Date of Approval: January 7, 2021

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-336

Aivlosin®

62.5% w/w tylvalosin as tylvalosin tartrate

Granules for Solution

Swine Intended for Slaughter

This supplement provides for the addition of *Mycoplasma hyopneumoniae* to the list of pathogens in the indication for control of swine respiratory disease.

Sponsored by:

ECO LLC

Executive Summary

Aivlosin® (62.5% w/w tylvalosin as tylvalosin tartrate) is approved for control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica*, *Haemophilus parasuis*, *Pasteurella multocida*, *Streptococcus suis*, and *Mycoplasma hyopneumoniae* in groups of swine intended for slaughter in buildings experiencing an outbreak of SRD. The drug is already approved for control of SRD associated with the first four above-listed pathogens. This supplemental approval adds *Mycoplasma hyopneumoniae* to the list of pathogens. Aivlosin® is an antimicrobial drug that is administered in the pigs' drinking water.

Proprietary Name	Established Name	Application Type and Number	Sponsor
Aivlosin®	62.5% w/w tylvalosin as tylvalosin tartrate	New Animal Drug Application (NADA) 141-336	ECO LLC

Safety and Effectiveness
The sponsor conducted an experimentally-induced infection model study to show that Aivlosin® has an effect against *M. hyopneumoniae*. Commercial cross-bred male and female pigs were sourced from litters that were serologically negative for *M. hyopneumoniae*. All pigs were administered inoculum containing *M. hyopneumoniae* endotracheally on Day 0 and Day 1. Treatment began when four of eight randomly selected non-treatment pigs were confirmed by necropsy to have lung lesions consistent with *M. hyopneumoniae* infection.

Pigs in the treatment group were administered Aivlosin® in their drinking water for 5 consecutive days. Pigs in the control group were given non-medicated water for the same period. Compared to the control group, the treatment group had a significant reduction in lung lesion scores. Scores were calculated based on the percentage of lesions in each lung lobe and the approximate volume of each lobe compared to the entire lung volume. No adverse reactions were seen in the study.

For a previous supplemental approval of Aivlosin®, dated July 19, 2017, the sponsor had conducted a multi-site field study to show that the drug was effective at controlling SRD. The sponsor confirmed the presence of *M. hyopneumoniae* in lung samples from pigs in that field study using a quantitative polymerase chain reaction (PCR) test. A sufficient number of samples were PCR-positive for *M. hyopneumoniae*. In addition, a sufficient number of *M. hyopneumoniae* isolates were cultured from the study animals, demonstrating that *M. hyopneumoniae* contributed to SRD in the pigs. The data from this previous study showed that Aivlosin® is effective for control of SRD associated with *M. hyopneumoniae*.

The Freedom of Information (FOI) Summary for the original approval of Aivlosin®, dated July 6, 2012, contains a summary of target animal safety studies.

Human Food Safety
The FOI Summaries for the original approval of Aivlosin®, dated July 6, 2012, and a supplemental approval, dated July 19, 2017, contain summaries of the information used to assess human food safety. There is no change to the previously established withdrawal period; it remains zero-day.

User Safety
The labeling for Aivlosin® describes the precautions people should take when handling the drug and preparing the medicated drinking water.

Conclusions
Based on the data submitted by the sponsor for the approval of Aivlosin®, FDA determined that the drug is safe and effective for control of SRD associated with *M. hyopneumoniae* in groups of swine intended for slaughter in buildings experiencing an outbreak of SRD, when used according to the label.

Table of Contents

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. Drug Product Established Name

62.5% w/w tylvalosin as tylvalosin tartrate

E. Pharmacological Category

Antimicrobial

F. Dosage Form

Granules for solution

G. Amount of Active Ingredient

62.5% w/w tylvalosin as tylvalosin tartrate

H. How Supplied

160 g and 400 g sachets

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

50 ppm tylvalosin continuously in drinking water for 5 consecutive days

K. Route of Administration

Oral

L. Species/Class

Swine intended for slaughter

M. Indication

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

N. Effect of Supplement

This supplement provides for the addition of *Mycoplasma hyopneumoniae* to the list of pathogens in the indication for control of swine respiratory disease.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage regimen. The Freedom of Information (FOI) Summary for a supplemental approval dated July 19, 2017, contains dosage characterization information for swine when administered at 50 ppm tylvalosin in drinking water for 5 consecutive days.

