Date of Approval: September 1, 2011

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-375

HEIFERMAX 500 plus RUMENSIN and TYLAN
(melengestrol acetate plus monensin and tylosin phosphate)

Type A Medicated Articles to be Used in the Manufacture of Combination of Type C Medicated Feeds

Heifers Fed in Confinement for Slaughter

This supplement provides for an increase in the upper dose limit of monensin to 480 mg per head per day based upon the October 19, 2009, supplemental approval (NADA 138-870, C-0036) for RUMENSIN and an update of the name of the tylosin targeted bacteria to *Arcanobacterium pyogenes* based on the November 7, 2006, approval (NADA 012-491,C-0318) for TYLAN.

Sponsored by:

Ivy Laboratories
Division of Ivy Animal Health, Inc.

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I. GENERAL INFORMATION:

A. File Number: ANADA 200-375

B. Sponsor: Ivy Laboratories
Division of Ivy Animal Health, Inc.
8857 Bond Street
Overland Park, KS 66214
Drug Labeler Code: 021641

C. Proprietary Names: HEIFERMAX 500 plus RUMENSIN and TYLAN

D. Established Names: Melengestrol acetate plus monensin and tylosin phosphate

E. Pharmacological Category: Melengestrol acetate: steroid hormone

Monensin: ionophore/anticoccidial

Tylosin phosphate: antimicrobial

F. Dosage Form: Type A medicated articles to be used in the manufacture of combination Type C medicated feeds

G. Amount of Active Ingredients: Melengestrol acetate: 500 g/lb

Monensin: 80 g/lb

Tylosin phosphate: 40 and 100 g/lb

H. How Supplied: Melengestrol acetate: 40 lb container (liquid)

Monensin: 50 lb bag

Tylosin phosphate: 50 lb bag

I. How Dispensed: OTC

J. Dosages: Melengestrol acetate is added to the diet of heifers 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 per head per day.

Monensin is added to feedlot cattle diets at

concentrations of 10 to 40 g of monensin per ton of complete feed at a rate of 0.14 to 0.42 mg monensin per pound of body weight depending on severity of coccidiosis challenge up to 480 mg per head per day.

Tylosin is added to the cattle diets at concentrations of 8 to 10 g of tylosin phosphate per ton of complete feed to provide 60 to 90 mg tylosin per head per day.

K. Route of Administration: Oral, in feed

L. Species/Class: Heifers fed in confinement for slaughter

M. Indications: For increased rate of weight gain, improved feed efficiency, suppression of estrus (heat); prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*; and reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium pyogenes* in heifers fed in confinement for slaughter.

N. Approved original generic Type A medicated article: HEIFERMAX 500; melengestrol acetate; ANADA 200-343; Ivy Laboratories, Division of Ivy Animal Health Inc.

O. Reference listed new animal drugs: MGA/RUMENSIN/TYLAN; melengestrol acetate/monensin/tylosin phosphate; NADA 138-870; Pharmacia & Upjohn Co., a Division of Pfizer, Inc.

Each individually approved as below:
MGA; melengestrol acetate; NADA 039-402; Pharmacia & Upjohn Co., a Division of Pfizer, Inc.

RUMENSIN; monensin; 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.

P. Effect of Supplement: This supplement provides for an increase in the upper dose limit of monensin to 480 mg per head per day based on the October 19, 2009, approval (NADA 138-870, C-0036) for RUMENSIN; and an update of the name of the tylosin targeted bacteria to *Arcanobacterium pyogenes* based on the November 7, 2006, approval (NADA 012-491, C-0318) for TYLAN.

II. BIOEQUIVALENCE:

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 (reference listed new animal drug). 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 is required to show that the generic product is bioequivalent to the RLNAD, 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 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. Monensin is codified under 21 CFR 558.355. Tylosin phosphate is codified under 21 CFR 558.625. The combination of melengestrol acetate plus monensin and tylosin phosphate is codified under 21 CFR 558.342(e)(1)(vii).

III. EFFECTIVENESS:

CVM did not require effectiveness studies for this supplemental approval.

IV. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval.

V. HUMAN FOOD SAFETY:

The following are assigned to this product for cattle:

- **Tolerances for Residues:**

  The tolerances established for the pioneer product apply to the generic product. A tolerance of 25 part per billion (ppb) is established for residues of melengestrol acetate in fat of cattle, under 21 CFR 556.380. A tolerance of 0.10 part per million (ppm) is established for residues of monensin in cattle liver, 0.05 ppm in muscle, kidney, and fat, under 21 CFR 556.420. A tolerance of 0.2 ppm is established for residues of tylosin in uncooked fat, muscle, liver, and kidney in cattle, under 21 CFR 556.740.

  The acceptable daily intake (ADI) for total residues of monensin is 12.5 micrograms per kilogram of body weight per day, under 21 CFR 556.420(a). The ADI was not established for melengestrol acetate and tylosin phosphate.

- **Withdrawal Times:**

  Because a waiver of the *in vivo* bioequivalence study was granted, the withdrawal times are those previously assigned to the pioneer product.

  Melengestrol acetate, monensin and tylosin phosphate are approved with a zero withdrawal period.

- **Regulatory Method for Residues:**

  The validated regulatory method for the determination and confirmation of residues of melengestrol acetate, monensin and tylosin phosphate are on file at the Center for Veterinary Medicine, 7500 Standish Place, Rockville, MD 20855.

VI. USER SAFETY:

CVM did not require user safety studies for this supplemental approval.

VII. AGENCY CONCLUSIONS:

This information submitted according in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act satisfies the requirements and demonstrates that HEIFERMAX 500 plus RUMENSIN and TYLAN, when used according to the label, is safe and effective for increased rate of weight gain, improved feed efficiency, suppression of estrus (heat), and prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii*; and reduction of incidence of liver abscesses caused by *Fusobaterium necrophorum* and *Arcanobacterium pyogenes* in heifers fed in confinement for slaughter.