

Date of Approval: December 30, 2009

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-479

HEIFERMAX 500 plus ZILMAX and RUMENSIN
(melengestrol acetate plus zilpaterol hydrochloride and monensin USP)

Type A Medicated Articles
For Use in the Manufacture of Type B and C Medicated Feeds

Heifers fed in Confinement for Slaughter

For increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, and suppression of estrus (heat) in heifers fed in confinement for slaughter for the last 20 to 40 days on feed

Sponsored by:

Ivy Laboratories,
Div. of Ivy Animal Health, Inc.

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

- a. File Number: ANADA 200-479
- b. Sponsor: Ivy Laboratories,
Div. of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214
- Drug Labeler Code: 021641
- c. Established Name: Melengestrol acetate plus zilpaterol
hydrochloride and monensin USP
- d. Proprietary Name: HEIFERMAX 500 plus ZILMAX and
RUMENSIN
- e. Dosage Form: Type A medicated articles for use in the
manufacture of three-way combination Type B
and C medicated feeds
- f. How Supplied: HEIFERMAX 500 (melengestrol acetate) – 40 lb
container (liquid premix)
- ZILMAX (zilpaterol hydrochloride) – 22.05 lb
(10 kg) bag
- RUMENSIN (monensin USP) – 50 lb bag
- g. How Dispensed: OTC
- h. Amount of Active Ingredient: Melengestrol acetate – 500 mg (liquid) per
pound of premix
- Zilpaterol hydrochloride – 21.77 grams per
pound of premix (48 grams per kilogram)
- Monensin USP – 80 grams per lb
- i. Route of Administration: Oral in feed
- j. Species/Class: Heifers fed in confinement for slaughter
- k. Recommended Dosage: Melengestrol acetate is top dressed or mixed

with a complete ration containing monensin (10-40 g/ton) and zilpaterol (6.8 g/ton) at 0.5 to 2.0 pounds per head per day of medicated feed containing 0.125 to 1.0 mg melengestrol acetate per pound to provide 0.25 to 0.5 mg melengestrol acetate/head/day. Feed melengestrol acetate in this combination for the final 20-40 days.

Zilpaterol is fed at a concentration of 6.8 g of zilpaterol hydrochloride per ton of complete feed to provide 60 to 90 mg zilpaterol/head/day in cattle fed in confinement for slaughter.

Monensin is fed at concentrations of 10 to 40 g of monensin USP per ton of complete feed at a rate of 0.14 to 0.42 mg monensin/lb of body weight, depending on severity of coccidiosis challenge, up to 480 mg/head/day.

l. Pharmacological Category:

Melengestrol acetate – steroid hormone

Zilpaterol hydrochloride – beta adrenergic agonist

Monensin USP – ionophore/anticoccidial

m. Indications:

For increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, and suppression of estrus (heat) in heifers fed in confinement for slaughter for the last 20 to 40 days on feed.

n. Generic Products:

HEIFERMAX 500; melengestrol acetate; ANADA 200-343; Ivy Laboratories, Div. of Ivy Animal Health, Inc.

HEIFERMAX 500 plus ZILMAX and RUMENSIN; melengestrol acetate plus zilpaterol hydrochloride and monensin USP; ANADA 200-479; Ivy Laboratories, Div. of Ivy Animal Health, Inc.

o. Pioneer Products:

MGA 500; melengestrol acetate; NADA 039-402;

Pharmacia & Upjohn Co., a Division of Pfizer, Inc.

ZILMAX; zilpaterol hydrochloride; NADA 141-258; Intervet, Inc.

RUMENSIN; monensin USP; NADA 095-735; Elanco Animal Health, A Division of Eli Lilly & Co.

ZILMAX plus RUMENSIN plus MGA 500; zilpaterol hydrochloride, monensin USP, and melengestrol acetate; NADA 141-282; Intervet Inc.

2. TARGET ANIMAL SAFETY AND DRUG EFFECTIVENESS:

Under the provisions of the Federal Food, Drug, and Cosmetic Act, as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, an Abbreviated New Animal Drug Application (ANADA) may be submitted for a generic version of an approved new animal drug (pioneer product). New target animal safety and effectiveness data and human food safety data (other than tissue residue data) are not required for approval of an ANADA.

Ordinarily, the ANADA sponsor shows that the generic product is bioequivalent to the pioneer, which has been shown to be safe and effective. If bioequivalence is demonstrated through a clinical endpoint study, then a tissue residue study to establish the withdrawal time for the generic product should also be conducted. For certain dosage forms, the agency will grant a waiver from the requirement of an *in vivo* bioequivalence study. (55 FR 24645, June 18, 1990; Fifth GADPTRA Policy Letter; Bioequivalence Guideline, October 9, 2002).