B. Substantial Evidence

The effectiveness of tylvalosin for control of swine respiratory disease (SRD) associated with *Mycoplasma hyopneumoniae* was demonstrated using 1) an experimentally-induced infection model study to demonstrate that the drug has an effect against *M. hyopneumoniae*, and 2) the results and *M. hyopneumoniae* prevalence data from the SRD field study (Study EFF.US.130298) previously conducted for the July 19, 2017, supplemental approval of tylvalosin to demonstrate that the drug is effective for the labeled indication.

1. Experimentally-Induced Infection Model Study

   Title: Determination of the effectiveness of Aivlosin® Water Soluble Granules (62.5% w/w tylvalosin) in drinking water of pigs for control of swine respiratory disease (SRD) associated with *Mycoplasma hyopneumoniae* in a model challenge study. (Study No. EFF.US.180616)

   Study Dates: January 2020 to July 2020

   Study Location: Ames, Iowa

   Study Design:

   Objective: To demonstrate that 50 ppm tylvalosin administered in drinking water for 5 consecutive days has an effect against *M. hyopneumoniae*.

   Study Animals: Healthy commercial cross-bred castrated male and female pigs were sourced from litters that were serologically negative for *M. hyopneumoniae.* Two hundred and forty pigs that weighed between 6.9 and 10.5 kg and were approximately 5 weeks of age on Day -8, were

endotracheally challenged with an inoculum containing a representative isolate of *M. hyopneumoniae* on 2 consecutive days (Day 0 and Day 1). One hundred ninety-two (192) pigs were included in the two treatment groups as further described below.

Experimental Design: This study was a randomized, masked, block design with two treatment groups. The study was conducted in accordance with Guidance for Industry (GFI) #85 "Good Clinical Practice (GCP)" (VICH GL9).

A total of 240 pigs were assigned to 16 weight blocks and randomized to 40 pens (16 tylvalosin-treated, 16 non-medicated control, and 8 non-treatment [NTX]) containing 6 pigs in each pen. Treatment began when four of eight randomly selected NTX pigs (one from each NTX pen) were confirmed by necropsy to have a minimum 3% proportional gross pneumonic lung lesions consistent with *M. hyopneumoniae* infection. This occurred on Day 5, which was defined as day of medication (DM). Assigned treatments were administered for 5 consecutive 24-hour periods starting on Day DM. All tylvalosin-treated and non-medicated control group pigs were euthanized on Day DM+10 for lung lesion scoring. The treatment groups are shown in Table II.B.1.

Table II.B.1. Treatment Groups.

Treatment Group	Number of Pens	Number of Pigs
50 ppm tylvalosin	16	96
0 ppm tylvalosin	16	96

Challenge Administration: Pigs received 10 mL of *M. hyopneumoniae* inoculum by endotracheal administration on Day 0 and Day 1. The *M. hyopneumoniae* challenge strain used in the study was shown to be representative of current North American strains.

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 DM and pigs were administered the test article or control article *ad libitum* for 5 consecutive days. Medicated water was prepared fresh daily.

Measurements and Observations: During the acclimation period (Day -8) through the end of study (Day DM+10), pigs were observed twice daily for general health. Respiration and depression were scored once daily from Day -8 through Day DM+10 to assess for secondary respiratory infection. Coughing was scored once daily from Day -8 through Day DM+10. Body weight, feed consumption, and water consumption were measured at specified intervals from Day -8 through Day DM+10. Beginning on Day 5, pre-selected sentinel NTX pigs were euthanized and lung lesions scored to determine the start of treatment. On Day DM+10, all remaining pigs in the tylvalosin-treated and non-medicated control were euthanized and lung lesions were scored.

Lung lesion score was calculated for each pig as the sum of the lung lesion percentage observed in each lobe multiplied by the approximate volume that each lobe contributes to the entire lung volume. The proportional volume of each lobe relative to the total lung volume was calculated as: left cranial lobe – 10%, left middle lobe – 10%, left caudal lobe – 25%, right cranial lobe – 10%, right middle lobe – 10%, right caudal lobe – 25%, and accessory lobe – 10%.

