Date of Approval: October 15, 2015

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-442

LUTALYSE HighCon Injection

Dinoprost Tromethamine Injection

Lactating dairy cows, beef cows, beef heifers, and replacement dairy heifers

This supplement provides for the addition of the subcutaneous route of administration.

Sponsored by:

Zoetis Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-442

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

LUTALYSE HighCon Injection

D. Established Name

Dinoprost tromethamine injection

E. Pharmacological Category

Prostaglandin

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

12.5 mg dinoprost/mL as dinoprost tromethamine

H. How Supplied

20, 100, and 250 mL vials

I. Dispensing Status

Rx

J. Dosage Regimen

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 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 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.

For unobserved (silent) 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 estrus.

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.

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.

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 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 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.

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.

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).
- 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.

K. Route of Administration

Intramuscular or subcutaneous injection

L. Species/Class

Lactating dairy cows, beef cows, beef heifers, and replacement dairy heifers

M. Indications

- 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

N. Effect of Supplement

This supplement provides for addition of the subcutaneous route of administration.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-442 dated August 17, 2015, contains dosage characterization information for species, dosage, or other applicable information.

B. Substantial Evidence

The requirement for substantial evidence of effectiveness was fulfilled by a pharmacokinetic study (Study A431N-US-13-179) comparing the relative bioavailability of the subcutaneous (SC) administration of 25 mg of LUTALYSE HighCon Injection (12.5 mg/mL) to the approved intramuscular (IM) administration of 25 mg of LUTALYSE Injection (5 mg/mL; NADA 108-901). The effectiveness data for LUTALYSE Injection at doses of 25 and 35 mg IM were used to support an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals (CI) of 80 - 164% for maximum plasma concentration (C_{max}) and area under the plasma curve concentration vs. time curve from time of injection to the limit of quantification of the assay (AUC_{last}) to demonstrate therapeutic equivalence. For effectiveness, both an upper and lower bound for comparability was established. The lower bound defined a

minimal effective concentration. The upper bound was established to avoid potential negative feedback loops that could impact effectiveness.

1. Type of Study: Pharmacokinetic Study

   a. Title: Pharmacokinetic Comparisons between Lutalyse Sterile Solution Dosed Intramuscularly and Lutalyse Sterile Solution Dosed Subcutaneously or Lutalyse HC Dosed Subcutaneously in Dairy Heifers. Study No. A431N-US-13-179.

   b. Study Location: Kalamazoo, MI

   c. Study Design:

      (1) Objective: To assess the relative bioavailability of the subcutaneous administration of 25 mg of LUTALYSE HighCon Injection (12.5 mg dinoprost as dinoprost tromethamine/mL) to the currently-approved intramuscular administration of 25 mg of LUTALYSE Injection (NADA 108-901, 5 mg dinoprost as dinoprost tromethamine/mL).

      (2) Experimental Design: Holstein heifers (n=24) were subjected to an estrous synchronization program using a progesterone intravaginal insert (EAZI-BREED CIDR) for seven days, and injected with 25 mg dinoprost (LUTALYSE Injection) and randomly assigned to treatment sequence according to the table below. LUTALYSE Injection intramuscular = T01, LUTALYSE Injection subcutaneous = T02, and LUTALYSE HighCon Injection subcutaneous = T03.

      Table 1. Treatment sequence assignment

Sequence	**Period 1**	**Period 2**	**Period 3**	**N**
A	T01	T02	T03	4
B	T02	T03	T01	4
C	T03	T01	T02	4
D	T01	T03	T02	4
E	T02	T01	T03	4
F	T03	T02	T01	4

      (3) Treatment Groups: The study consisted of three treatment groups: LUTALYSE Injection intramuscular, LUTALYSE Injection subcutaneous, and LUTALYSE HighCon Injection subcutaneous.

