Date of Approval: August 17, 2015

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-442

LUTALYSE HighCon Injection

Dinoprost tromethamine injection

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

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 of 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; and 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.

Sponsored by:

Zoetis Inc.

Table of Contents

I. GENERAL INFORMATION 3
II. EFFECTIVENESS 5
A. Bioequivalence Waiver for Higher Concentration 5
III. TARGET ANIMAL SAFETY 6
A. Injection Site Safety 6
IV. HUMAN FOOD SAFETY 8
A. Antimicrobial Resistance 8
B. Impact of Residues on Human Intestinal Flora 8
C. Toxicology 9
D. Residue Chemistry 9
E. Analytical Method for Residues 10
V. USER SAFETY 10
VI. AGENCY CONCLUSIONS 10
A. Marketing Status 11
B. Exclusivity 11
C. Patent Information: 11

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 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) 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.

For treatment of pyometra (chronic endometritis) in cattle: Inject a dose of 2 mL LUTALYSE HighCon Injection (25 mg dinoprost) intramuscularly.

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 25 mg dinoprost (2 mL) intramuscularly. 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 LUTALYSE HighCon Injection (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 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 2 mL LUTALYSE HighCon 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).
- Inject 2 mL LUTALYSE HighCon Injection (equivalent to 25 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.

K. Route of Administration

Intramuscular injection

L. Species/Class

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

M. Indication

- 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

II. EFFECTIVENESS

A. Bioequivalence Waiver for Higher Concentration

Based on the formulation characteristics, in conjunction with the reported lack of serious adverse effect at the injection site when the higher drug concentration is administered, Zoetis Inc. was granted a waiver from the requirement to demonstrate *in vivo* bioequivalence for the intramuscular use of LUTALYSE HighCon (dinoprost tromethamine injection) Injection with the approved intramuscular use of LUTALYSE Injection (NADA 108-901). The product is administered as an injectable solution and contains a higher concentration (12.5 mg/mL) of the same active ingredient as LUTALYSE Injection (NADA 108-901), is the same dosage form, and contains the same inactive ingredients in the same concentrations as LUTALYSE Injection.

The originally approved formula for LUTALYSE Injection contains 5 mg/mL dinoprost as dinoprost tromethamine. The labeled dose for LUTALYSE Injection is 5 mL per cow, to deliver 25 mg dinoprost as dinoprost tromethamine for the following indications for cattle:

- 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

The LUTALYSE HighCon Injection formulation contains 12.5 mg/mL dinoprost as dinoprost tromethamine, and would be administered at a dose of 2 mL per cow. Note that "FACTREL (gonadorelin injection) Injection" contains the active ingredient gonadorelin hydrochloride and is approved under 21 CFR 522.1077.

III. TARGET ANIMAL SAFETY

A. Injection Site Safety

1. Title: "Injection site tolerance of dinoprost tromethamine administered intramuscularly in dairy cows." [Study Number: 1433N-60-10-849] December 2010 to January 2011

2. Study Location: Kalamazoo, MI

3. Study Design:

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

   b. Study Animals: Eight open, non-lactating, Holstein cows were used in this study. Cows ranged in weight from 554 kg to 820 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: All eight animals received the same treatment. There was no control group.

   d. Test Article Administration: Dinoprost tromethamine (12.5 mg dinoprost/mL) at a dose of 25 mg (2 mL volume) was administered intramuscularly in the left neck of all animals on Day 0 and in the right neck of all animals on Day 10.

   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, and once daily from Day 0 until 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 (redness), 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 then 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, calculating the volume as half a sphere. Swelling volume was summarized with summary statistics (mean, standard deviation, minimum and maximum) by injection site and time point.

All animals were euthanized on Day 11 for gross pathology evaluation of the injection sites. On necropsy, the following gross pathology was examined at the injection site on all animals: external skin surface, subcutaneous tissue, surface of the neck musculature, and deep interior of the neck musculature. If gross pathology was noted on necropsy, samples 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 was noted at either injection site in any animal during the study. Firmness was observed on four animals on the left neck four days after injection. By Day 9, no firmness was observed on the left neck. On the right neck, firmness was observed on three animals one day after injection.

Swelling was noted on five animals on the left neck starting one day after injection. Swelling volume was minimal. Six animals had swelling on the left neck. The maximal swelling volume in any animal on the left neck was 0.008 cm^3. All swelling on the left neck resolved by Day 9. Three animals had swelling on the right neck one day after the Day 10 injection. The maximum swelling volume observed in any animal on the right neck was 0.009 cm^3.

