Date of Approval: January 14, 2015

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-280

ZILMAX plus RUMENSIN plus TYLAN plus MGA

(zilpaterol hydrochloride 4.8 %; monensin, USP; tylosin phosphate; and melengestrol acetate)

Type A Medicated Articles

For Use in the Manufacture of Type C Medicated Feeds

Heifers Fed in Confinement for Slaughter

Effect of Supplement:

1) component feeding of 60 mg zilpaterol hydrochloride/head/day in combination with feed containing monensin, USP; tylosin phosphate; and melengestrol acetate for increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, 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 during the last 20 to 40 days on feed,

   and

2) adding the following statement to the labeling for the use of zilpaterol hydrochloride in complete feed when fed in combination with monensin, USP; tylosin phosphate; and melengestrol acetate: "CAUTION: "Not to be fed to cattle in excess of 90 mg/head/day in complete feed. If pen consumption of complete feed exceeds 26.5 lb/head/day (90 percent dry matter basis), zilpaterol should not be fed in complete feed."

Sponsored by:

Intervet, Inc.

TABLE OF CONTENTS

I. GENERAL INFORMATION

A. File Number

NADA 141-280

B. Sponsor

Intervet, Inc.
556 Morris Ave.
Summit, NJ 07901

Drug Labeler Code: 000061

C. Proprietary Name

ZILMAX plus RUMENSIN plus TYLAN plus MGA

D. Established Name

Zilpaterol hydrochloride 4.8%; monensin, USP; tylosin phosphate; and melengestrol acetate

E. Pharmacological Category

Zilpaterol hydrochloride - Beta adrenergic agonist
Monensin, USP - Ionophore/anticoccidial
Tylosin phosphate - Antibacterial
Melengestrol acetate - Steroid hormone

F. Dosage Form

Type A medicated articles to be used in the manufacture of Type C medicated feeds

G. Amount of Active Ingredient

Zilpaterol hydrochloride - 21.77 g/lb (48 g/kg)
Monensin, USP - 90 g/lb
Tylosin phosphate - 40 and 100 g/lb
Melengestrol acetate - 200 and 500 mg/lb

H. How Supplied

Zilpaterol hydrochloride - 22.05 lbs (10 kg) bag
Monensin, USP - 50 lb bag
Tylosin phosphate - 50 lb bag
Melengestrol acetate - 50 lb bag (dry), 40 lb container (liquid)

I. Dispensing Status

OTC

J. Dosage Regimen

Zilpaterol hydrochloride - Component feed: Feed continuously to cattle during the last 20 to 40 days on feed, in a component feed containing 6.8 to 24 g/ton zilpaterol to provide 60 mg/head/day zilpaterol.

Monensin, USP: Feed continuously to cattle during the last 20 to 40 days on feed, in a feed containing 10 to 40 g/ton monensin, to provide 0.14 to 0.42 mg/lb body weight/day monensin, depending on the severity of the coccidiosis challenge, up to 480 mg/head/day monensin.

Tylosin phosphate: Feed continuously to cattle during the last 20 to 40 days on feed, in a feed containing 8 to 10 g/ton tylosin to provide 60 to 90 mg/head/day tylosin.

Melengestrol acetate: Feed continuously to heifers during the last 20 to 40 days on feed, 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.

K. Route of Administration

Oral in feed

L. Species/Class

Heifers fed in confinement for slaughter

M. Indication

For increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, 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 during the last 20 to 40 days on feed.

N. Effect of Supplement

This supplement provides for: 1) component feeding of 60 mg zilpaterol hydrochloride/head/day in combination with feed containing monensin, USP; tylosin phosphate; and melengestrol acetate for increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, 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 during the last 20 to 40 days on feed, and 2) adding the following statement to the labeling for the use of zilpaterol hydrochloride in complete feed when fed in combination with monensin, USP; tylosin phosphate; and melengestrol acetate: "CAUTION: Not to be fed to cattle in excess of 90 mg/head/day in complete feed. If pen consumption of complete

feed exceeds 26.5 lb/head/day (90 percent dry matter basis), zilpaterol should not be fed in complete feed."

II. EFFECTIVENESS

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act (ADAA) of 1996, if the animal drugs or active ingredients intended for use in combination in an animal feed have already been separately approved for the particular uses and conditions for which they are intended for use in combination, the Center for Veterinary Medicine (CVM) will not refuse to approve an NADA for the combination on effectiveness grounds unless the FDA finds that the sponsor fails to demonstrate that:

- there is substantial evidence to indicate that any active ingredient or animal drug intended only for the same use as another active ingredient or animal drug in the proposed combination makes a contribution to the labeled effectiveness
- each of the active ingredients or animal drugs intended for at least one use that is different from all other active ingredients or animal drugs used in the combination provides appropriate concurrent use for the intended target population
- where the combination contains more than one nontopical antibacterial active ingredient or animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients or animal drugs makes a contribution to the labeled effectiveness.

