for time insemination in cattle. *J. Animal Sci.* 74: 1084-1091.

Souza, A.H., A.P. Cunha, E. P. B. Silva, A. Gumen, H. Ayres, J. N. Guenther, M. C. Wiltbank. (2009). Comparison of gonadorelin products in lactating dairy cows: Efficacy based on induction of ovulation of an accessory follicle and circulating luteinizing hormone profiles. *Theriogenology*. 72:271-279.

Stevenson, J.S., Kobayashi, Y., Shipka, M.P., & Rauchholz, K.C. (1996). Altering conception of dairy cattle by gonadotrophin-releasing hormone preceding luteolysis induced by prostaglandin F2a. *J. Dairy Sci.* 79: 402-410.

Stevenson, J.S., Kobayashi, Y., & Thomjason, K.E. (1999). Reproductive performance of dairy cows in various programmed breeding systems including OvSynch and combinations of gonadotrophin-releasing hormone and prostaglandin F2 alpha. *J. Dairy Sci.* 82: 506-515.

Thatcher, W.W., Macmillan, K.L., Hansen, P.J., & Drost, M. (1989). Concepts for regulation of corpus luteum function by the conceptus and ovarian follicles improve fertility. *Theriogenology*. 31:149-164.

Twagiramungu, H., Guilbault, L.A., & Dufour, J.J. (1995). Synchronization of ovarian follicular waves with a gonadotropin-releasing hormone agonist to increase precision of estrus in cattle: a review. *J. Animal Sci.* 73:3141-3151.

B. Substantial Evidence

1. Multi-Center Dose Titration Effectiveness Study

a. Title:

Pivotal, Dose Titration, Multi-location, Field Efficacy Study for the Sequential Use of FACTREL Sterile Solution (gonadorelin hydrochloride) and LUTALYSE Sterile Solution for Synchronization of Estrous Cycles to Allow Fixed Time Artificial Insemination in Dairy Cows (Study No. 1930C-60-11-912).

b. Investigators and Locations:

The study was conducted at six commercial dairies (California, Colorado, Florida, Michigan, Minnesota, and New York), representative of the U.S. dairy industry under a common protocol. Site selection covered a broad range of management conditions related to items such as nutrition, housing, breeding and genetics, health, reproduction, lactation, and environment/climate. Locations and the associated clinical investigators are listed in Table 1.

Table 1. Clinical investigators and study locations

Investigator	Location
Paul Busman, DVM	Bailey, MI
Kenneth Mitchell, DVM	Tulare, CA
Michael Capel, DVM	Mount Morris, NY
Greg Goodell, DVM	Fort Lupton, CO
Ricardo Chebel, DVM	Nicollet, MN
Jose Santos, DVM	Trenton, FL

c. Study Design:

(1) Objective:

To evaluate the clinical effectiveness of FACTREL Injection (gonadorelin injection) at three doses (100, 150, and 200 mcg gonadorelin) used with LUTALYSE (dinoprost tromethamine) Sterile Solution (LUTALYSE) for increasing pregnancy rates to FTAI compared to LUTALYSE alone when used in an FTAI reproductive synchrony program.

(2) Experimental Design:

This study was conducted in accordance with Good Clinical Practices (CVM Guidance No. 85 (VICH GL9)). Cows were randomized to treatment in blocks of four within a pen. Cows were assigned to pens



according to routine farm management (e.g., high production group, first lactation group), and study cows were co-housed with non-study cows. If there were not enough eligible cows to complete a block within a pen, then the block was left incomplete and a new block started in the next pen. Pens contained animals from all treatment groups, so that cow was the experimental unit. Most locations enrolled cows in two or more cohorts, such that all cows in a cohort were inseminated on the same day. Each cohort included animals from each treatment group. The majority of personnel involved in the study were masked to treatment assignment. Masked study personnel were not permitted to be present when treatments were administered to study cows. At each location only the Treatment Administrator and Treatment Administrator Scribe were aware of treatment assignments and were not allowed to collect study data.