      (4) Drug Administration: Injections were administered on alternating sides of the lateral neck and observed for injection site reactions. The reference article was 5 mL LUTALYSE Injection (5 mg dinoprost/mL) administered IM and the two test articles administered SC were 5 mL LUTALYSE Injection (5 mg dinoprost/mL) and 2 mL LUTALYSE HighCon Injection (12.5 mg dinoprost/mL). Each animal received each treatment once. There was a 48 hour washout between treatments.

      (5) Study Animals, Housing, and Management: Twenty-four healthy, estrous cycling, non-lactating Holstein heifers with a minimum weight of 250 kg at time of dosing were housed under typical dairy conditions

according to the Guide for Care and Use of Agricultural Animals, third edition, 2010, Federation of Animal Science Societies, Savoy, IL. Heifers were fed a total mixed ration to meet or exceed requirements for dairy heifers according to the Nutrient Requirements for Dairy Cattle, seventh edition, 2001, National Research Council, Washington, D.C. Feed and water were available for *ad libitum* consumption.

(6) Measurements and Observations: General health observations were conducted at least once daily by masked technicians trained in bovine management. Injection sites were observed by masked technicians at approximately 3, 12, and 24 hours after dose administration. 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. Plasma was separated and stored at -10ºC until analyzed for prostaglandin F metabolite (PGFm), the primary metabolite of prostaglandin $F_{2\alpha}$ (PGF2α), using a validated ultra-performance liquid chromatography – mass spectrometry/mass spectrometry (UPLC-MS/MS) method. PGFm was selected as the analyte of interest due to its longer half-life and less blood level fluctuation than the parent PGF2α, making it a better representation, after correction for baseline, of exogenous administration. PGFm plasma concentration was corrected for baseline levels prior to estimation of C_{max}, and AUC_{last} for each animal within each period.

(7) Pharmacokinetic and Statistical Methods: Non-compartmental pharmacokinetic parameters were determined for each individual animal using Phoenix 64 WinNonlin version 6.3 (Pharsight Corp.). AUC_{last} was estimated using the linear trapezoidal method. The C_{max} was the highest observed plasma concentration for each cow.

Plasma concentrations and PK variables were analyzed using a general linear mixed model in SAS. C_{max} and AUC_{last} were logarithmically transformed prior to statistical analysis. The PK variables used to evaluate relative bioavailability were C_{max} and AUC_{last}. The criteria to demonstrate equivalence were an adjusted Test/Reference (T/R) ratio of 1.4 and 90% Confidence Intervals of 80 - 164% for C_{max} and AUC_{last}.

d. Results

Acceptable confidence limits were established using data contained in the original approval for LUTALYSE Injection as well as published literature to establish a safe and effective upper dose of 35 mg, yielding a test to reference ratio of 35/25, or 1.4.

The results of the relative bioavailability study are summarized in Table 2. The C_{max} and AUC_{last} of LUTALYSE HighCon Injection were within the adjusted T/R ratio and 90% Confidence Intervals to demonstrate equivalence.

Table 2. Relative bioavailability results for LUTALYSE HighCon Injection

Product	Route	Variable	LS Mean	Ratio (T/R)	Lower 90% CI	Upper 90% CI
LUTALYSE Injection	IM	C_{max} (ng/mL)	41.26			
LUTALYSE Injection	SC	C_{max} (ng/mL)	50.80	1.23	110.99	136.60
LUTALYSE HighCon Injection	SC	C_{max} (ng/mL)	55.12	1.34	120.42	148.20
LUTALYSE Injection	IM	AUC_{last} (hr*ng/mL)	66.85			
LUTALYSE Injection	SC	AUC_{last} (hr*ng/mL)	67.25	1.00	96.26	105.12
LUTALYSE HighCon Injection	SC	AUC_{last} (hr*ng/mL)	65.81	0.98	94.20	102.87

e. Adverse Events: The only adverse reaction was minor swelling of the injection sites in nine animals in the 12.5 mg/mL subcutaneous dose.

f. Conclusion: Based on the relative bioavailability criteria supported by effectiveness data at doses of 25 and 35 mg, 25 mg of LUTALYSE HighCon Injection administered SC is clinically equivalent to 25 mg LUTALYSE Injection (NADA 108-901) administered IM.

