Date of Approval: June 9, 2014

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 108-901

LUTALYSE Injection

Dinoprost injection

Lactating dairy cows, beef cows, and replacement beef and 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.

Sponsored by:

Zoetis, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 108-901

B. Sponsor

Zoetis, Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

LUTALYSE Injection

D. Established Name

Dinoprost injection

E. Pharmacological Category

Prostaglandin

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

5 mg dinoprost per mL as dinoprost tromethamine

H. How Supplied

30 and 100 mL vials

I. Dispensing Status

Rx

J. Dosage Regimen

For use with FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows:

- 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.

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.

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.

K. Route of Administration

Intramuscular injection

L. Species/Class

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

M. Indications

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 following indications: 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. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 108-901 dated November 2, 1979, contains dosage characterization information for use in beef cows, replacement beef and dairy heifers and lactating dairy cows.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summary for the original approval for LUTALYSE Injection (NADA 108-901 dated November 2, 1979), FACTREL Injection (NADA 139-237, dated June 28, 2013, and for EAZI-BREED CIDR Cattle Insert NADA 141-200, dated May 2, 2002, and supplemental approval dated July 22, 2010) contain summaries of effectiveness studies for the following indications: 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; for use with FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination (FTAI) in lactating dairy cows.

III. TARGET ANIMAL SAFETY:

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval for LUTALYSE Injection (NADA 108-901 dated November 7, 1979), FACTREL Injection (NADA 139-237, dated November 11, 1989), and for EAZI-BREED CIDR Cattle Insert (NADA 141-200, dated May 2, 2002, and supplemental approval dated July 22, 2010) contain summaries of target animal safety studies for lactating dairy cows, beef cows, and beef and dairy replacement heifers.

IV. HUMAN FOOD SAFETY:

A. Antimicrobial Resistance:

Decision Statement:

The concurrent use of injectable LUTALYSE (dinoprost injection) Injection with either 1) FACTREL (gonadorelin injection) Injection to synchronize estrous cycles to allow fixed-time artificial insemination in lactating dairy cows, or 2) EAZI-BREED CIDR (progesterone intravaginal insert) Cattle Insert for synchronization of estrus in suckled beef cows and replacement beef and dairy heifers, for advancement of first postpartum estrus in suckled beef cows, for advancement of first pubertal estrus in replacement beef heifers, and for estrus synchronization in lactating dairy cows 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 concurrent use of injectable LUTALYSE (dinoprost injection) Injection with either 1) FACTREL (gonadorelin injection) Injection in lactating dairy cattle, or 2) EAZI-BREED CIDR (progesterone intravaginal insert) Cattle 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:

Decision Statement:

Residues and metabolites of injectable LUTALYSE (dinoprost injection) Injection, FACTREL (gonadorelin injection) Injection, and EAZI-BREED CIDR (progesterone intravaginal insert) Cattle Insert in or on the edible tissues and milk of treated beef or 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 injectable LUTALYSE (dinoprost injection) Injection, FACTREL (gonadorelin injection) Injection, and EAZI-BREED CIDR (progesterone intravaginal insert) Cattle 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 was not necessary at this time.

C. Toxicology:

A toxicological acceptable daily intake (ADI), final ADI and safe concentrations for total residues of LUTALYSE Injection, FACTREL Injection or EAZI-BREED CIDR Cattle Insert were not needed for these approvals. The FOI Summaries for the original and supplemental approvals of NADA 108-901 for LUTALYSE Injection; NADA 139-237 for FACTREL Injection; and NADA 141-200 for EAZI-BREED CIDR Cattle Insert contain summaries of all toxicological and/or safety information for their individual use.

D. Residue Chemistry:

CVM did not require residue chemistry studies for this supplemental approval. 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 FOI Summary for the supplemental approval of NADA 139-237 for FACTREL Injection, dated June 28, 2013, and the FOI Summaries for the original approval of NADA 141-200 for EAZI-BREED CIDR Cattle Insert, dated May 2, 2002, and the supplemental approval of NADA 141-200, dated July 22, 2010, contain summaries of residue chemistry studies for cattle.

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 FOI Summary for the supplemental approval of NADA 139-237 for FACTREL Injection, dated June 28, 2013, and the FOI Summaries for the original approval of NADA 141-200 for EAZI-BREED CIDR Cattle Insert, dated May 2,

2002, and the supplemental approval of NADA 141-200, dated July 22, 2010, contain information on methods available for measurement of dinoprost tromethamine, gonadorelin hydrochloride, and progesterone in cattle tissues and/or milk.

V. USER SAFETY:

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to LUTALYSE 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 use 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. To report suspected adverse events, for technical assistance or to obtain a copy of the Material Safety Data Sheet (MSDS) contact Zoetis Inc. at 1-888-963-8471.

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 Injection, when used according to the label, is safe and effective for the following indications: 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 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 (Rx marketing status). Adequate directions for lay use cannot be written because veterinary experience is required to safely administer the product, and because the use of this product for the synchronization of estrous cycles requires the use of FACTREL Injection, which also has Rx marketing status.

B. Exclusivity:

This supplemental approval for LUTALYSE 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 indications 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, for which this supplement applies.

C. Supplemental Applications:

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

D. Patent Information:

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