

Date of Approval: December 2, 2015

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-258

ZILMAX

zilpaterol hydrochloride 4.8%

Type A medicated article to be used in the manufacture of Type B
and C medicated feeds

Cattle fed in confinement for slaughter

This supplement provides for the replacement of the previously approved determinative and confirmatory procedures for cattle liver with new LC-MS/MS methods, addition of determinative and confirmatory procedures for cattle muscle, and inclusion of a tolerance of 10 ppb for zilpaterol in cattle muscle.

Sponsored by:

Intervet, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-258

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

ZILMAX

D. Established Name

Zilpaterol hydrochloride 4.8%

E. Pharmacological Category

Beta adrenergic agonist

F. Dosage Form

Type A medicated article to be used in the manufacture of Type B and C medicated feeds

G. Amount of Active Ingredient

21.77 g/lb (48 g/kg)

H. How Supplied

22.05 lbs (10 kg) bag

I. Dispensing Status

OTC

J. Dosage Regimen

Complete feed: Feed continuously to cattle during the last 20 to 40 days on feed as the sole ration, containing 6.8 g/ton zilpaterol (7.5 ppm on a 90% dry matter basis), to provide 60 to 90 mg zilpaterol hydrochloride per head per day.

Component feed: Feed continuously to cattle during the last 20 to 40 days on feed, in a feed containing no less than 6.8 g/ton and no more than 24 g/ton zilpaterol (90% dry matter basis), to provide 60 mg zilpaterol hydrochloride per head per day.

K. Route of Administration

Oral in feed

L. Species/Class

Cattle fed in confinement for slaughter

M. Indication

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.

N. Effect of Supplement

This supplement provides for the replacement of the previously approved determinative and confirmatory procedures for cattle liver with new LC-MS/MS methods, addition of determinative and confirmatory procedures for cattle muscle, and inclusion of a tolerance of 10 ppb for zilpaterol in cattle muscle.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage range for zilpaterol hydrochloride. The Freedom of Information (FOI) Summary for the original approval of NADA 141-258 dated August 10, 2006, contains dosage characterization information for cattle fed in confinement for slaughter when zilpaterol hydrochloride is administered in a total mixed ration (complete feed) during the last 20 to 40 days on feed. The FOI summary for the supplemental approval of NADA 141-258 dated October 30, 2014, contains dosage characterization information for cattle fed in confinement for slaughter when zilpaterol hydrochloride is administered as a component feed during the last 20-40 days on feed.

B. Substantial Evidence

CVM did not require effectiveness studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-258 dated August 10, 2006, and a supplemental approval dated October 30, 2014, contain summaries of studies that demonstrate effectiveness of the drug for cattle fed in confinement for slaughter when zilpaterol hydrochloride is administered in a total mixed ration (complete feed) and by component feeding during the last 20 to 40 days on feed.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-258 dated August 10, 2006, contains a summary of a target animal safety study for beef cattle fed 0, 10.2 or 68 g/ton zilpaterol hydrochloride in a complete diet during a 40-day feeding period, and animal health observations in cattle fed in confinement for slaughter the intended range of doses of 60-90 mg per head per day in a complete diet (6.8 g/ton) during the effectiveness studies. The FOI Summary for a supplemental approval dated October 30, 2014, provided animal health observations from the effectiveness studies and additional animal health information for component feeding of zilpaterol hydrochloride.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

The feeding of zilpaterol hydrochloride to beef cattle (60 to 90 mg/head/day) in Type C Medicated feeds is not thought or been reported to impact antimicrobial resistance among bacteria of public health concern in or on treated animals. The Agency determined that an assessment of the microbial food safety (antimicrobial resistance) associated with this use of zilpaterol hydrochloride in beef cattle was not necessary at this time.

