

Date of Approval: June 25, 2013

**FREEDOM OF INFORMATION SUMMARY**  
**ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION**

ANADA 200-547

ZILMAX plus RUMENSIN plus TYLOVET 100

zilpaterol hydrochloride plus monensin USP plus tylosin phosphate

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

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 20 to 40 days on feed.

Sponsored by:

Huvepharma AD

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I. GENERAL INFORMATION:

A. File Number

ANADA 200-547

B. Sponsor

Huvepharma AD  
5<sup>th</sup> Floor, 3A Nikolay Haytov Str.  
1113 Sofia, Bulgaria

Drug Labeler Code: 016592

U.S. 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

D. Established Name

zilpaterol hydrochloride plus monensin USP plus tylosin phosphate

E. Pharmacological Category

Zilpaterol 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 (dry and liquid)  
and Type 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

H. How Supplied

ZILMAX (zilpaterol hydrochloride) – 22.05 lb (10 kg) bag  
RUMENSIN (monensin USP) – 50 lb (22.68 kg) bag  
TYLOVET (tylosin phosphate) 100 – 50 lb (22.68 kg) bag

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.

## K. Route of Administration

Oral, in feed

## L. Species/Class

Cattle 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 incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* in cattle 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; zilpaterol hydrochloride plus monensin USP plus tylosin phosphate; NADA 141-276; 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 (GADPTRA), 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, and tylosin phosphate is codified under 21 CFR 558.625. The combination of zilpaterol hydrochloride, monensin USP, and tylosin phosphate is codified under 21 CFR 558.665(e)(5).

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:

- 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 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 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).

- 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 B and Type C medicated feeds are those previously assigned to the RLNAD.

When used together, monensin, tylosin phosphate, and zilpaterol hydrochloride are approved with a 3-day withdrawal period.

- 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.

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<sub>2</sub>-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, when used according to the label, is safe and effective.