(3) Study Animals, Housing, and Management:

A total of 1142 cows were enrolled, of which 1090 cows were included in the analysis. Cows were healthy, free of reproductive disorders, and had a body condition score between 2 and 4 (on a 5 point scale). All cows had calved at least once, were not detectably pregnant on day 0, and were between 40 and 150 days post-partum at the beginning of the study. The predominant breed was Holstein, although some Jersey, Holstein-Jersey crosses, and other breeds and crossbreds were included in the study. Approximately one-third of the cows on this study were in their first lactation, and the remaining cows were multiparous, which is typical for U.S. dairy herds. The study began on October 31, 2011, when the first cohort was enrolled, and finished on April 3, 2012, when the last cow exited the study. Locations and investigators are in Table 1, above. Cows were housed in freestall barns at five sites and dry lot pens at one site. One site milked cows twice daily, but the other five sites milked three times per day. Milking parlors were either parallel or herringbone configuration. Cows were fed according to normal herd practices to meet or exceed NRC recommendations (NRC 2001). All locations routinely bred cows by AI on observed estrus prior to the study.

(4) Treatment Groups:

The study consisted of four treatment groups, with three levels of FACTREL: 2 mL (T02), 3 mL (T03), or 4 mL (T04). The control group (T01) received only LUTALYSE followed by FTAI at  $72 \pm 2$  hrs later. Each milliliter of FACTREL contained 50  $\mu\text{g}$  gonadorelin as gonadorelin hydrochloride.

(5) Drug Administration:

Two FTAI programs were incorporated into the protocol to allow greater flexibility in labeling. Each location selected one FTAI program to use throughout the study at that location. The two programs are described below.

- Day 0: FACTREL
- Day 7: 25 mg LUTALYSE
- Option 1: FACTREL 48 ± 2 hrs post LUTALYSE with FTAI 24 ± 2 hrs later; or,
- Option 2: FACTREL 56 ± 2 hrs post LUTALYSE with FTAI 17 ± 2 hrs later

Three locations selected Option 1, and three locations selected Option 2. Data from all locations were pooled for the final statistical analysis for effectiveness.

(6) Measurements and Observations:

Cows were observed at least once daily for general health and signs of estrus according to normal herd procedures. Cows detected in estrus prior to FTAI were not inseminated until FTAI. Cows returning to estrus after FTAI were considered not pregnant, and therefore treatment failures. In cows not returning to estrus, pregnancy was diagnosed by trans-rectal ultrasound or palpation 42 to 65 days post insemination.

(7) Statistical Methods:

The Pregnancy Rate to FTAI was analyzed as a binary variable (1 = pregnant, 0 = not pregnant) using a generalized linear mixed model with a binomial error distribution and a logit link function. The statistical model included fixed effects of treatment and random effects of site, site by treatment, cohort within site, and residual. The model included parity (first parity vs. second and greater) as a covariate.

d. Results

A total of 1142 cows were enrolled, of which 1090 cows were included in the analysis. Reasons for removal included protocol deviations (n = 20), injury (n = 9), mastitis (n = 11), pneumonia (n = 3), digestive disorders (n = 8), and hypocalcemia (n = 1). According to the protocol, each site was targeted to enroll 188 cows, with 47 cows per treatment. Table 2 lists the abnormal health observations and number of cows affected by each abnormality. There was no obvious relationship between treatment and health abnormalities.

Table 2. Abnormal health observations and number of cows affected during study

Health Abnormality	Number Cows Affected
Mammary gland disorders	90
Lameness/injury	27
Digestive tract disorders	12
Respiratory disorders	9
Neurological disorders	1
Hypocalcemia	1

Pregnancy rates were variable across study sites. A number of factors can influence pregnancy rate, including herd management procedures, environmental conditions, service sire, AI technician, and physiological condition (body condition score, days postpartum, milk yield). Regardless, the pregnancy rates in the FACTREL treatment groups were higher than the pregnancy rate in the control treatment group at each location. Numbers of pregnant cows per cows in treatment group completing the study are in Table 3.

Table 3. Cows pregnant per number of cows completing study

Site	T01	T02	T03	T04	Total
A	10/46	15/45	22/44	20/48	67/183
B	4/44	13/50	15/48	15/46	47/188
C	8/45	18/44	8/44	14/44	48/177
D	8/44	5/45	11/43	13/46	37/178
E	10/46	14/46	16/47	15/44	55/183
F	8/41	14/47	11/48	14/45	47/181
All sites	48/266	79/277	83/274	91/273	301/1090

Table 4 provides the least square means and p-values by treatment. Each FACTREL treatment group resulted in statistically significantly higher pregnancy rates compared to the control group. Statistical tests were set up to compare each FACTREL treatment group to the control.

