Date of Approval: February 29, 2008

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-280

ZILMAX plus RUMENSIN plus TYLAN plus MGA

(Zilpaterol Hydrochloride and Monensin USP and Tylosin Phosphate and 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*, 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:

Intervet Inc.

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I. GENERAL INFORMATION:

A. File Number:	NADA 141-280
B. Sponsor:	Intervet Inc. P.O. Box 318 29160 Intervet Lane Millsboro, DE 19966 Drug Labeler Code: 057926
C. Proprietary Names:	ZILMAX plus RUMENSIN plus TYLAN plus MGA
D. Established Names:	Zilpaterol hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate
E. Pharmacological Categories:	Zilpaterol hydrochloride – Beta adrenergic agonist Monensin USP – Ionophore/anticoccidial Tylosin phosphate – Antibacterial Melengestrol acetate – Steroid hormone
F. Dosage Forms:	Type A medicated articles to be used in the manufacture of Type B and C medicated feeds
G. Amount of Active Ingredients:	Zilpaterol hydrochloride - 21.77 grams per pound (48 grams per kilogram) Monensin USP - 80 grams per pound Tylosin phosphate - 40 and 100 grams per pound Melengestrol acetate - 200 and 500 mg per pound
H. How Supplied:	Zilpaterol hydrochloride – 22.05 lb (10 kg) bag Monensin USP – 50 lb bag Tylosin phosphate – 50 lb bag Melengestrol acetate – 50 lb bag (dry), 40 lb container (liquid)
I. How Dispensed:	OTC

J. Dosages:	Zilpaterol 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 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 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:	Heifers fed in confinement for slaughter
M. Indications:	For increased rate of weight gain, increased carcass leanness, improved feed efficiency, 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 for the last 20 to 40 days on feed.

II. EFFECTIVENESS:

In accordance with the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by the Animal Drug Availability Act of 1996, if the animal drugs/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, FDA 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/drug intended only for the same use as another active ingredient/animal drug in 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/animal drug, there is substantial evidence that each of the nontopical antibacterial active ingredients/animal drugs makes a contribution to the labeled effectiveness

Zilpaterol hydrochloride as provided by Intervet Inc., has previously been separately approved for use in 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 (21 CFR 558.665(e)(2)). Monensin USP, as provided by Elanco Animal Health, has previously been separately approved (in a supplemental approval dated December 1, 2006) for use in 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 cattle fed in confinement for slaughter 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 Pfizer, Inc., has previously been separately approved for use for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) in heifers fed in confinement for slaughter (21 CFR 558.342(e)(1)). Effectiveness of each drug, zilpaterol hydrochloride, monensin USP, and tylosin phosphate, 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, and Elanco Animal Health's NADAs 095-735 for monensin USP and 012-491 for tylosin phosphate, and Pfizer, Inc.'s NADAs 039-402 and 034-254 for melengestrol acetate, to which Intervet Inc. has right of reference.

Zilpaterol hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate are each intended for a different use therefore the NADA need not demonstrate, by substantial evidence, that zilpaterol hydrochloride, monensin USP, tylosin phosphate or melengestrol acetate, contributes to the labeled effectiveness of the combination. Zilpaterol hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate provide appropriate concurrent use because these drugs are intended to treat different conditions likely to occur simultaneously in heifers fed in confinement for slaughter

during the last 20 to 40 days on feed. Zilpaterol hydrochloride is approved for increased rate of weight gain, improved feed efficiency, and increased carcass leanness. Monensin USP is approved for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*. Tylosin phosphate is approved for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes*. Melengestrol acetate is approved for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat).

III. TARGET ANIMAL SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, FDA 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 FDA 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 FDA 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 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 (21 CFR 558.665(e)(2)). Monensin USP, as provided by Elanco Animal Health, has previously been separately approved (in a supplemental approval dated December 1, 2006) for use in 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 cattle fed in confinement for slaughter 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 Pfizer, Inc., has previously been separately approved for use for increased rate of weight gain, improved feed efficiency, and suppression of estrus (heat) in heifers fed in confinement for slaughter (21 CFR 558.342(e)(1)).

Under the provisions of ADAA, this original approval allows for the combination of zilpaterol hydrochloride (as provided by Intervet Inc.), monensin USP and tylosin phosphate (as provided by Elanco Animal Health), and melengestrol acetate (as provided by Pfizer, Inc.). Target animal safety 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, Elanco Animal Health's NADAs 95-735, and 12-491, respectively, and Pfizer, Inc.'s NADAs 39-402 and 34-254 for melengestrol acetate, to which Elanco Animal Health 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. Thus, pursuant to FFDCA, as amended by the Animal Drug Availability Act of 1996, no specific target animal safety studies are required for approval of NADA 141-280.

IV. HUMAN FOOD SAFETY:

In accordance with the FFDCA, as amended by the Animal Drug Availability Act of 1996, if the animal drugs/active ingredients or intended for use in combination in animal feed have previously been approved separately for the particular uses and conditions of use for which they are intended for use in combination, FDA will not refuse to approve an NADA for the combination on human safety grounds unless FDA 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 drug in the combination.