B. Impact of Residues on Human Intestinal Flora

Residues and metabolites of zilpaterol hydrochloride in or on the edible tissues of treated beef cattle are not thought or been reported to impact the intestinal flora of human consumers. The Agency determined that an assessment of the impact of residues or metabolites of zilpaterol hydrochloride in the edible tissues of treated beef cattle on human intestinal flora was not necessary at this time.

C. Toxicology

Reassessment of the toxicological acceptable daily intake (ADI) was not needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-258, dated August 10, 2006, contains a summary of all toxicology studies and information.

D. Establishment of the Final Acceptable Daily Intake (ADI)

The final ADI for total residues of zilpaterol hydrochloride is the toxicological ADI of 0.083 µg/kg BW/day derived from a study in asthmatic humans (Study No. FF/88/173/05). The codified ADI is listed under 21 § CFR 556.765.

E. Safe Concentrations for Total Residues in Edible Tissues

The safe concentrations for total residues of zilpaterol hydrochloride in each edible tissue of cattle are 20 ppb for muscle, 50 ppb for liver, 100 ppb for kidney, and 100 ppb for fat. Because the residue method measures zilpaterol free base, rather than zilpaterol hydrochloride residues, the safe concentrations for total residues of zilpaterol free base residues in each edible tissue of cattle are 18 ppb for muscle, 44 ppb for liver, 88 ppb for kidney, and 88 ppb for fat.

F. Residue Chemistry

1. Summary of Residue Chemistry Studies

The FOI Summary for the original approval of NADA 141-258, dated August 10, 2006, contains a summary of all residue chemistry studies and information, with the exception of the new LC-MS/MS analytical method validation Study No. S11213-00 described below in section G.

2. Target Tissue and Marker Residue

No reassessments of target tissue and marker residue were needed for this approval. The marker residue for zilpaterol hydrochloride is zilpaterol free

base and the target tissue in cattle is liver (NADA 141-258 dated August 10, 2006).

3. Tolerances

The tolerance for zilpaterol free base is 12 ppb in cattle liver and 10 ppb in cattle muscle (21 CFR 556.765).

4. Withdrawal Period

Based on the data summarized in NADA 141-258, a 3-day withdrawal is assigned for cattle fed in confinement before slaughter treated with zilpaterol via complete feed at 60 to 90 mg zilpaterol/head/day continuously during the last 20 to 40 days on feed or component feed at 60 mg zilpaterol/head/day continuously during the last 20 to 40 days on feed.

G. Analytical Method for Residues

1. Description of Analytical Method

The determinative analytical procedure utilizes ground bovine tissue containing zilpaterol (ZIL) fortified with the deuterated internal standard (ZIL-d7) and extracted with methanol. After clean-up with the mixed cation exchange solid phase extraction fixed well plate, the extract is analyzed by LC-MS/MS. Quantitation is based on the m/z 262 to m/z 185 and m/z 269 to m/z 185 transitions for zilpaterol (ZIL) and ZIL-d7, respectively. The method is capable of measuring the marker residue, zilpaterol free base, in cattle liver at concentrations from 2.0 to 30 ppb and in cattle muscle from 2.0 to 24 ppb. The procedure successfully completed a sponsor monitored multi-laboratory method trial.

The sample extraction, preparation, and LC-MS/MS analysis for the confirmatory procedure are identical to those for the determinative procedure. Zilpaterol-specific ion transitions (m/z 262 to m/z 185, m/z 262 to m/z 202, and m/z 262 to m/z 130) are monitored to obtain ion ratios, signal to noise ratios, and retention times that meet the required acceptability criteria.

2. Availability of the Method

The method is on file with the Center for Veterinary Medicine, Food and Drug Administration, 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 beta₂-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.”

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 demonstrate that ZILMAX, when used according to the label, is safe and effective 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. Additionally, data demonstrate that residues in food products derived from species treated with ZILMAX 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

ZILMAX, as approved in our approval letter, does not qualify for marketing exclusivity under section 512(c)(2)(F) of the FD&C 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.