Statistical Methods: The primary variable for determining effectiveness was pen mean lung lesion score for pigs on Day DM+10. The experimental unit of analysis was pen. The primary variable was analyzed with a linear mixed model with treatment as a fixed effect and weight block as a random effect. Results of a two-sided t-test were used to assess significance.

Results: The analysis included 95 pigs in the tylvalosin-treated group and 93 pigs in the non-medicated control group. One pig in the tylvalosin-treated group and three pigs in the non-medicated control group were excluded from the analysis due to post-mortem evidence of secondary respiratory infection. Lung lesion scores on Day DM+10 were significantly reduced in the tylvalosin-treated group compared with the non-medicated control group. The estimated mean lung lesion scores were 5.1% for the tylvalosin group and 10.9% for the control group ($P<0.0001$).

Adverse Reactions: There were no adverse reactions in the study.

Conclusions: This study demonstrates that Aivlosin® Water Soluble Granules administered to swine at 50 ppm in drinking water for 5 consecutive days has an effect against *M. hyopneumoniae*.

2. SRD Field Study EFF.US.130298

A multi-site field study (Study EFF.US.130298) was previously conducted to demonstrate the effectiveness of Aivlosin® Water Soluble Granules administered to swine at 50 ppm in drinking water for 5 consecutive days for the control of SRD. This study was summarized in the Freedom of Information (FOI) Summary for the supplemental approval of NADA 141-336 dated July 19, 2017.

To confirm the presence of *M. hyopneumoniae*, lung samples from pigs in study EFF.US.130298 were screened with a quantitative polymerase chain reaction (qPCR) test. Of the 976 samples tested, 185 (19%) were PCR positive for *M. hyopneumoniae*. In addition, a sufficient number of *M. hyopneumoniae* isolates were successfully cultured from the study animals to demonstrate that *M. hyopneumoniae* was contributing to SRD in the study animals.

In conjunction with the experimentally-induced infection model study described above (Study EFF.US.180616), the data from this multicentric study demonstrates that tylvalosin is effective for control of SRD associated with *M. hyopneumoniae*.

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 target animal safety studies for tylvalosin in swine when administered at 50 ppm in drinking water for 5 consecutive days.

IV. HUMAN FOOD SAFETY

A. Microbial Food Safety

CVM did not require additional information for microbial food safety (antimicrobial resistance) for this supplemental approval. The FOI Summaries for the original approval of NADA 141-336, dated July 6, 2012, and a supplemental approval, dated July 19, 2017, contain summaries of all information used to assess microbial food safety (antimicrobial resistance) risks.

B. Toxicology

Reassessment of the toxicological acceptable daily intake (ADI) or the microbiological 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.

C. Establishment of the Final ADI

The final ADI is the microbiological ADI of 47.7 µg/kg body weight/day for total residues of tylvalosin. The codified ADI is listed under 21 CFR §556.748.

D. Safe Concentrations for Total Residues in Edible Tissues

Reassessment of the safe concentrations for total residues of tylvalosin was not needed for this approval. The safe concentrations for total residues of tylvalosin in individual 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.

E. Residue Chemistry

CVM did not require residue chemistry studies for this supplemental approval. The FOI Summaries for the original approval of NADA 141-336, dated July 6, 2012, and a supplemental approval, dated July 19, 2017, contain summaries of residue chemistry studies for swine.

This supplement does not result in any changes to the previously established withdrawal period. The withdrawal period remains zero-day. Refer to the FOI Summary for the original approval of NADA 141-336, dated July 6, 2012.

F. Analytical Method for Residues

Because a tolerance for tylvalosin in swine is not required, an official analytical method for monitoring tylvalosin residues in swine is not necessary.

V. USER SAFETY

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

USER SAFETY 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 Pharmgate Animal Health LLC. at 1-833-531-0114.

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 control of SRD associated with *M. hyopneumoniae* in groups of swine intended for slaughter 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 order of a licensed veterinarian (Rx marketing status). This decision was based on the following factors: adequate directions cannot be written to enable lay persons to appropriately diagnose and subsequently use this drug product, and restricting this drug product to use by or on the order of a licensed veterinarian is critical for assuring the safe and appropriate use of this drug product in animals in order to mitigate the potential for the development of bacterial resistance to antimicrobial drugs.

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 *Mycoplasma hyopneumoniae* in groups of swine intended for slaughter 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 Green Book Reports in the Animal Drugs @ FDA database.