Date of Approval:July 27, 2014

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-566

OPTAFLEXX 45 plus RUMENSIN plus TYLOVET 100

ractopamine hydrochloride plus monensin USP plus tylosin phosphate

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

Cattle 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 reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium* (*Actinomyces*) *pyogenes* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed

Sponsored by:

Huvepharma AD

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GENERAL INFORMATION:

A. File Number

ANADA 200-566

B. Sponsor

Huvepharma AD
5th Floor, 3A Nikolay Haytov Str.
1113 Sofia, Bulgaria

Drug Labeler Code: 016592

Representative Name and Address: Kelly W. Beers, Ph.D.
Huvepharma, Inc.
525 Westpark Drive, Suite 230
Peachtree City, GA 30269

C. Proprietary Name

OPTAFLEXX 45 plus RUMENSIN plus TYLOVET 100

D. Established Name

ractopamine hydrochloride plus monensin USP plus tylosin phosphate

E. Pharmacological Category

Ractopamine hydrochloride – beta-adrenergic agonist
Monensin USP – ionophore/anticoccidial
Tylosin phosphate – antimicrobial

F. Dosage Form:

Type A medicated articles for use in the manufacture of Type B and Type C medicated feeds.

G. Amount of Active Ingredient in Currently Marketed Products*

Ractopamine hydrochloride – 45.4 g/lb
Monensin USP – 90.7 g/lb
Tylosin phosphate – 100 g/lb

*The sponsors of these individual currently marketed Type A medicated articles may have approvals for other strengths of these products that are for use in the same species and class, for the same indications, and at the same dosages, but are not currently marketing those strengths of these Type A medicated articles. Such strengths, when legally marketed, are also approved for use in the manufacture of the Type C medicated feed that is the subject of this approval.

H. How Supplied

OPTAFLEXX (ractopamine hydrochloride) 45 – 25 lb (11.34 kg) bag

RUMENSIN (monensin USP) – 55.12 lb (25 kg) bag
TYLOVET (tylosin phosphate) 100 – 50 lb (22.68 kg) bag

I. Dispensing Status

OTC

J. Dosage Regimen

There are three approved dosage regimens:

Ractopamine is fed at concentrations of 8.2 to 24.6 g ractopamine hydrochloride per ton of complete feed to provide 70 – 430 mg ractopamine/head/day for increased rate of weight gain and improved feed efficiency in cattle fed in confinement for slaughter during the last 28 to 42 days on feed; or

Ractopamine is fed at concentrations of 9.8 to 24.6 g of ractopamine hydrochloride per ton of complete feed to provide 90 to 430 mg ractopamine/head/day for increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

Monensin USP is added to the cattle ration 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/lb of body weight, depending on severity of coccidiosis challenge, up to 480 mg/head/day.

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

Ractopamine top dress for complete feeds containing monensin and tylosin:

Ractopamine hydrochloride is fed as a top dress at a minimum of 1.0 lb/head/day to provide 70 to 400 mg/head/day ractopamine for the last 28 to 42 days on feed. This top dress is added to a ration containing 10 to 40 g of monensin and 8 to 10 g of tylosin phosphate per ton of complete feed to provide 0.14 to 0.42 mg monensin /lb of body weight, depending on the severity of the coccidiosis challenge, up to 480 mg/head/day, and 60 to 90 mg tylosin/head/day.

K. Route of Administration

Oral, in feed

L. Species / Class

Cattle fed in confinement for slaughter

M. Indications

Amount: Ractopamine hydrochloride (8.2 to 24.6 g/ton) in combination with monensin USP (10 to 40 g/ton) and tylosin phosphate (8 to 10 g/ton).
Indications: For increased rate of weight gain, improved feed efficiency,

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* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed.

Amount: Ractopamine hydrochloride (9.8 to 24.6 g/ton) in combination with monensin USP (10 to 40 g/ton) and tylosin phosphate (8 to 10 g/ton). 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* in cattle fed in confinement for slaughter for the last 28 to 42 days on feed.