Table 4. Least square means, standard error of the mean (SEM), and P-values for pregnancy rates by treatment

Treatment	Pregnancy rate ( $\pm$ SEM)	P-values
Control (T01)	17.1 ( $\pm$ 2.6)	
2 mL FACTREL (T02)	27.3 ( $\pm$ 3.2)	0.0123
3 mL FACTREL (T03)	29.1 ( $\pm$ 3.3)	0.0051
4 mL FACTREL (T04)	32.2 ( $\pm$ 3.4)	0.0011

e. Adverse Reactions:

There were no adverse effects on animal health attributable to the test article.

f. Conclusion:

FACTREL Injection (2-4 mL; 100 – 200 mcg gonadorelin) used with LUTALYSE in a fixed time artificial insemination (FTAI) reproductive synchrony regimen in lactating dairy cows significantly ( $P < 0.05$ ) increased pregnancy rate to FTAI compared to LUTALYSE alone.

## 2. Literature Cited

National Research Council Committee on Animal Nutrition, Subcommittee on Dairy Cattle Nutrition (2001) Nutrient Requirements of Dairy Cattle. National Academies Press. Washington, D.C.

### III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summaries for the original approvals for FACTREL (NADA 139-237) and LUTALYSE (NADA 108-901) contain summaries of target animal safety studies. In addition, Pfizer, Inc. provided pharmacovigilance data from January 1, 2007, to December 31, 2011, covering the use of FACTREL and LUTALYSE in estrous synchronization programs. Six cases were reported with a total of 249 animals having adverse reactions in that five year period. Five of the six cases also involved the use of an intravaginal progesterone-releasing device. The adverse reactions reported were vulvovaginitis and clostridial myositis. All of the vulvovaginitis reports were associated with the concurrent use of the intravaginal device. Clostridial myositis was reported in the original target animal safety studies for LUTALYSE, and a target animal safety warning is included on package labeling.

Both drugs are rapidly metabolized, and reports in the literature indicate that levels of gonadorelin and prostaglandin in plasma return to baseline levels within three hours of administration. The drugs have their effect through different, highly specific receptors. Thus, no drug interactions leading to adverse effects are anticipated.

Estrous synchronization programs using gonadorelin products with dinoprost tromethamine have been extensively researched since the mid-1990s. Pregnancy rates to FTAI using these products are similar to unsynchronized cattle, ranging approximately between 25 – 45%, and can be affected by various factors, including timing of artificial insemination following the second gonadorelin administration; environmental factors; parity; breed; and cycling status of the cattle. Repeated exposure to prostaglandin and gonadorelin do not appear to cause any adverse effects on reproduction.

## A. Literature Cited:

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Pursley J.R., Wiltbank M.C., Stevenson J.S., et al. (1997). Pregnancy rates per artificial insemination for cows and heifers inseminated at a synchronized ovulation or synchronized estrus. *J. Dairy Sci.* 80:295-300.

Santos J.E.P., Juchem S.O., Cerri R.L.A., et al. (2004). Effect of bST and reproductive management on reproductive performance of Holstein dairy cows. *J. Dairy Sci.* 87:868-81.

Sealfon S.C., Weinstein H., Millar R.P.. (1997). Molecular mechanisms of ligand interaction with the gonadotropin-releasing hormone receptor. *Endocr Rev.* 18:180-205.

Souza A.H., Cunha A.P., Silva E.P.B., et al. (2009). Comparison of gonadorelin products in lactating dairy cows: Efficacy based on induction of ovulation of an accessory follicle and circulating luteinizing hormone profiles. *Theriogenology.* 72:271-9.

