Date of Approval: November 13, 2008

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-424

OPTAFLEXX (ractopamine hydrochloride), RUMENSIN (monensin sodium), TYLAN (tylosin phosphate) and HEIFERMAX 500 (melengestrol acetate)

Type A Medicated Articles

Effect of Supplement: This supplement provides for revised dosing in the combined use of ractopamine hydrochloride, monensin sodium, tylosin phosphate and melengestrol acetate Type A medicated articles based on the December 1, 2006, supplemental approval for RUMENSIN (under NADA 095-735). This supplement also updates the name of one of tylosin's targeted bacteria to Arcanobacterium (Actinomyces) pyogenes, based on the November 7, 2006, supplemental approval for TYLAN (under NADA 012-491). In addition, this supplement references an increased monensin tolerance in cattle liver from 0.05 to 0.10 ppm, based on the September 11, 2007, supplemental approval for OPTAFLEXX plus RUMENSIN plus TYLAN plus MGA (under NADA 141-233).

Sponsored by:
Ivy Laboratories,
Div. of Ivy Animal Health, Inc.

FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION:

a. File Number:	ANADA 200-424
b. Sponsor:	Ivy Laboratories, Div. of Ivy Animal Health, Inc. 8857 Bond Street Overland Park, KS 66214 Drug Labeler Code: 021641
c. Established Names:	Ractopamine hydrochloride, monensin sodium, tylosin phosphate, and melengestrol acetate
d. Proprietary Names:	OPTAFLEXX, RUMENSIN, TYLAN, and HEIFERMAX 500
e. Dosage Form:	Type A medicated articles for use in the manufacture of four-way combination Type C medicated feeds
f. How Supplied:	OPTAFLEXX – dry premix RUMENSIN – dry granulated premix TYLAN – dry premix HEIFERMAX 500 – liquid premix
g. How Dispensed:	OTC
h. Amount of Active Ingredients:	OPTAFLEXX: 45 g ractopamine hydrochloride per pound of premix RUMENSIN: 20, 30, 45, 60, 80, or 90.7 g of monensin sodium activity per pound of premix TYLAN: 10, 40 or 100 g of tylosin phosphate activity per pound of premix HEIFERMAX 500: 500 mg of melengestrol acetate activity per pound of premix
i. Route of Administration:	Orally in feed
j. Species/Class:	Heifers fed in confinement for slaughter

k. Recommended Dosage:

Ractopamine is fed at a concentration of 9.8 to 24.6 g per ton of complete feed to provide 90 to 430 mg ractopamine/head/day.

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

Tylosin is fed at a concentration of 8 to 10 g per ton of complete feed to provide 60 to 90 mg tylosin/head/day.

Melengestrol acetate is top dressed or mixed in a complete ration containing ractopamine (9.8 to 24.6 g/ton), monensin (10 to 40 g/ton), and tylosin (8 to 10 g/ton) and fed at a concentration of 0.125 to 1.0 mg per pound to provide 0.25 to 0.5 mg melengestrol acetate/head/day. Feed this ration at the rate of 0.5 to 2.0 pounds/head/day for the final 28 to 42 days on feed.

l. Pharmacological Category:

Steroid hormone (melengestrol acetate), beta adrenergic agonist (ractopamine hydrochloride), antibiotic (tylosin phosphate), and ionophore/anticoccidial (monensin sodium)

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 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 28 to 42 days on feed.

n. Pioneer Product:

OPTAFLEXX; ractopamine hydrochloride; NADA 141-221; Elanco Animal Health, A Division of Eli Lilly & Co.

RUMENSIN; monensin sodium; 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.

MGA 500; melengestrol acetate; NADA 039-402; Pharmacia & Upjohn Co., a Division of Pfizer, Inc.

OPTAFLEXX, RUMENSIN, TYLAN, and MGA 500; ractopamine hydrochloride, monensin sodium, tylosin phosphate, and melengestrol acetate; NADA 141-233; Elanco Animal Health, A Division of Eli Lilly & Co.

o. Effect of Supplement: This supplement provides for an increase in the upper dose limit of monensin to 40 g/ton in the combined use of ractopamine hydrochloride, monensin sodium, tylosin phosphate and melengestrol acetate Type A medicated articles, based on the December 1, 2006, supplemental approval for RUMENSIN (under NADA 095-735). This supplement also updates the name of one of tylosin's targeted bacteria to *Arcanobacterium (Actinomyces) pyogenes*, based on the November 7, 2006, supplemental approval for TYLAN (under NADA 012-491). In addition, this supplement references an increased monensin tolerance in cattle liver from 0.05 to 0.10 ppm, based on the September 11, 2007, supplemental approval for OPTAFLEXX plus RUMENSIN plus TYLAN plus MGA (under NADA 141-233).

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 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. Tylosin is codified under 21 CFR 558.625. The combination of melengestrol acetate ractopamine, monensin, and tylosin is codified under 21 CFR 558.500(e)(2).

3. HUMAN SAFETY:

- **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) in liver is 0.09 ppm, in muscle 0.03 parts per million (ppm) in cattle as codified under 21 CFR 556.570.

  The tolerance for residues of monensin are: Cattle, 0.10 ppm in liver, 0.05 ppm in muscle, kidney, and fat, and not required for milk as codified under 21 CFR 556.420.

  A tolerance of 0.2 ppm is established for negligible residues of tylosin in uncooked fat, muscle, liver, and kidney in cattle as codified under 21 CFR 556.740.

- **Withdrawal Time**
  Because the generic sponsor is entitled to approval for all the feed-mixed combinations for which the pioneer is approved, the withdrawal times are those previously assigned to the pioneer product.

  For this reason, a withdrawal period is not required for the use of this generic feed use combination.

- **Regulatory Method for Residues**
  Withdrawal times are not assigned for any of the drug ingredients in this combination product. Therefore, regulatory methods for residues are not available.

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

use combination new animal drug product containing four Type A medicated articles, OPTAFLEXX, RUMENSIN, TYLAN, and HEIFERMAX 500, 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 200-424:
Blue Bird labeling for Type C medicated feeds:
Liquid Heifer Supplement (melengestrol acetate)
Ractopamine, Monensin, and Tylosin Plus Type C Medicated Cattle Feed

Pioneer Labeling for NADA 141-233:
Blue Bird labeling for Type C medicated feeds:
Liquid Heifer Supplement (melengestrol acetate)
Ractopamine, Monensin, and Tylosin Plus Type C Medicated Cattle Feed