III. TARGET ANIMAL SAFETY

A. Injection Site Safety

1. Title: Injection site tolerance of dinoprost tromethamine administered subcutaneously to dairy cows. Study number: A335N-US-13-223, December 2013 to January 2014

2. Study Location: Kalamazoo, MI

3. Study Design:

   a. Objective: To demonstrate the injection site tolerance of dinoprost tromethamine when injected subcutaneously to dairy cows at a dose of 25 mg dinoprost/animal twice at an interval of 10 days.

   b. Study Animals: Sixteen non-pregnant, non-lactating, Holstein cows were used in this study. Cows ranged in weight from 579 kg to 840 kg. All had body condition scores of 2 to 4 on a scale of 1 to 5. Animals were group housed and identified by individually numbered ear tags.

   c. Treatment Groups: Eight animals received 25 mg of dinoprost as dinoprost tromethamine and eight animals received sterile saline at the same volume (2 mL) and same regimen as the treated animals.

d. Drug Administration: Dinoprost tromethamine as LUTALYSE HighCon (12.5 dinoprost/mL) at a dose of 25 mg (2 mL volume) was administered subcutaneously in the left neck of eight animals on Day 0 and in the right neck of the same eight animals on Day 10. Control animals received saline in the same volume, at the same time points, and in the same anatomical locations.

e. Measurements and Observations: General observations were performed on animals once daily from Day -14 to the end of the in-life phase (Day 11). Clinical observations consisting of physical examinations performed by the study veterinarian were conducted on Day -14, Day -1, Day 0, Day 1, Day 2, Day 10, and Day 11. Injection sites were evaluated on all animals once each on Day -14 and Day -1 and once daily from Day 0 to Day 11. Injection sites were evaluated for the presence of erythema, heat, sensitivity, firmness, necrosis, scaling, erosion, and drainage by visual observation and palpation. Swelling was measured with a ruler. The shortest and longest superficial dimensions and the elevation of the swelling were measured in centimeters. If no swelling was present, the dimensions were recorded as 0. Swelling volume was calculated for each animal at each injection site and time point that observations were collected, using the formula for the volume of half a sphere.

   All animals were euthanized on Day 11 for gross pathologic evaluation of the injection sites. On necropsy, the injection sites on all animals were evaluated for gross pathology: external skin surface, subcutaneous tissue, surface of the neck musculature, and deep interior of the neck musculature. Representative samples of all injection sites were taken for histopathology.

4. Results:

   There were no abnormal general health observations or clinical observations related to test article administration.
   No erythema, heat, sensitivity, necrosis, drainage, scaling, or erosion were noted at either injection site in any animal during the study. Hardness was observed in two dinoprost-treated animals on the right side of the neck on Day 11. In one animal, this hardness was small and unmeasurable. In the second animal, swelling was noted and its volume measured 3.53 cm^3.
   Altered tissue was observed during gross pathologic examination, corresponding to both injections on Day 0 and Day 10 in all eight animals receiving the test article. Areas of altered tissue were characterized by discoloration (dark red, tan, gray, yellow or mottled). Microscopic findings are summarized in Table 3 below.

Table 3: Microscopic findings at injection sites one and eleven days post injection

	Dinoprost group (n=8)	**Dinoprost group (n=8)**	**Saline group (n=8)**	**Saline group (n=8)**
Microscopic finding	**One day post injection**	**11 days post injection**	**One day post injection**	**11 days post injection**
Edema	4/8, mild to moderate	3/8, minimal	0/8	0/8
Fibrin	8/8, mild to moderate	8/8, mild to moderate	2/8, minimal to mild	0/8
Hematoidin deposition	0/8	3/8, minimal to mild	0/8	0/8
Hemorrhage	8/8, mild to marked	8/8, minimal to moderate	4/8, minimal to moderate	1/8, mild
Inflammation	8/8, minimal to moderate neutrophilic infiltrate	6/8, minimal to mild mixed cell infiltrate	2/8, minimal to mild neutrophilic infiltrate	1/8, minimal mixed cell infiltrate
Skeletal muscle degeneration	2/8, minimal	0/8	0/8	0/8
Necrosis	0/8	2/8, minimal	0/8	0/8

No altered tissue was noted in the deep muscle layer in any animal. There was no evidence of clostridial infection at any injection site.