## IV. HUMAN FOOD SAFETY:

## A. Antimicrobial Resistance:

The sequential use of injectable FACTREL (gonadorelin hydrochloride) Injection and injectable LUTALYSE (dinoprost tromethamine) Sterile Solution for the synchronization of estrous cycles to allow fixed time artificial insemination in lactating dairy cattle is not thought and has not been reported to impact antimicrobial resistance among bacteria of public health concern in or on treated animals. The Agency determined that an assessment of the microbial food safety (antimicrobial resistance) associated with this sequential use of injectable FACTREL Injection and injectable LUTALYSE Sterile Solution in lactating dairy cattle was not necessary at this time.

B. Impact of Residues on Human Intestinal Flora:

Residues and metabolites of FACTREL (gonadorelin hydrochloride) or LUTALYSE (dinoprost tromethamine) in or on the edible tissues of treated lactating dairy cattle are not thought and have not been reported to impact the intestinal flora of human consumers. The Agency determined that an assessment of the impact of residues or metabolites of FACTREL (gonadorelin hydrochloride) or LUTALYSE (dinoprost tromethamine) in the edible tissues of treated lactating dairy cattle on human intestinal flora was not necessary at this time.

C. Toxicology:

1. Summary of Toxicology Studies

The FOI Summaries for the original approval of NADA 139-237, dated November 11, 1989, for gonadorelin hydrochloride and the supplemental approvals of NADA 108-901 for dinoprost tromethamine, dated November 2, 1979, February 20, 1981, and February 2, 1983, contain summaries of all toxicological and safety information for their individual use. Following intramuscular injection of gonadorelin hydrochloride or dinoprost tromethamine, their serum concentrations rapidly return to baseline values; because the intervals between the administrations of the two drugs are 30 hours or greater, no potential interaction between the two drug products is anticipated.

D. Assignment of the Final ADI :

No ADI was needed for this approval. The FOI Summaries for the original approval of NADA 139-237 for gonadorelin hydrochloride dated November 11, 1989, and the supplemental approvals of NADA 108-901, dated November 2, 1979, February 20, 1981, and February 2, 1983, for dinoprost tromethamine contain summaries of all toxicological information.

E. Safe Concentrations for Total Residues (edible tissues and injection sites, if applicable):

No safe concentrations for total residues were needed for this approval. The FOI Summaries for the original approval of NADA 139-237, dated November 11, 1989, for gonadorelin hydrochloride and the supplemental approvals of NADA 108-901, dated November 2, 1979, February 20, 1981, and February 2, 1983, for dinoprost tromethamine, contain summaries of all toxicological information.

F. Residue Chemistry:

1. Summary of Residue Chemistry Studies

a. Gonadorelin Residues

CVM did not require residue chemistry studies to determine gonadorelin residues in edible tissues or milk for the sequential use of FACTREL Injection and LUTALYSE Sterile Solution. The FOI Summary for the original approval of FACTREL Injection (100 mcg gonadorelin, NADA 139-237, dated November 11, 1989) contains a summary of residue chemistry studies. The

studies investigated the effects of FACTREL treatment at a dose up to 1000 mcg gonadorelin per cow on gonadorelin concentrations in serum and milk. The approval for the use of 100 mcg gonadorelin requires no withdrawal period or milk discard time.

For this approval, CVM assessed the drug residues in the edible tissues, including the injection site, and milk of cows receiving the sequential treatment. The assessment is summarized below:

#### (1) Gonadorelin Residues in Edible Tissues

Based on the biochemical characteristics of gonadorelin, CVM considered that gonadorelin residues at the injection site at 8 to 12 hrs after the treatment (the nominal zero withdrawal period for cattle) represent a worst-case scenario for the residues in all edible tissues (injection site, liver, muscle, kidney and fat) at a zero withdrawal. If gonadorelin residues at injection sites at 8 to 12 hrs after the treatment are not of human food safety concern, then gonadorelin residues in all edible tissues of treated animals are not of human food safety concern at a zero withdrawal.

Based on the study, Trial BN-86-10 (FOI Summary for NADA 139-237, dated November 11, 1989), CVM concluded that at the nominal zero withdrawal, gonadorelin residues at the injection site of cows treated with FACTREL Injection by intramuscular administration at a dose up to 200 mcg do not cause human food safety concern. The study showed that, following an intramuscular injection of gonadorelin at 100, 250 or 1000 mcg per cow, gonadorelin concentrations in serum started to increase within 5 minutes, peaked within 15 minutes, returned to pre-injection baseline within 90 minutes after the injection, and remained at baseline thereafter. (The last time point assayed was 12 hours post treatment.) The study results indicate that gonadorelin residues deplete rapidly from the injection site.

