Date of Approval: May 24, 2013

FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-544

ZILMAX plus RUMENSIN plus TYLOVET 100 plus MGA

zilpaterol hydrochloride plus monensin USP plus tylosin phosphate plus melengestrol acetate

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

Heifers 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*, and suppression of estrus (heat) in heifers fed in confinement for slaughter for the last 20 to 40 days on feed.

Sponsored by:

Huvepharma AD

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-544

B. Sponsor

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

Drug Labeler Code: 016592

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

C. Proprietary Name

ZILMAX plus RUMENSIN plus TYLOVET 100 plus MGA

D. Established Name

zilpaterol hydrochloride plus monensin USP plus tylosin phosphate plus melengestrol acetate

E. Pharmacological Category

Zilpaterol hydrochloride – beta-adrenergic agonist
Monensin USP – ionophore/anticoccidial
Tylosin phosphate – antimicrobial
Melengestrol acetate – steroid hormone

F. Dosage Form

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

G. Amount of Active Ingredient

Zilpaterol hydrochloride – 21.77 g/lb
Monensin USP – 80 g/lb
Tylosin phosphate – 40 and 100 g/lb
Melengestrol acetate – 100 and 200 mg/lb (dry) and 500 mg/lb (liquid)

H. How Supplied

ZILMAX (zilpaterol hydrochloride) – 22.05 lb (10 kg) bag
RUMENSIN (monensin USP) – 50 lb bag
TYLOVET (tylosin phosphate) 100 – 50 lb (22.68 kg) bag
MGA (melengestrol acetate) – 50 lb bag (dry), 40 lb container (liquid)

I. Dispensing Status

OTC

J. Dosage Regimen

Zilpaterol hydrochloride 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 during the last 20 to 40 days on feed.

Monensin USP is added to diets for cattle fed in confinement for slaughter 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 phosphate 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/head/day.

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/head/day in heifers being fed in confinement for slaughter.

K. Route of Administration

Oral, in feed

L. Species/Class

Cattle, heifers fed in confinement for slaughter

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 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. Approved Original Generic Type A Medicated Article

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

O. Reference Listed New Animal Drug (RLNAD)

ZILMAX plus RUMENSIN plus TYLAN plus MGA; zilpaterol hydrochloride plus monensin USP plus tylosin phosphate plus melengestrol acetate; NADA 141-280; Intervet, Inc.

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 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). Zilpaterol hydrochloride is codified under 21 CFR 558.665, monensin USP is codified under 21 CFR 558.355, tylosin phosphate is codified under 21 CFR 558.625, and melengestrol acetate is codified under 21 CFR 558.342. The combination of zilpaterol hydrochloride, monensin USP, tylosin phosphate and melengestrol acetate is codified under 21 CFR 558.665(e)(6).

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 heifers fed in confinement for slaughter:

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 zilpaterol freebase is 12 parts per billion (ppb) in cattle liver under 21 CFR 556.765(b)(1). The acceptable daily intake (ADI) for total residues of zilpaterol is 0.083 micrograms per kilogram of body weight per day under 21 CFR 556.765(a).

The tolerances for monensin in cattle are 0.05 parts per million (ppm) for muscle, kidney, and fat, and 0.10 ppm for liver under 21 CFR 556.420 (b)(1). The ADI for total residues of monensin is 12.5 micrograms per kilogram of body weight per day under 21 CFR 556.420(a).

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

A tolerance of 25 ppb is established for residues of melengestrol acetate, in fat of cattle under 21 CFR 556.380.

B. Withdrawal Times:

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

Monensin, tylosin phosphate, zilpaterol hydrochloride, and melengestrol acetate are approved with a 3-day withdrawal period.

C. Regulatory Method for Residues:

The regulatory analytical method for the determination of zilpaterol freebase, the marker residue, 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.

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, MD 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, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855.

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.

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 zilpaterol hydrochloride:

WARNING:
Zilpaterol hydrochloride is a beta$_2$-adrenergic agonist. Not for use in humans. An anti-dust process has been applied to the drug product, zilpaterol hydrochloride, 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 eye wear, if there is a potential for eye contact. If accidental eye contact occurs, immediately rinse with water and consult a physician.

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, ZILMAX plus RUMENSIN plus TYLOVET 100 plus MGA, when used according to the label, are safe and effective.