Date of Approval: February 16, 2010

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-448

HEIFERMAX 500, OPTAFLEXX and RUMENSIN
(melengestrol acetate, ractopamine hydrochloride, and monensin USP)

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

Heifers fed in Confinement for Slaughter

This supplement provides for an increase in the upper dose limit of Type A medicated article RUMENSIN (monensin USP) from 30 g/ton to 40 g/ton for use in combination with OPTAFLEXX (ractopamine hydrochloride) and HEIFERMAX 500 (melengestrol acetate) for the manufacture of dry and liquid three-way combination Type C medicated feeds.

Sponsored by:

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

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number: ANADA 200-448

b. Sponsor: Ivy Laboratories,
Div. of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214

Drug Labeler Code: 021641

c. Established Names: Melengestrol acetate, ractopamine hydrochloride, and monensin USP

d. Proprietary Names: HEIFERMAX 500, OPTAFLEXX, and RUMENSIN

e. Dosage Form: Type A medicated articles for use in the manufacture of three way combination Type C medicated feeds

f. How Supplied: HEIFERMAX 500 (melengestrol acetate) – 40 lb container (liquid)

OPTAFLEXX (ractopamine hydrochloride) – 25 lb bag

RUMENSIN (monensin USP) – 50 lb bag

g. How Dispensed: OTC

h. Amount of Active Ingredients: Melengestrol acetate – 500 mg (liquid) per pound of premix

Ractopamine hydrochloride - 45.4 grams of ractopamine hydrochloride per pound of premix (100 grams per kilogram)

Monensin USP – 80 grams per pound of premix

i. Route of Administration: Oral in feed

j. Species/Class: Cattle/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 ractopamine (9.8 to 24.6 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 28-42 days.

Ractopamine is fed at a concentration of 9.8 to 24.6 grams of ractopamine hydrochloride per ton of completed feed to provide 90 to 430 mg ractopamine /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

Ractopamine hydrochloride – beta adrenergic agonist

Monensin sodium – 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 28 to 42 days on feed

n. Generic Products :	HEIFERMAX 500; melengestrol acetate; ANADA 200-343; Ivy Laboratories, Div. of Ivy Animal Health, Inc. HEIFERMAX 500, OPTAFLEXX and RUMENSIN; melengestrol acetate, ractopamine hydrochloride and monensin USP; ANADA 200-448; 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. OPTAFLEXX; ractopamine hydrochloride; NADA 141-221; Elanco Animal Health, A Division of Eli Lilly & Co. RUMENSIN; monensin USP; NADA 095-735; Elanco Animal Health, A Division of Eli Lilly & Co. OPTAFLEXX plus RUMENSIN plus MGA 500; ractopamine hydrochloride, monensin USP and melengestrol acetate; NADA 141-234; Elanco Animal Health, A Division of Eli Lilly & Co.
p Effect of supplement	This supplement provides for an increase in the upper dose limit of Type A medicated article RUMENSIN (monensin USP) from 30 g/ton to 40 g/ton for use in combination with OPTAFLEXX (ractopamine hydrochloride) and HEIFERMAX 500 (melengestrol acetate) for the manufacture of dry and liquid three-way combination Type C medicated feeds.

2. TARGET ANIMAL SAFETY AND 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 Guidance, revised 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 feed-mixed combinations for which the pioneer is approved. Bioequivalence and tissue residue studies are not required for the approval of the generic feed use combinations (Type B or C medicated feeds). Melengestrol acetate is codified under 21 CFR 558.342. Ractopamine is codified under 21 CFR 558.500. Monensin is codified under 21 CFR 558.355. The combination of melengestrol acetate, ractopamine hydrochloride and monensin is codified under 21 CFR 558.500(e)(2).

3. HUMAN SAFETY:

Human Warnings are provided on the product label as follows:

"WARNING: The active ingredient ractopamine hydrochloride is a beta-adrenergic agonist. Individuals with cardiovascular disease should exercise special caution to avoid exposure. Not for use in humans. Keep out of the reach of children. The ractopamine hydrochloride formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling ractopamine hydrochloride, use protective clothing, impervious gloves, protective eye wear, and a NIOSH-approved dust mask. Operators should wash thoroughly with soap and water after handling. If accidental eye contact occurs, immediately rinse eyes thoroughly with water. If irritation persists, seek medical attention. The material safety data sheet contains more detailed occupational safety information. To report adverse effects, access medical information, or obtain additional product information, call 1-800-428-4441.

- **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 ractopamine hydrochloride (the marker residue) is 0.09 parts per million (ppm) in cattle liver and 0.03 ppm in cattle muscle as codified under 21 CFR 556.570.

The tolerances for residues of 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 for 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, no withdrawal times are required for the use of this generic feed use combination new animal drug product.

- **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.

  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.

  Ractopamine hydrochloride

  The determination of residues of ractopamine in the liver and muscle of cattle and swine is by High Performance Liquid Chromatography (HPLC). The confirmation of residues of ractopamine in the liver and muscle of cattle and swine is by Liquid Chromatography/Electrospray Ionization Triple Tandem Quadrupole Mass Spectrometry (LC/ESI-MS-MS). The validated regulatory methods for determination and confirmation of residues of ractopamine are available from CVM, FDA, 7500 Standish Place, Rockville, MD 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, OPTAFLEXX 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 C medicated feed are attached as indicated below:

Generic Labeling for ANADA 200-448:
Blue Bird labeling for Type C medicated feeds:
Ractopamine and Monensin Plus, Type C Medicated Cattle Feed
Liquid Heifer Supplement for Beef and Dairy Heifers
Heifer Supplement for Beef and Dairy Heifers

Pioneer Labeling for NADA 141-234:
Blue Bird labeling for Type C medicated feeds:
Ractopamine and Monensin Plus, Type C Medicated Cattle Feed
Liquid Heifer Supplement for Beef and Dairy Heifers
Heifer Supplement for Beef and Dairy Heifers