PRODUCT PROFILE

AIVLOSIN®

(62.5% w/w Tylvalosin as Tylvalosin Tartrate)

Water Soluble Granules

Product Description

- Water-soluble antibiotic for oral use by administration in the drinking water
- Contains 62.5% w/w tylvalosin (as tylvalosin tartrate), a novel macrolide antibiotic
- Veterinary prescription; for use in drinking water of swine

Formulation

- Water-soluble granules; suitable for both drinking water and stock solutions.

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.
- Control of porcine proliferative enteropathy (PPE) associated with *Lawsonia intracellularis* infection in groups of swine intended for slaughter in buildings experiencing an outbreak of PPE.

Packaging

- Cartons containing either 10 x 160-g or 5 x 400-g sachets.

Dosage / Administration

- May be mixed directly into the drinking water system or first mixed as a stock solution (e.g., for automatic water proportioners).
- Prepare a fresh batch of medicated stock solution or medicated drinking water daily.
- Prepare drinking water medicated with 50 ppm tylvalosin daily. Administer continuously for 5 consecutive days.
- Based on a theoretical daily water consumption rate of 10% of body weight, 50 ppm tylvalosin in drinking water provides the target dose rate of 5 mg tylvalosin/kg body weight per day.

Precautions

- **Do not mix or administer medicated water using equipment made of galvanized metal.** Galvanized metal adversely affects the stability of tylvalosin in water and may reduce the effectiveness of the product.
- **Not for use in male swine intended for breeding.**

Withdrawal Period

- 0-days (no withdrawal needed).

Storage

- Store at or below 25°C (77°F).
- 2-year shelf-life for unopened sachets.

Key Features

- Quick-acting, potent macrolide antibiotic that is not used in human health.
- Broadest label indication for SRD control now that it is approved to control *Mycoplasma hyopneumoniae*.
- Accumulates rapidly in lung and small intestinal tissue after treatment.[1]
- Enters into white blood cells within two hours (*in vitro*).[2]
- No withdrawal period (0 days).
- Wide safety margin; compatible when treating pigs with ionophores.
- Palatable, non-clogging formulation.
- Supports responsible use of antibiotics through fewer milligrams of antibiotic per use per pig.

The labeling contains complete use information, including cautions and warnings. Always read, understand and follow the labeling and use directions. See the back page for use directions and additional information.

Pharmgate ANIMAL HEALTH

Important Safety Information: Available under prescription only. AIVLOSIN® is indicated for control of porcine proliferative enteropathy (PPE) associated with *Lawsonia intracellularis* infection in groups of swine intended for slaughter in buildings experiencing an outbreak of PPE. 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 and female swine intended for breeding in buildings experiencing an outbreak of SRD. For use only in drinking water of pigs. Not for use in male swine intended for breeding. People with known hypersensitivity to tylvalosin tartrate should avoid contact with this product. When used in accordance with label directions, no withdrawal period is required before slaughter for human consumption.

Approved by FDA
under NADA # 141-336

AIVLOSIN®

(62.5% w/w Tylvalosin as Tylvalosin Tartrate)

Water Soluble Granules

For use only in the drinking water of swine intended for slaughter and female swine intended for breeding.
Not for use in male swine intended for breeding.

CAUTION:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

PRODUCT DESCRIPTION:
Aivlosin® (tylvalosin tartrate) Water Soluble Granules is a water soluble granular powder for oral use by administration in the drinking water. Each gram of Aivlosin® Water Soluble Granules contains 0.625 grams of tylvalosin as tylvalosin tartrate.

ANTIBIOTIC CLASSIFICATION:
Tylvalosin, the active ingredient in Aivlosin® Water Soluble Granules, is a macrolide antibiotic.