5. Conclusions: Gross necropsy and histopathologic findings in all treated animals are considered acceptable for this subcutaneous injection because histopathologic findings reduced in number and severity over time, and clinical signs of swelling were seen to a minimal degree in only one animal. This study demonstrated that dinoprost tromethamine administered subcutaneously at a dose of 25 mg dinoprost/animal at a concentration of 12.5 mg/mL was well tolerated when given twice at an interval of ten days.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

LUTALYSE HighCon Injection (12.5 mg dinoprost/mL for subcutaneous injection) is not known to have antimicrobial properties; additionally LUTALYSE HighCon has not been shown to impact antimicrobial resistance among bacterial populations. The Agency does not think that this use of LUTALYSE HighCon as a standalone treatment, with FACTREL (gonadorelin) or with EAZI-BREED CIDR (progesterone) in beef and dairy cattle will impact antimicrobial resistance among bacteria of public health concern in or on treated animals; therefore, no microbial food safety (antimicrobial resistance) information or data were required at this time.

B. Impact of Residues on Human Intestinal Flora

Residues and metabolites of LUTALYSE HighCon Injection (12.5 mg dinoprost/mL for subcutaneous injection) in or on the edible tissues of treated beef and dairy cattle are not thought, and have not been reported to impact the intestinal flora of human consumers. An assessment of microbial food safety (impact on human intestinal flora) associated with this use of LUTALYSE HighCon as a standalone treatment, with FACTREL (gonadorelin) or with EAZI-BREED CIDR (progesterone) in beef and dairy cattle was not required for this approval.

C. Toxicology

Toxicological acceptable daily intakes (ADI) and safe concentrations for total residues of dinoprost tromethamine, gonadorelin hydrochloride or progesterone were not needed for this approval. The FOI Summaries for the supplemental approvals of NADA 108-901 for dinoprost tromethamine (LUTALYSE Injection), dated November 2, 1979, February 20, 1981, and February 11, 1983; the original and supplemental approvals of NADA 139-237 for gonadorelin hydrochloride (FACTREL Injection), dated November 11, 1989, and June 28, 2013; and the original approval of NADA 141-200 for progesterone (EAZI-BREED CIDR Cattle Insert), dated May 2, 2002, contain summaries of all toxicological and/or safety information for their individual uses.

D. Residue Chemistry

1. Summary of Residue Chemistry Information

   CVM did not require residue chemistry studies for this approval. The sponsor conducted a pharmacokinetic study in dairy heifers (Study Number A431N-US-13-179, summarized in Section II.B.1. above), and submitted white papers to provide justifications for addressing the residue chemistry component based on the pharmacokinetic study and the existing approval for the use of LUTALYSE Injection for intramuscular administration (NADA 108-901). CVM's assessment on the safety of potential human exposure to the drug residues resulting from the use of LUTALYSE HighCon Injection for subcutaneous administration in cattle is summarized below:

a. Background

LUTALYSE Injection (NADA 108-901) is approved for intramuscular administration in cattle at a dose of 25 mg dinoprost *per* injection for use as a standalone treatment, with FACTREL Injection (NADA 139-237), or with EAZI-BREED CIDR Cattle Insert (NADA 141-200). LUTALYSE HighCon Injection contains a higher concentration of the same active ingredient (dinoprost tromethamine) as LUTALYSE Injection, and the same inactive ingredients in the same concentrations as LUTALYSE Injection. LUTALYSE HighCon Injection and LUTALYSE Injection also are the same dosage form. The use of LUTALYSE HighCon Injection *via* subcutaneous administration in cattle will deliver the same amount of dinoprost (25 mg dinoprost) *per* injection as the approved use of LUTALYSE Injection *via* intramuscular administration. Like LUTALYSE Injection, LUTALYSE HighCon Injection is for use in cattle as a standalone treatment, with FACTREL Injection, or with EAZI-BREED CIDR Cattle Insert, and is for the same indications as LUTALYSE Injection.