Some altered tissue was observed during gross pathology corresponding to both injections on Day 0 and Day 10. Areas of altered tissue were characterized by discoloration (dark red, tan, or tan and white mottled) and correlated microscopically with minimal to mild hemorrhage at most sites. Six out of eight animals had discoloration noted on necropsy on the left neck. Five of these animals had discoloration noted in the deep muscle layer. Six out of eight animals also had discoloration noted on necropsy on the right neck and three of these six had discoloration extending to the deep muscle layer.

Mild to moderate hemorrhage was observed at six of the six sites examined microscopically for the left neck (ten days post injection) and the right neck (one day post injection). One animal at one day post injection had moderate skeletal muscle degeneration associated with moderate hemorrhage in the deep muscle. Two other animals had small foci of skeletal muscle

degeneration in the external muscle layer ten days post injection. One animal had chronic-active inflammation ten days post injection.

5. Conclusions:

Mild swelling and mild to moderate hemorrhage were the most common findings observed at the injection sites, both grossly and microscopically. Resultant maximal swelling volume was considered small relative to the target animal and, therefore, acceptable for this intramuscular injection. This study demonstrated that dinoprost tromethamine administered intramuscularly at a dose of 25 mg dinoprost/animal at a concentration of12.5 mg/mL was well tolerated when given twice at an interval of ten days.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

The use of injectable LUTALYSE HighCon Injection (12.5 mg dinoprost per mL as dinoprost tromethamine 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 of beef cows, beef heifers and replacement dairy heifers, and for use with 1) FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows, 2) EAZI-BREED CIDR (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in lactating dairy cows, and 3) 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 is not thought, nor has it 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 the standalone use and the concurrent use of LUTALYSE HighCon Injection (12.5 mg dinoprost per mL as dinoprost tromethamine injection) with either 1) injectable FACTREL Injection (gonadorelin injection) in lactating dairy cows, or 2) intravaginal EAZI-BREED CIDR Cattle Insert (progesterone intravaginal insert) in or on the edible tissues and milk of treated beef or dairy cattle was not necessary at this time.

B. Impact of Residues on Human Intestinal Flora

Residues and metabolites of injectable LUTALYSE HighCon Injection (12.5 mg dinoprost per mL as dinoprost tromethamine injection), injectable FACTREL Injection (gonadorelin injection), and intravaginal EAZI-BREED CIDR Cattle Insert (progesterone intravaginal insert) in or on the edible tissues and milk of treated beef or dairy cattle are not thought, nor have they been reported, to impact the intestinal flora of human consumers. The Agency determined that an assessment of the impact of residues or metabolites of injectable LUTALYSE HighCon Injection (12.5 mg dinoprost per mL as dinoprost tromethamine injection), injectable FACTREL Injection (gonadorelin injection), and intravaginal EAZI-BREED CIDR Cattle Insert (progesterone intravaginal insert) in or on the edible tissues and milk of treated beef

or dairy cattle on human intestinal flora, and establishment of a microbiological acceptable daily intake were not necessary at this time.

C. Toxicology

A toxicological acceptable daily intake (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 Studies

No residue chemistry studies were required for this approval. The sponsor was granted a waiver from the requirement to demonstrate *in vivo* bioequivalence for the intramuscular use of LUTALYSE HighCon (12.5 mg dinoprost/mL) Injection with the approved intramuscular use of LUTALYSE (5 mg dinoprost/mL) Injection for cattle (NADA 108-901). The residue chemistry requirements for LUTALYSE HighCon Injection were satisfied by relying on the residue chemistry data in support of the approval of LUTALYSE Injection for cattle, including the concurrent use of LUTALYSE Injection with FACTREL (gonadorelin injection) Injection (NADA 139-237), and with EAZI-BREED CIDR (progesterone intravaginal insert) Cattle Insert (NADA 141-200).

The FOI Summaries for the supplemental approvals of NADA 108-901 for LUTALYSE Injection, dated November 2, 1979, February 20, 1981, February 11, 1983, and June 9, 2014, 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 summaries of residue chemistry studies for cattle.

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. Progesterone is regulated on the basis of allowable incremental increases for the 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

No withdrawal period or milk discard time is required (*i.e.*, zero - day withdrawal period and zero milk discard time).

E. Analytical Method for Residues

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.

V. 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.*

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

- 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 approval for LUTALYSE HighCon Injection qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(ii).

C. Patent Information:

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