INDICATIONS:
Control of porcine proliferative enteropathy (PPE) associated with *Lawsonia intracellularis* infection in groups of swine intended for slaughter and female swine intended for breeding in buildings experiencing an outbreak of PPE. Not for use in male swine intended for breeding.
Control of swine respiratory disease (SRD) associated with B*ordetella bronchiseptica, Glaesserella (Haemophilus) parasuis, Pasteurella multocida, Streptococcus suis*, and *Mycoplasma hyopneumoniae* in groups of swine intended for slaughter and female swine intended for breeding in buildings experiencing an outbreak of SRD. Not for use in male swine intended for breeding.

DOSAGE AND ADMINISTRATION:
Prepare drinking water medicated with 50 parts per million tylvalosin as shown in the following table.

Aivlosin® Water Soluble Granules sachet size	160 grams	400 grams
Tylvalosin content of sachet (grams)	100	250
Recommended volume of stock solution (US gallons)	4	10
Volume of drinking water (US gallons)	528	1320
Final tylvalosin inclusion rate in drinking water	50 parts per million (ppm)	

Administer continuously in drinking water for five (5) consecutive days. Keep water supply equipment clean and in good operating condition. Clean water medication equipment before and after each use. Do not mix or administer tylvalosin medicated water using equipment made of galvanized metal. Galvanized metal adversely affects the stability of tylvalosin in water and may reduce the effectiveness of the product. Prepare a fresh batch of medicated stock solution or medicated drinking water daily.

MIXING DIRECTIONS:
Aivlosin® Water Soluble Granules may be mixed directly into the drinking water system or first mixed as a stock solution in a smaller amount of water, which is then added to the drinking water system, for example, using an automatic water proportioner.
Direct mixing: When mixing the product directly into the drinking water system, the contents of the sachet should be sprinkled onto the surface of the water and mixed slowly and thoroughly for at least 3 minutes. Prepare a fresh batch of medicated drinking water daily.
Stock solution: When preparing a stock solution, the recommended concentration is one 160 g sachet per four (4) US gallons or one 400 g sachet per 10 US gallons. Sprinkle sachet contents onto the surface of the water of the stock solution and mix slowly and thoroughly for at least 10 minutes. Use the stock solution for dilution into the drinking water system as soon as it is prepared. Add one (1) fluid ounce of this stock solution per 131 fluid ounces (1 US gallon, 3 fluid ounces) of drinking water to provide a final concentration of 50 ppm.
If using an automatic water proportioner, set the flow rate to add stock solution at a rate of 1 fluid ounce per 131 fluid ounces of drinking water (1:131). Prepare a fresh batch of medicated stock solution daily.

WARNINGS:
WITHDRAWAL PERIOD:
When used in accordance with label directions, no withdrawal period is required before slaughter for human consumption.

ANTIBACTERIAL WARNINGS:
Use of antibacterial drugs in the absence of a susceptible bacterial infection is unlikely to provide benefit to treated animals and may increase the development of drug-resistant pathogenic bacteria.

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.

PRECAUTIONS:
Not for use in males intended for breeding. The effects of tylvalosin on male swine reproductive performance have not been determined. Sows may exhibit decreased water consumption at the start of treatment. Ensure animals consume adequate amounts of water.
The safety and efficacy of this formulation in species other than swine have not been determined. To assure both food safety and responsible use in swine, concurrent use of tylvalosin in medicated drinking water and tylvalosin or another macrolide in medicated feed or by any other route of administration should be avoided.
Tylvalosin belongs to the macrolide antimicrobial drug class. Macrolides are ranked as a critically important drug in human medicine; therefore, minimizing the risk of development of antimicrobial resistance to this class of drug is very important. The following conditions of use and restrictions listed below are critical for the FDA's strategy of risk management associated with tylvalosin:
Always treat the fewest number of animals necessary to control a respiratory disease or PPE outbreak.
Do not immediately follow this macrolide treatment with another macrolide treatment via any route.
Prescriptions should not be renewed or refilled for animals already treated with one course of therapy with tylvalosin as directed (See Dosage and Administration above).