b. Pharmacokinetic Study

Based on the pharmacokinetic study in dairy heifers (Study Number A431N-US-13-179), CVM calculated the pharmacokinetic parameters for plasma PGFm following the subcutaneous administration of LUTALYSE HighCon Injection, and the pharmacokinetic parameters following the intramuscular administration of LUTALYSE Injection (Table 4). PGFm is a metabolite of PGF2α and a marker for PGF2α in plasma.

Table 4. Means and standard deviations of pharmacokinetic parameters for plasma PGFm in dairy heifers (n=24) following intramuscular administration of LUTALYSE Injection or subcutaneous administration of LUTALYSE HighCon Injection

PGFm	LUTALYSE Injection (Intramuscular)	LUTALYSE HighCon Injection (Subcutaneous)
C_{max} (ng/mL)	43.15±12.66	56.71±13.76
T_{max} (hr)	0.31±0.10	0.28±0.06
AUC_{last} (hr*ng/mL)	67.42±8.95	66.47±9.62
$AUC_{4.5}$ (hr*ng/mL)	57.72±8.08	58.89±8.76
C_{12} (ng/mL)	0.37±0.31	0.39±0.27

CVM concluded that there was a significant difference ($p< 0.05$) between the C_{max} (the highest observed plasma concentration) following the intramuscular administration of LUTALYSE Injection and the C_{max} following the subcutaneous administration of LUTALYSE HighCon Injection. However, there were no significant differences ($p< 0.05$) between the values for T_{max} (time to the highest observed plasma concentration), AUC_{last} (area under the plasma concentration-time curve to the last quantifiable time point), and C_{12} (plasma concentration at 12 hours after treatment) from the two treatments. The $AUC_{4.5}$ (area under the plasma concentration-time curve to 4.5 hrs. time point) following the intramuscular administration of LUTALYSE Injection also appears to be similar to the $AUC_{4.5}$ following the subcutaneous administration of

LUTALYSE HighCon Injection, although a statistical analysis for differences in the $AUC_{4.5}$ values was not conducted.

c. PGF2α (dinoprost) Residues at the Injection Site

CVM assessed the safety of PGF2α residues at the injection site following subcutaneous administration of LUTALYSE HighCon Injection by comparing the pharmacokinetic profile in dairy heifers following the subcutaneous administration of LUTALYSE HighCon Injection with the pharmacokinetic profile following the intramuscular administration of LUTALYSE Injection. Because the individual administrations delivered a same amount of PGF2α at the injection site, and had similar T_{max}, $AUC_{4.5}$ and AUC_{last} values, the slightly higher C_{max} observed in the study following the subcutaneous administration of LUTALYSE HighCon Injection indicates that PGF2α absorption following the subcutaneous administration is not likely to be slower than that following the intramuscular administration of LUTALYSE Injection. As such, the PGF2α residues remaining at the injection site at zero withdrawal following subcutaneous administration of LUTALYSE HighCon Injection are not likely to be more than those following intramuscular administration of LUTALYSE Injection.

d. PGF2α Residues in the Edible Tissues and Milk

CVM assessed the safety of PGF2α residues in the four edible tissues and milk following subcutaneous administration of LUTALYSE HighCon Injection by comparing the pharmacokinetic profile in dairy heifers following the subcutaneous administration of LUTALYSE HighCon Injection with the pharmacokinetic profile following the intramuscular administration of LUTALYSE Injection. CVM found that the slightly higher C_{max} following the subcutaneous administration of LUTALYSE HighCon Injection is not likely an indicator of higher PGF2α residues in the edible tissues or milk at zero withdrawal or zero milk discard, because the nominal zero withdrawal and zero milk discard are 8 to 12 hours after the last dose administration, which would encompass many elimination half-lives for PGF2α in the plasma. In addition, the finding that the subcutaneous and intramuscular administrations resulted in similar $AUC_{4.5}$ and AUC_{last} values indicates that the amounts of total PGF2α residues for distribution to the edible tissues and milk following the individual administrations are essentially equivalent. As such, the PGF2α residues in the edible tissues and milk following the subcutaneous and intramuscular administrations would be similar.