Zilpaterol hydrochloride, as provided by Intervet, Inc., has previously been separately approved for use in feed for cattle for increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 20 to 40 days on feed when fed in complete feed (21 CFR 558.665(e)(1)). Effectiveness of zilpaterol hydrochloride for increased rate of weight gain, improved feed efficiency, increased carcass leanness in cattle fed in confinement for slaughter during the last 20 to 40 days on feed when fed in component feeds was established in Intervet, Inc.'s NADA 141-258, approved October 30, 2014 (C-0054) (21 CFR 558.665(e)(7)). Monensin, USP; as provided by Elanco Animal Health, has previously been separately approved for use in feed for cattle fed in confinement for slaughter for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* (21 CFR 558.355(f)(3)(vii)(a)). Tylosin phosphate, as provided by Elanco Animal Health, has previously been separately approved for use in feed for cattle fed in confinement for slaughter for reduction in incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* (21 CFR 558.625(f)(1)(i)(b)). Melengestrol acetate, as provided by Zoetis, Inc., has previously been separately approved for use in feed for heifers fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) (21 CFR 558.342(e)(1)).

Effectiveness of each drug, zilpaterol hydrochloride; monensin, USP; tylosin phosphate; and melengestrol acetate when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Intervet, Inc.'s approved NADA 141-258 for zilpaterol hydrochloride, in Elanco Animal Health's

approved NADAs 095-735 and 012-491 for monensin; and tylosin phosphate, respectively, for which Intervet, Inc. has right of reference, and in Zoetis, Inc.'s approved NADA 039-402 for melengestrol acetate for which Intervet, Inc. has right of reference.

Because zilpaterol hydrochloride; monensin, USP; tylosin phosphate; and melengestrol acetate each have at least one use that is different from all other animal drugs used in the combination, the NADA must also demonstrate that zilpaterol hydrochloride plus monensin, USP plus tylosin phosphate plus melengestrol acetate provide appropriate concurrent use for the intended target population. The use of zilpaterol hydrochloride plus monensin, USP plus tylosin phosphate plus melengestrol acetate provides appropriate concurrent use because these drugs are intended to treat different conditions (zilpaterol hydrochloride – increased rate of weight gain, improved feed efficiency, and carcass leanness; monensin, USP – prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*; tylosin phosphate – reduced incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes*; and melengestrol acetate – suppression of estrus (heat)) likely to occur simultaneously with sufficient frequency in heifers fed in confinement for slaughter. There is no more than one nontopical antibacterial contained in this combination animal drug intended for use in Type C medicated feed.

III. TARGET ANIMAL SAFETY

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have previously been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on target animal safety grounds unless:

- there is a substantiated scientific issue specific to an active ingredient or animal drug used in the combination that cannot adequately be evaluated based on the information contained in the application for the combination, and CVM finds that the application fails to show that the combination is safe, or
- there is a scientific issue raised by target animal observations contained in the studies submitted to the NADA for the combination, and CVM finds that the application fails to show that the combination is safe.

Zilpaterol hydrochloride, as provided by Intervet, Inc., has previously been separately approved for use in feed for cattle for increased rate of weight gain, improved feed efficiency, and increased carcass leanness in cattle fed in confinement for slaughter during the last 20 to 40 days on feed when fed in complete feed (21 CFR 558.665(e)(1)). Zilpaterol hydrochloride has previously been separately approved for use in feed for cattle for increased rate of weight gain, improved feed efficiency, increased carcass leanness in cattle fed in confinement for slaughter during the last 20 to 40 days on feed when fed in component feed (21 CFR 558.665(e)(7)). Monensin, USP, as provided by Elanco Animal Health, has previously been separately approved for use in feed for cattle fed in confinement for slaughter for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii* (21 CFR 558.355(f)(3)(vii)(a)). Tylosin phosphate, as

provided by Elanco Animal Health, has previously been separately approved for use in feed for beef cattle for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* (21 CFR 558.625(f)(1)(i)(b)). Melengestrol acetate, as provided by Zoetis, Inc., has previously been separately approved for use in feed for heifers fed in confinement for slaughter for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) (21 CFR 558.342(e)(1)).

Under the provisions of ADAA, this supplemental approval allows for the combination of zilpaterol hydrochloride (as provided by Intervet, Inc.); monensin, USP (as provided by Elanco Animal Health); tylosin phosphate (as provided by Elanco Animal Health); and melengestrol acetate (as provided by Zoetis Inc.). Target animal safety for each drug, zilpaterol hydrochloride; monensin, USP; tylosin phosphate; and melengestrol acetate when administered alone in accordance with its approved uses and conditions of use, is demonstrated in Intervet, Inc.'s approved NADA 141-258 for zilpaterol hydrochloride; in Elanco Animal Health's approved NADAs 095-735 and 012-491 for monensin, USP; and tylosin phosphate; respectively, for which Intervet, Inc. has right of reference, and in Zoetis, Inc.'s approved NADA 039-402 for melengestrol acetate for which Intervet, Inc. has right of reference. The Agency has found no substantiated scientific issue relating to the target animal safety of zilpaterol hydrochloride; monensin, USP; tylosin phosphate; and melengestrol acetate when used in combination under this NADA and no scientific issue has been raised by target animal observations submitted as part of the NADA for this combination. Therefore, in accordance with the FFDCA, as amended by the ADAA of 1996, no specific target animal safety studies are required for approval of this application.

