Date of Approval: December 30, 2009

FREEDOM OF INFORMATION (FOI) SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-480

HEIFERMAX 500 plus ZILMAX, RUMENSIN and TYLAN
(melengestrol acetate, zilpaterol hydrochloride, monensin USP and tylosin phosphate)

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

Heifers fed in Confinement for Slaughter

For the increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium* (*Actinomyces) pyogenes*, 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 200-480
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, zilpaterol hydrochloride, monensin USP, and tylosin phosphate
d. Proprietary Name:	HEIFERMAX 500 plus ZILMAX, RUMENSIN and TYLAN
e. Dosage Form:	Type A medicated articles for use in the manufacture of four-way combination Type B and C medicated feeds
f. How Supplied:	HEIFERMAX 500 (melengestrol acetate) – 40 lb container (liquid) ZILMAX (zilpaterol hydrochloride) – 22.05 lb (10 kg) bag RUMENSIN (monensin USP) – 50 lb bag TYLAN (tylosin phosphate) – 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 Tylosin phosphate – 40 and 100 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. Tylosin is fed at concentrations of 8 to 10 g of tylosin phosphate per ton of complete feed to provide 60 to 90 mg tylosin/head/day.
l. Pharmacological Category:	Melengestrol acetate – steroid hormone Zilpaterol hydrochloride – beta adrenergic agonist Monensin USP– ionophore/anticoccidial Tylosin phosphate – antibacterial
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*, reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes*, 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, RUMENSIN and TYLAN; melengestrol acetate, zilpaterol hydrochloride, monensin USP and tylosin phosphate; ANADA 200-480; 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.
	TYLAN; tylosin phosphate; NADA 012-491; Elanco Animal Health, A Division of Eli Lilly & Co.
	ZILMAX plus RUMENSIN plus TYLAN plus MGA 500; zilpaterol hydrochloride, monensin USP, tylosin phosphate and melengestrol acetate; NADA 141-280; 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 USP is codified under 21 CFR 558.355. Tylosin is codified under 21 CFR 558.625. The combination of melengestrol acetate, zilpaterol hydrochloride, monensin USP, and tylosin phosphate 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 residues of monensin in cattle are 0.10 parts 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.

  The tolerance for tylosin is 0.2 part per million (negligible residue) in cattle liver, muscle, kidney and uncooked fat, and 0.05 ppm (negligible residue) in milk as codified under 21 CFR 556.740.

- **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.

  Tylosin:
  The analytical method for the determination of tylosin residues in tissues uses a microbiological assay procedure. This method is found in the Food Additives Analytical Manual on file at the Center for Veterinary Medicine, 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 plus ZILMAX, RUMENSIN and TYLAN 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 feeds is attached as indicated below:

Generic Labeling for ANADA 200-480:
Blue Bird labeling for Type B medicated feeds:
Zilpaterol, Monensin, and Tylosin Liquid Type B Medicated Cattle Feed
Zilpaterol, Monensin, and Tylosin Type B Medicated Cattle Feed

Blue Bird labeling for Type C medicated feeds:
Zilpaterol, Monensin, and Tylosin 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 141-280:
Blue Bird labeling for Type B medicated feeds:
Zilpaterol, Monensin, and Tylosin Liquid Type B Medicated Cattle Feed
Zilpaterol, Monensin, and Tylosin Type B Medicated Cattle Feed

Blue Bird labeling for Type C medicated feeds:
Zilpaterol, Monensin, and Tylosin 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