e. Safety of Potential Human Exposure to Drug Residues Resulting from the Use of LUTALYSE HighCon Injection for Subcutaneous Administration in Cattle as a Standalone Treatment, with FACTREL Injection, or with EAZI-BREED CIDR Cattle Insert

Based on the above assessment for PGF2α residues at the injection site, and in the four edible tissues and milk, CVM found that the potential human exposure to PGF2α residues resulting from the use of LUTALYSE HighCon Injection for subcutaneous administration in cattle as a standalone treatment is not likely to cause safety concerns beyond those that have been addressed for the approved use of LUTALYSE Injection for intramuscular administration in cattle as a standalone treatment. Likewise, CVM found that the potential human exposure to PGF2α residues resulting

from the use of LUTALYSE HighCon Injection for subcutaneous administration in cattle with FACTREL Injection, or with EAZI-BREED CIDR Cattle Insert is not likely to cause safety concerns beyond those that have been addressed for the approved use of LUTALYSE Injection for intramuscular administration in cattle with FACTREL Injection, or with EAZI-BREED CIDR Cattle Insert. Therefore, like the approved use of LUTALYSE Injection for intramuscular administration in cattle (NADA 108-901), the use of LUTALYSE HighCon Injection for subcutaneous administration in cattle as a standalone treatment, with FACTREL Injection, or with EAZI-BREED CIDR Cattle Insert qualifies for a zero-day withdrawal period and zero milk discard time.

2. Target Tissue and Marker Residue

   Neither a target tissue nor a marker residue assignment is needed for dinoprost residues in cattle.

   Neither a target tissue nor a marker residue assignment is needed for gonadorelin residues in cattle.

   Neither a target tissue nor a marker residue assignment is needed for progesterone residues in cattle.

3. Tolerances

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

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

   A tolerance for progesterone in tissues or milk is not required. Residues of progesterone are regulated on the basis of allowable incremental increases in the edible tissues (21 CFR §556.540). It is not necessary to establish an allowable incremental increase for progesterone in milk.

4. Withdrawal Period and Milk Discard Time

   A withdrawal period or milk discard time is not required (*i.e.*, zero-day withdrawal period and zero milk discard time).

E. Analytical Method for Residues:

A regulatory analytical method for dinoprost is not required.

A regulatory analytical method for gonadorelin is not required.

A regulatory analytical method for progesterone is not required.

The FOI Summaries for the supplemental approvals of NADA 108-901 for LUTALYSE Injection, dated November 2, 1979, February 20, 1981, and February 11, 1983; the original and supplemental approvals of NADA 139-237 for FACTREL Injection, dated November 11, 1989, and June 28, 2013; and the original and supplemental approvals of NADA 141-200 for EAZI-BREED CIDR Cattle Insert, dated May 2, 2002, July 29, 2003, and July 22, 2010, contain

information on methods available for the measurement of dinoprost, gonadorelin, and progesterone residues in cattle.

IV. USER SAFETY

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

*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.*

V. 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 LUTALYSE HighCon Injection, when used according to the label, is safe and effective:

- 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

Additionally, data demonstrate that residues in food products derived from species treated with LUTALYSE HighCon Injection will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian. Adequate directions for lay use cannot be written because professional expertise is required to monitor safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

This supplemental approval for LUTALYSE HighCon Injection qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act because the supplemental approval included safety and effectiveness studies. This exclusivity begins as of the date of our

approval letter and only applies to the new subcutaneous injection route of administration.

C. Supplemental Applications

This supplemental NADA required a reevaluation of the safety data in the original NADA (21 CFR 514.106(b)(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.