Date of Approval: July 19, 2017

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-336

Aivlosin®

62.5% (w/w) tylvalosin as tylvalosin tartrate

Water Soluble Granules

Swine

Control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Pasteurella multocida*, and *Streptococcus suis* in groups of swine in buildings experiencing an outbreak of SRD.

Sponsored by:

ECO LLC

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I. GENERAL INFORMATION

A. File Number

NADA 141-336

B. Sponsor

ECO LLC
344 Nassau St.
Princeton, NJ 08540

Drug Labeler Code: 066916

C. Proprietary Name

Aivlosin®

D. Product Established Name

62.5% (w/w) tylvalosin as tylvalosin tartrate

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Water soluble granules

G. Amount of Active Ingredient

62.5% (w/w) tylvalosin as tylvalosin tartrate

H. How Supplied

Aivlosin® Water Soluble Granules is packaged in 40 g, 160 g, and 400 g sachets supplied in boxes holding 20, 10, and 5 sachets respectively

I. Dispensing Status

Rx

J. Dosage Regimen

50 ppm tylvalosin continuously in drinking water for five (5) consecutive days

K. Route of Administration

Oral via drinking water

L. Species/Class

Swine

M. Indication

Control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Pasteurella multocida*, and *Streptococcus suis* in groups of swine in buildings experiencing an outbreak of SRD.

N. Effect of Supplement

This supplement provides for the addition of an indication for the control of SRD.

II. EFFECTIVENESS

A. Dosage Characterization

Aivlosin® (62.5% w/w tylvalosin as tylvalosin tartrate) Water Soluble Granules is currently approved under NADA 141-336 for the control of porcine proliferative enteropathy (PPE) associated with *Lawsonia intracellularis* infection in groups of swine in buildings experiencing an outbreak of PPE. The approved dosage is 50 ppm tylvalosin in drinking water for 5 consecutive days. ECO Animal Health LLC conducted a pilot study to evaluate the effectiveness of Aivlosin® for the control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica, Haemophilus parasuis, Pasteurella multocida,* and *Streptococcus suis* using the same dosage regimen.

A total of 144 pigs were assigned to pens (six pigs per pen), and pens were assigned to treatment (0 ppm or 50 ppm tylvalosin per day, 12 pens per treatment) using a randomized complete block design. Treatment was initiated on study Day 0 when 17% of the study candidate population was deemed to be "clinically affected" by SRD. The clinically affected pigs were randomly assigned first, followed by the remaining pigs. The treatment period ended on Day 5 and the pigs were necropsied on Day 7.

The primary variable was treatment success, which was evaluated using a clinical scoring system. The proportion of pigs meeting the success criteria on Day 7 was significantly greater (P = 0.0356) in the 50 ppm treated group than in the 0 ppm treated group. These results support the use of the same dosage regimen for SRD that is currently approved for PPE.

B. Substantial Evidence

1. Clinical Field Study

   Title: "Determination of the effectiveness of Aivlosin® Water Soluble Granules (62.5% w/w tylvalosin) in drinking water of pigs for the control of swine respiratory disease (SRD)". Study No. EFF.US.130298.

   Study Dates: December 2014 to October 2016.

   Study Locations:

   Oakland, Nebraska
   Saskatoon, Saskatchewan, Canada
   Ames, Iowa
   Rice, Minnesota

Study Design:

Objective: To determine the effectiveness of 50 ppm tylvalosin administered in drinking water for 5 consecutive days for the control of SRD associated with *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Pasteurella multocida*, and *Streptococcus suis* in groups of swine in buildings experiencing an outbreak of SRD. The study was conducted in accordance with Guidance for Industry (GFI) #85 "Good Clinical Practice (GCP)" (VICH GL9).

Study Animals: A total of 980 commercial crossbred male and female pigs, weighing between 5 kg and 46.2 kg, and approximately 4 to 11 weeks of age were enrolled across four sites.

Experimental Design: Candidate pigs arrived at the study sites between 2 and 28 days prior to enrollment (Day 0). At each site, Day 0 was defined when at least 15% (cumulative) of the candidate pigs were classified as "clinically affected" (defined under Measurements and Observations below). On Day 0, the clinically affected pigs were randomly assigned to pens first, followed by the remaining pigs, until there were 14 pigs assigned to each pen. Pens were randomly allocated within location blocks to treatment with tylvalosin or non-medicated water. Each site enrolled 16 to 18 pens. Assigned treatments were administered from Day 0 through Day 5. All pigs were scored for treatment success/treatment failure on Day 7 (see description in Results below). Pigs were randomly assigned to euthanasia and necropsy on Day 7 or Day 8.