IV. HUMAN FOOD SAFETY

In accordance with the FFDCA, as amended by the ADAA of 1996, if the animal drugs or active ingredients intended for use in combination in animal feed have already been separately approved for the particular uses and conditions of use for which they are intended for use in combination, CVM will not refuse to approve an NADA for the combination on human food safety grounds unless CVM finds that the application fails to establish that:

- none of the active ingredients or animal drugs used in combination at the longest withdrawal for any of the active ingredients or animal drugs in the combination exceeds the established tolerance, or
- none of the active ingredients or animal drugs in combination interferes with the method of analysis for another active ingredient or animal drug in the combination.

A. Toxicology

CVM did not require toxicology studies for this supplemental approval. Safety of the individual drugs in this combination drug have been established by data in NADA 141-258 for zilpaterol hydrochloride (FOI Summary dated August 10, 2006), NADAs 095-735 and 038-878 for monensin (35 FR 7734 dated May 20, 1970, 40 FR 58289 dated December 16, 1975, and FOI Summary dated December 16, 1998), NADA 012-491 for tylosin phosphate

(26 FR 4359 dated May 19, 1961), and NADAs 034-254 and 039-402 for melengestrol acetate (FOI Summary dated June 29, 1994).

B. Residue Chemistry

1. Summary of Residue Chemistry Studies

   CVM did not require residue chemistry studies for this approval. Data demonstrating residue depletion and assay noninterference for zilpaterol hydrochloride; monensin, USP; tylosin phosphate; and melengestrol acetate have been summarized in the original approval of NADA 141-280 (dated February 29, 2008).

2. Target Tissue and Marker Residue Assignment

   No reassessments of target tissue and marker residue were needed for this approval. The marker residue for zilpaterol hydrochloride is zilpaterol freebase and the target tissue in cattle is liver (NADA 141-258 dated January 10, 2008). Neither a target tissue nor a marker residue is codified for monensin, tylosin phosphate, or melengestrol acetate.

3. Tolerance Assignments

   The tolerance for zilpaterol freebase is 12 ppb in cattle liver (21 CFR § 556.765). The tolerance for residues of monensin is 0.1 ppm in cattle liver, and 0.05 ppm in cattle muscle, kidney, and fat (21 CFR § 556.420). The tolerance for residues of tylosin is 0.2 ppm in cattle liver, muscle, kidney, and fat (21 CFR § 556.740). The tolerance for parent melengestrol acetate is 25 ppb in cattle fat (21 CFR § 556.380).

4. Withdrawal Time

   A 3-day withdrawal is assigned for heifers fed in confinement for slaughter treated with zilpaterol via component feed at 60 mg zilpaterol/head/day plus monensin at up to 40 g/ton plus tylosin at up to 10 g/ton plus melengestrol acetate at up to 0.5 mg/head/day continuously during the last 20 to 40 days on feed.

C. Microbial Food Safety

With respect to the human food safety evaluation for these types of combination new animal drug approvals, the agency is permitted only to evaluate whether any active ingredient or drug intended for use in the combination exceeds its established tolerance at the longest withdrawal time of any of the active ingredients or drugs in the combination, and whether any of the active ingredients or drugs of the combination interferes with the methods of analysis of another active ingredient or drug in the combination (section 512(d)(4)(A) of the Federal Food, Drug, and Cosmetic Act). Therefore, we did not 1) assess the impact of this combination of zilpaterol hydrochloride and monensin and tylosin phosphate and melengestrol acetate on antimicrobial resistance among bacteria of public health concern in or on treated cattle, or 2) assess the impact of residues of zilpaterol hydrochloride

and monensin and tylosin phosphate and melengestrol acetate in edible food products from treated cattle on human intestinal flora, or need to establish a microbiological acceptable daily intake .

D. Analytical Method for Residues

Refer to NADA 141-258 for zilpaterol, NADA 095-735 for monensin, NADA 012-491 for tylosin, and to NADA 039-402 for melengestrol acetate for the approved regulatory analytical methods.

The methods are available from the Center for Veterinary Medicine, FDA, 7500 Standish Place, Rockville, Maryland, 20855.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to the Type C medicated feed:

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

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR part 514. The data contained in the previously approved NADAs for ZILMAX plus RUMENSIN plus TYLAN plus MGA demonstrate that, when used according to the label, they are safe and effective for increased rate of weight gain, improved feed efficiency, increased carcass leanness, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, 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 during the last 20 to 40 days on feed. Additionally, data demonstrate that residues in food products derived from cattle fed in confinement for slaughter treated with ZILMAX plus RUMENSIN plus TYLAN plus MGA will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product can be marketed over-the-counter (OTC) because the approved labeling contains adequate directions for use by laypersons and the conditions of use prescribed on the label are reasonably certain to be followed in practice.

B. Exclusivity

This approval does not qualify for marketing exclusivity under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR §514.106(b)(2)).

D. Patent Information

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.