#### (2) Gonadorelin Residues in Milk

Based on the study, Trial BN-86-10 (FOI Summary for NADA 139-237, dated November 11, 1989), CVM concluded that the use of FACTREL Injection in lactating dairy cows at a dose up to 200 mcg gonadorelin does not cause human food safety concern for gonadorelin residues in milk. The study showed that over a 24-hour period following an intramuscular administration of 250 mcg gonadorelin per cow, gonadorelin concentrations in milk were not above those of placebo-treated control cows.

#### b. Dinoprost Residues

CVM did not require residue chemistry studies to determine dinoprost residues in tissues or milk for the sequential use of FACTREL Injection and LUTALYSE Sterile Solution. The FOI Summaries for the approvals of LUTALYSE Sterile Solution under NADA 108-901 contain summaries of residue

chemistry information. No withdrawal period or milk discard time is required for the approvals. The dose of LUTALYSE Sterile Solution for the sequential use is the same as the dose approved under NADA 108-901.

c. Potential Interference Between Depletion of Gonadorelin and Dinoprost Residues

For the sequential use, FACTREL Injection is to be administered 6 to 8 days before the administration of LUTALYSE Sterile Solution and again at 30 to 72 hours after the administration of LUTALYSE Sterile Solution. Because both gonadorelin and dinoprost residues deplete rapidly after administration to cattle, the proposed dosing intervals between the administration of FACTREL Injection and LUTALYSE Sterile Solution are sufficiently long such that interference of depletion of residues of either of the drugs by the residues of the other drug is not anticipated.

d. Conclusion

We conclude that the gonadorelin and dinoprost residues in the edible tissues and milk of cows receiving the sequential treatment with FACTREL Injection and LUTALYSE Sterile Solution do not cause human food safety concern. The sequential use qualifies for a zero withdrawal and zero milk discard.

2. Target Tissue and Marker Residue

It is not necessary to assign a target tissue or a marker residue for gonadorelin residues in cattle.

It is not necessary to assign a target tissue or a marker residue for dinoprost residues in cattle.

3. Tolerances

A tolerance for gonadorelin in tissues or milk of cattle is not required. A tolerance for dinoprost in tissues or milk of cattle is not required.

4. Withdrawal Period and Milk Discard Time

The sequential use of FACTREL Injection and LUTALYSE Sterile Solution in lactating dairy cows does not require a withdrawal period or milk discard time.

G. Analytical Method for Residues:

A regulatory method for gonadorelin is not required.

A regulatory method for dinoprost is not required.

V. USER SAFETY:

CVM did not require user safety studies for this approval.



The product labeling contains the following information regarding safety to humans handling, administering, or exposed to FACTREL:

*"For use in animals only. Not for use in humans. Keep out of reach of children."*

The labeling for LUTALYSE Sterile Solution contains the following warning regarding safety to humans handling, administering, or exposed to LUTLAYSE:

*"Not for human use. 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. Accidental spillage on the skin should be washed off immediately with soap and water."*

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data demonstrate that FACTREL, when used according to the label, is safe and effective for use with LUTALYSE (dinoprost tromethamine) Sterile Solution to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows. Additionally, data demonstrate that residues in food products derived from species treated with FACTREL and LUTALYSE will not represent a public health concern when the products are used according to the label.

A. Marketing Status:

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because veterinary experience is required to properly diagnose ovarian follicular cysts and prescribe appropriate treatment, and because the use of this product for the synchronization of estrous cycles requires the use of LUTALYSE, which also has Rx marketing status.

B. Exclusivity:

Under section 512(c)(2) (F)(iii) of the Federal Food Drug and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval. The three years of marketing exclusivity applies only to the new indication for use with LUTALYSE (dinoprost tromethamine) Sterile Solution to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows, for which this supplement applies.

C. Supplemental Applications:

This supplemental NADA required a reevaluation of the safety data in the original NADA 139-237 (21 CFR 514.106(b)(1) or (2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.