Drug Administration: The test article was Aivlosin® (62.5% w/w tylvalosin as tylvalosin tartrate) Water Soluble Granules administered in drinking water at 50 ppm tylvalosin. Non-medicated water was used as the control article. Treatment began on Day 0 and pigs were administered the test article or control article *ad libitum* for 5 consecutive days. Medicated water was prepared fresh daily. Across the study, 490 pigs were enrolled in the tylvalosin group and 490 pigs were enrolled in the control group.

Measurements and Observations: During the pre-treatment period (arrival to Day 0), candidate pigs were observed twice daily for signs of SRD and general health status. Candidate pigs were considered clinically affected with SRD if they had a respiratory score ≥2 (on a scale from 0 [normal] to 3 [severe]), and a depression score ≥2 (on a scale from 0 [normal] to 3 [severe]), and a rectal temperature of ≥104.0 °F. On Day 0 to Day 7 or Day 8 (depending on necropsy day) respiratory scores, depression scores, and rectal temperatures as well as general health were recorded once daily for all pigs. All pigs were evaluated on Day 7 for treatment success/treatment failure. Body weight, feed consumption, and water consumption were measured, but were not used in the determination of effectiveness. Pigs were euthanized and necropsied on Day 7 or Day 8 for evaluation of lung lesions and for collection of lung tissue samples for the culture of *B*. *bronchiseptica*, *H*. *parasuis*, *P*. *multocida*, and *S. suis*.

Statistical Methods: The study used a randomized complete block design with pen as the experimental unit. Pens were blocked (paired) by barn location. The primary variable for determining effectiveness was treatment success. Each pig was classified as a success or failure on Day 7. Treatment success was defined as a pig that had a respiratory score = 0 or 1, and a

depression score = 0 or 1, and a rectal temperature <104.0 °F. Pigs that did not meet the success criteria were considered treatment failures. Pigs removed from the study or found dead up to Day 7 that had SRD lung lesions at necropsy were considered treatment failures. Pigs removed from the study due to severe respiratory distress up to Day 7 were also considered treatment failures.

Analysis of treatment success, pooled across all four sites, was conducted using a generalized linear mixed model with the binomial distribution for the response pen proportion of successes and a logit link function. Treatment was a fixed effect and site, treatment by site interaction, block nested within site, and block by treatment interaction nested within site were random effects. A two-sided comparison of tylvalosin versus control was conducted at a 0.05 significance level. A Kenward-Rogers adjustment was used to determine the denominator degrees of freedom for the statistical comparison.

Results: Two pigs were removed from the effectiveness analysis. One was found dead and necropsy revealed no pathological lesions. A second pig was found dead and its data was excluded due to a recording error. A statistically significant difference (p=0.0353) was observed between the success rate (based on inverse links (percentage) of least squares means on logit scale) for the treated group (48.5%) compared to the control group (41.6%).

A total of 107 isolates of *B. bronchiseptica*, 166 isolates *of H. parasuis*, 124 isolates *of P. multocida,* and 115 isolates of *S. suis* were identified in study pigs.

Adverse Reactions: There were no adverse reactions attributed to the test article in the study. One pig in the tylvalosin-treated group was found dead on Day 3. The definitive cause of death was not determined, but was considered unlikely to be related to test article administration.

Conclusions: This study demonstrated that Aivlosin® Water Soluble Granules administered at 50 ppm tylvalosin in drinking water for 5 consecutive days is effective for the control of SRD associated with *B. bronchiseptica*, *H. parasuis*, *P. multocida,* and *S. suis.*

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 141-336 dated July 6, 2012, contains a summary of a target animal safety study for tylvalosin in swine when administered at 50 ppm in drinking water for five consecutive days.

IV. HUMAN FOOD SAFETY

A. Antimicrobial Resistance

Microbial food safety (antimicrobial resistance) information for tylvalosin was evaluated using an updated hazard characterization and qualitative risk assessment procedure employed for the original approval. The dosage regimen evaluated was 50 ppm tylvalosin in the drinking water of swine for 5 consecutive days. The indication associated with this dosage regimen is, "for the control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica, Haemophilus parasuis, Pasteurella multocida,* and *Streptococcus suis,* in groups of swine in buildings experiencing an outbreak of SRD."

The qualitative risk assessment procedure involved conducting 1) a *release assessment* to describe the probability that tylvalosin and its use in swine will result in the emergence of macrolide-resistant bacteria or macrolide resistance determinants in treated swine under proposed conditions of use; 2) an *exposure assessment* to describe the likelihood of human exposure to macrolide-resistant bacteria or macrolide resistance determinants through consumption of edible products from treated swine; and 3) a *consequence assessment* to describe potential human health consequences arising from exposure to macrolide-resistant bacteria or macrolide resistance determinants by considering the human medical importance of macrolides used in the treatment of human infectious diseases.