According to CVM's fourth policy letter issued on November 2, 1989, with regard to the implementation of GADPTRA, after the approval of an ANADA for a generic Type A medicated article, the generic sponsor is entitled to approval for all the medicated feed combinations for which the pioneer is approved. Bioequivalence and tissue residue studies are not required for the approval of the generic feed combinations (Type B or C medicated feeds). Melengestrol acetate is codified under 21 CFR 558.342. Zilpaterol hydrochloride is codified under 21 CFR 558.665. Monensin is codified under 21 CFR 558.355. The combination of melengestrol acetate, zilpaterol hydrochloride and monensin sodium is codified under 21 CFR 558.665(e)

3. HUMAN SAFETY:

Human Warnings are provided on the product label as follows:

“WARNING: The active ingredient in Zilmax® is zilpaterol hydrochloride, a beta₂-adrenergic agonist. Not for use in humans. An anti-dust process has been applied to the drug product, Zilmax®, in order to greatly reduce inhalation risk. Extended handling tasks with the potential for dust generation require respiratory protection. Wear appropriate skin protection (e.g. impervious gloves, apron, overalls) if there is a potential for extended skin contact. Wear protective eyewear, if there is a potential for eye contact. If accidental eye contact occurs, immediately rinse with water and consult a physician.”

- **Tolerances for Residues:**

The tolerances established for the reference listed feed use new animal drug product apply to the generic feed use combination new animal drug product.

A tolerance of 25 parts per billion (ppb) is established for residues of the parent compound, melengestrol acetate, in fat of cattle as codified under 21 CFR 556.380.

The tolerance for zilpaterol freebase (the marker residue) is 12 ppb in cattle liver as codified under 21 CFR 556.765.

The tolerances for monensin in cattle are 0.10 part per million (ppm) in liver, 0.05 ppm in muscle, kidney and fat, and one is not required in milk as codified under 21 CFR 556.420.

- **Withdrawal Time:**

The withdrawal period established for the pioneer product is also assigned to the generic product.

For this reason, a withdrawal period of 3 days has been established for zilpaterol hydrochloride in cattle (21 CFR 558.665).

- **Regulatory Method for Residues:**

Melengestrol acetate:

The analytical method for the determination of melengestrol acetate in tissues uses a gas chromatographic assay procedure. This method is found in *Official Methods of Analysis of AOAC International*, 16th edition.

Zilpaterol:

The determinative analytical procedure utilizes HPLC with fluorescence detection.

The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

Monensin:

The regulatory analytical method for monensin is the method developed by Eli Lilly & Co., Box 708, Greenfield, IN 46140 (Method 5801654, "Determination of Monensin in Tissues and Eggs") on file at the Center for Veterinary Medicine, Food and Drug Administration, HFV-199, 7500 Standish Place, Rockville, Maryland 20855.

4. AGENCY CONCLUSIONS:

This ANADA filed under section 512(b) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements of section 512(n) of the act and demonstrates that the generic feed combination product HEIFERMAX 500 plus ZILMAX and RUMENSIN, when used under its proposed conditions of use, is safe and effective for its labeled indications.

5. ATTACHMENTS:

The generic Blue Bird labeling for Type B and C medicated feed are attached as indicated below:

Generic Labeling for ANADA 200-479:

Blue Bird labeling for Type B medicated feeds:

Zilpaterol and Monensin Liquid Type B Medicated Cattle Feed

Zilpaterol and Monensin Type B Medicated Cattle Feed

Blue Bird labeling for Type C medicated feeds:

Zilpaterol and Monensin Type C Medicated Cattle Feed

Heifer Supplement (melengestrol acetate) Type C Medicated Feed for Beef and Dairy Heifers

Liquid Heifer Supplement (melengestrol acetate) Type C Medicated Feed for Beef and Dairy Heifers

Pioneer Labeling for NADA 141-282:

Blue Bird labeling for Type B medicated feeds:

Zilpaterol and Monensin Liquid Type B Medicated Cattle Feed

Zilpaterol and Monensin Type B Medicated Cattle Feed

Blue Bird labeling for Type C medicated feeds:

Zilpaterol and Monensin Type C Medicated Cattle Feed

Heifer Supplement (melengestrol acetate) Type C Medicated Feed for Beef and Dairy Heifers

Liquid Heifer Supplement (melengestrol acetate) Type C Medicated Feed for Beef and Dairy Heifers