Amount: Ractopamine hydrochloride top dress (not to exceed 800 g/ton) plus monensin USP (10 to 40 g/ton) in combination with tylosin phosphate (8 to 10 g/ton). Indications: For increased rate of weight gain, improved feed efficiency, 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* in cattle fed in confinement for slaughter during the last 28 to 42 days on feed.

N. Approved Original Generic Type A Medicated Article

TYLOVET 100; tylosin phosphate; ANADA 200-484; Huvepharma AD

O. Reference Listed New Animal Drug

OPTAFLEXX 45 plus RUMENSIN plus TYLAN; ractopamine hydrochloride plus monensin USP plus tylosin phosphate; NADA 141-224; Elanco Animal Health, A Division of Eli Lilly & Co.

The individual Type A medicated articles approved for use in the manufacture of combination medicated feeds:

OPTAFLEXX 45; 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.

TYLAN; tylosin phosphate; NADA 012-491; Elanco Animal Health, A Division of Eli Lilly & Co.

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.

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 RLNAD 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). Ractopamine hydrochloride is codified under 21 CFR 558.500, monensin USP is codified under 21 CFR 558.355, and tylosin phosphate is codified under 21 CFR 558.625. The combination of ractopamine hydrochloride, monensin USP, and tylosin phosphate is codified under 21 CFR 558.500(e)(2)(iv), 558.500(e)(2)(ix), and 558.500(e)(2)(xiii).

III. EFFECTIVENESS:

CVM did not require effectiveness studies for this approval.

IV. TARGET ANIMAL SAFETY:

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

V. HUMAN FOOD SAFETY:

The following are assigned to this product for cattle:

A. Tolerances for Residues

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

The tolerance for residues of ractopamine hydrochloride (the marker residue) is 0.09 parts per million (ppm) in the liver (the target tissue), and 0.03 ppm in the muscle, under 21 CFR 556.570(b)(1). The acceptable daily intake ADI for total residues of ractopamine hydrochloride is 1.25 micrograms per kilogram of body weight per day.

The tolerance for residues of monensin is 0.10 ppm in the liver, and 0.05 ppm in the muscle, kidney, and fat, under 21 CFR 556.420(b)(1). A tolerance for residues of monensin in milk is not required under 21 CFR 556.420. The ADI for total residues of monensin is 12.5 micrograms per kilogram of body weight per day.

The tolerance for residues of tylosin phosphate is 0.2 ppm (negligible residue) in uncooked fat, muscle, liver, and kidney, under 21 CFR 556.740(b), and 0.05 ppm (negligible residue) in milk under 21 CFR 556.740(d).

B. Withdrawal Periods

Because a waiver from the requirement to demonstrate bioequivalence was granted for the Type A medicated article TYLOVET 100, the withdrawal periods for the combination Type B and C medicated feeds are those previously assigned to the RLNAD product.

Ractopamine hydrochloride, monensin USP, and tylosin phosphate in combination are approved with a zero-day withdrawal period.

C. Regulatory Method for Residues

The determination of residues of ractopamine in the liver and muscle of cattle, swine and turkeys is by High Performance Liquid Chromatography (HPLC). The confirmation of residues of ractopamine in the liver and muscle of cattle, swine and turkeys is by Liquid Chromatography/Electrospray Ionization Triple Tandem Quadruple 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.

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.

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.

VI. USER SAFETY:

CVM did not require user safety studies for this approval.

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to ractopamine hydrochloride:

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 formulation (Type A Medicated Article) poses a low dust potential under usual conditions of handling and mixing. When mixing and handling ractopamine 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, contact your ractopamine supplier.

VII. AGENCY CONCLUSIONS:

This information submitted in support of this ANADA satisfies the requirements of section 512(n) of the Federal Food, Drug, and Cosmetic Act and demonstrates that OPTAFLEXX 45 plus RUMENSIN plus TYLOVET 100, when used according to the label, is safe and effective.