It was determined that the risk of development of transferable macrolide resistance elements from this use of tylvalosin in swine is low. This decision is supported by data from animal studies that have shown tylvalosin administration does not cause changes in tylvalosin susceptibility within *Campylobacter* spp. Also, changes have not been demonstrated among *Enterococcus* spp., and, due to pre-existing macrolide resistance, this is of less significance.

Macrolides are ranked as critically important drugs in human medicine; therefore, by default, the *consequence assessment* yields a high ranking. The overall risk estimation is derived to be high. The conditions of use and labeled restriction of use for only groups of swine in buildings experiencing an outbreak of SRD are compatible with the Agency's risk management strategies associated with a product having an overall risk estimation of high.

Decision Statement

The Agency's integration of the degree of risk derived from the three individual assessments (medium, medium, and high) gave an overall risk estimation of high. The conditions of use are compatible with the Agency's risk management strategies for a Category 1 drug, corresponding to the estimated high risk. Further, post-approval monitoring may be achieved from the testing of surrogate antimicrobials (erythromycin and azithromycin) in the current National Antimicrobial Resistance Monitoring System program.

B. Impact of Residues on Human Intestinal Flora

CVM did not require additional information or data on the impact of tylvalosin residues on human intestinal flora for this supplemental approval. The FOI Summary for the original Aivlosin® Water Soluble Granules approval under NADA

141-336, dated July 6, 2012, contains a summary of all information used to assess the impact of tylvalosin residues on human intestinal flora, and to determine a tylvalosin microbiological acceptable daily intake (ADI) of 2.86 mg/person/day, or 47.7 µg/kg bw/day.

C. Toxicology

Reassessment of the toxicological ADI was not needed for this supplemental approval. The FOI Summary for the original approval of NADA 141-336, dated July 6, 2012, contains a summary of all toxicology studies and information.

D. Establishment of the Final ADI

Because the microbiological ADI (47.7 µg/kg bw/day) is lower than the toxicological ADI (180 µg/kg bw/day) derived from a two-generation reproductive toxicity study in rats, the microbiological ADI is the final ADI for total tylvalosin residues. The codified ADI is listed under 21 CFR §556.748.

E. Safe Concentrations for Total Residues in Edible Tissues (and Injection Sites, if applicable)

The safe concentrations for total tylvalosin residues in the edible tissues of swine are 2.9 ppm for muscle, 8.6 ppm for liver, 17.3 ppm for kidney, and 17.3 ppm for fat.

F. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-336, dated July 6, 2012, contains a summary of residue chemistry studies for swine.

G. Analytical Method for Residues

A regulatory analytical method for monitoring tylvalosin residues in swine is not required.

V. USER SAFETY

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

WARNINGS:
NOT FOR USE IN HUMANS.
KEEP OUT OF REACH OF CHILDREN.

May cause skin irritation. Tylvalosin tartrate has been shown to cause hypersensitivity reactions in laboratory animals.

People with known hypersensitivity to tylvalosin tartrate should avoid contact with this product. In case of accidental ingestion, seek medical advice.

When handling Aivlosin® Water Soluble Granules and preparing medicated drinking water, avoid direct contact with the eyes and skin. Wear a dust mask, coveralls and impervious gloves when mixing and handling this product. Eye

protection is recommended. In case of accidental eye exposure, wash eyes immediately with water and seek medical attention. If wearing contact lenses, immediately rinse the eyes first, then remove contact lenses and continue to rinse the eyes thoroughly and seek medical attention. Avoid eating, chewing gum and smoking during handling. Wash contaminated skin.

The Safety Data Sheet contains more detailed occupational safety information.

To report adverse effects in users, to obtain more information or obtain a Safety Data Sheet, call the ASPCA Animal Product Safety Service at 1-800-345-4735.

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 (FD&C Act) and 21 CFR part 514. The data demonstrate that Aivlosin®, when used according to the label, is safe and effective for the control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Pasteurella multocida*, and *Streptococcus suis* in groups of swine in buildings experiencing an outbreak of SRD. Additionally, data demonstrate that residues in food products derived from species treated with Aivlosin® will not represent a public health concern when the product is used according to the label.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). The decision to restrict this drug to use by or upon the order of a licensed veterinarian was based on the following factors: (a) adequate directions cannot be written to enable lay persons to appropriately and safely use this product and (b) restricting this drug to use by or upon the order of a licensed veterinarian should help prevent indiscriminate use, which could result in violative tissue residues.

B. Exclusivity

This supplemental approval for Aivlosin® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Pasteurella multocida*, and *Streptococcus suis* in groups of swine in buildings experiencing an outbreak of SRD.

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.