A. Toxicology:

Safety of the individual drugs in this combination product has been established by data in NADA 141-258 for zilpaterol hydrochloride (FOI Summary dated August 10, 2006), NADA 095-735 for monensin USP (FOI Summary dated December 1, 2006), NADA 12-491 for tylosin phosphate (FOI Summary dated November 8, 1996) and NADA 034-254 for melengestrol acetate (FOI Summary dated June 29, 1994).

B. Residue Chemistry:

1. Residue Chemistry Study:

Data demonstrating residue depletion and assay noninterference for the drugs of this combination have been summarized in the FOI Summary for the approval of NADA 141-276 dated January 10, 2008.

2. Target Tissue and Marker Residue Assignment:

The marker residue for zilpaterol is zilpaterol freebase and the target tissue in cattle is liver (NADA 141-258, *op. cit.*). No marker residue and target tissue is specified for monensin, tylosin or melengestrol acetate.

3. Tolerance Assignments:

The tolerance for zilpaterol freebase is 12 ppb in cattle liver (21 CFR 556.765). The tolerances for monensin in cattle are 0.05 ppm for muscle, kidney, and fat, and 0.10 ppm for liver (21 CFR 556.420). The tolerances for tylosin in cattle are 0.2 ppm for muscle, kidney, fat, and liver (21 CFR 556.740). The tolerance for melengestrol acetate is 25 ppb in fat of cattle (21 CFR 556.380).

4. Withdrawal Period:

Monensin USP, melengestrol acetate, and tylosin phosphate are approved with a zero withdrawal period. The data in Study Number: 0238-0034-01 confirm that residues of these three drugs in the 4-way combination at zero withdrawal period are less than applicable tolerances, thereby establishing depletion noninterference.

To ascertain the noninterference of the other drugs on the depletion of zilpaterol, the data for zilpaterol collected at 3 days of withdrawal were statistically analyzed using FDA's 99% tolerance limit with 95% confidence algorithm. The analysis showed that the derived tolerance limit was less than the tolerance of 12 ppb. These results support the assignment of a 3-day withdrawal period for zilpaterol hydrochloride when used in combination with monensin USP, tylosin phosphate, and melengestrol acetate.

C. Microbial Food Safety:

The Agency determined that an assessment of the microbial food safety associated with this application for the combination of zilpaterol hydrochloride, monensin USP, tylosin phosphate, and melengestrol acetate for use in cattle, approvable pursuant to the provisions of the Animal Drug Availability Act (1996), was not necessary at this time.

D. Analytical Method for Residues:

Refer to NADA 141-258 for zilpaterol (*op. cit.*), to NADA 095-735 for monensin (*op. cit.*), to NADA 12-491 for tylosin (*op. cit.*), and to NADA 034-254 for melengestrol acetate (*op. cit.*) for the approved regulatory methods. The methods are available from the Center for Veterinary Medicine, FDA, 7500 Standish Place, Rockville, MD 20855.

V. USER SAFETY:

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

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 eye wear, if there is a potential for eye contact. If accidental eye contact occurs, immediately rinse with water and consult a physician.

The representative (blue bird) labeling for the Type B and Type C medicated feeds contains no information regarding safety to humans handling, administering, or exposed to the combination of RUMENSIN, TYLAN, and MGA. This is based upon review of the Material Safety Data Sheets (MSDS) for RUMENSIN, TYLAN, and MGA, as well as the MSDS sheet for ZILMAX, and the individually approved blue bird labeling.

VI. AGENCY CONCLUSIONS:

The data submitted in support of this NADA satisfy the requirements of section 512(d)(4) of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514. The data demonstrate that ZILMAX plus RUMENSIN plus TYLAN plus MGA, when used according to the label, is 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*, 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. 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.

The drugs are to be fed in Type C medicated feeds in accordance with section II and III of the FOI Summary and the Blue Bird labeling that is attached to this document.

A. Marketing Status:

The Center for Veterinary Medicine has concluded that, for this product, adequate directions for use by the lay person have been provided. Label directions provide detailed instruction in plain language. The drug product is not a controlled substance. Thus, the drug product is assigned OTC status, and the labeling is adequate for the intended use.

B. Exclusivity:

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

C. Patent Information:

ZILMAX is under the following US patent numbers:

U.S. Patent Number	Date of Expiration
4,900,735	December 11, 2008
5,731,028	June 6, 2016
7,207, 289	May 20, 2025

VII. ATTACHMENTS:

Final Printed Labeling:

Zilpaterol, Monensin, and Tylosin, Type B Medicated Cattle Feed
Zilpaterol, Monensin, Tylosin Liquid Type B Medicated Cattle Feed
Zilpaterol, Monensin, and Tylosin Type C Medicated Cattle Feed
Heifer Supplement Medicated (Type C Medicated Feed) for Beef and Dairy Heifers
Liquid Heifer Supplement Medicated (Type C Medicated Feed) For Beef and Dairy Heifers