ADVERSE REACTIONS IN ANIMALS:
No adverse reactions related to the drug were observed during clinical or target animal safety trials.
To report suspected adverse reactions in animals, contact Pharmgate Animal Health LLC. at 1-833-531-0114.
For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or at www.fda.gov/reportanimalae.

CLINICAL PHARMACOLOGY:
Tylvalosin is a 16-membered semi-synthetic macrolide antibiotic. Macrolides are generally considered to be bacteriostatic agents that exert their antibiotic effect by reversibly binding to the 23S rRNA of the 50S ribosomal subunit, thereby inhibiting bacterial protein synthesis. The spectrum of activity of most available macrolides used in veterinary medicine is primarily against Gram-positive bacteria and Mycoplasmas, with some activity against Gram-negative fastidious bacteria. These compounds have no activity against the naturally resistant Enterobacteriaceae including *Escherichia coli* and *Salmonella* spp. Typically, macrolides achieve higher concentrations in tissues than in plasma.

EFFECTIVENESS:
Control of Porcine Proliferative Enteropathy (PPE):
A multi-location challenge model study was conducted to confirm the effectiveness of Aivlosin® (tylvalosin tartrate) Water Soluble Granules for the control of PPE associated with *Lawsonia intracellularis*. Pigs were challenged by intragastric gavage with a mucosal homogenate containing a North American isolate of *Lawsonia intracellularis* isolated in 2005 that induces representative disease in challenged pigs. When at least 15% of the study pigs were showing signs of infection based on abnormal fecal scores, pigs were provided water containing tylvalosin at an inclusion rate of 50 ppm for five consecutive days, or were provided non-medicated water. Effectiveness was evaluated using clinical scores (pig demeanor score, abdominal appearance score, and fecal score) and clinically-validated gross PPE lesion scores.
A conclusion of the effectiveness of 50 ppm tylvalosin for the control of PPE was determined based on a statistically significant ($p = 0.0103$) improvement in the clinically-validated gross PPE lesion scores in the 50 ppm tylvalosin-treated group compared to the non-medicated group.

Control of Swine Respiratory Disease (SRD):
The effectiveness of Aivlosin® Water Soluble Granules for the control of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica, Glaesserella (Haemophilus) parasuis, Pasteurella multocida, Streptococcus suis* and *Mycoplasma hyopneumoniae* was investigated in a natural field infection study conducted in the United States (three study sites) and Canada (one study site). Day 0 was defined when at least 15% of the candidate pigs were deemed clinically affected with SRD (moderate or severe respiratory score, moderate or severe depression score, and rectal temperature greater than or equal to 104.0 °F). On Day 0 a total of 980 pigs were enrolled and randomly assigned to a tylvalosin-treated group (50 ppm tylvalosin in drinking water for 5 consecutive days) or a non-medicated control group. Treatment success was evaluated on Day 7 and was defined as a pig with normal or mild respiratory score, normal or mild depression score, and rectal temperature less than 104.0 °F. The proportion of pigs meeting the definition of treatment success was numerically higher in the tylvalosin-treated group (48.5%) compared to the proportion of pigs meeting the definition of treatment success in the non-medicated control group (41.6%), and the observed difference was statistically significant ($p=0.0353$).
Additional data to demonstrate the effectiveness of Aivlosin® Water Soluble Granules for the control of SRD associated with *Mycoplasma hyopneumoniae* was obtained in an experimentally-induced infection model study. Two hundred and forty (240) commercial crossbred pigs were challenged endotracheally with a representative isolate of *M. hyopneumoniae*. One hundred and ninety-two (192) study pigs were randomly assigned to either a tylvalosin-treated group (50 ppm tylvalosin in drinking water for 5 consecutive days) or a nonmedicated control group. Treatment was started when at least four of eight randomly pre-selected sentinel pigs exhibited a minimum of 3% weighted gross lung lesions consistent with *M. hyopneumoniae* infection.
After a 5-day treatment period and a 5-day post-treatment period, study pigs were euthanized and necropsy performed to determine lung lesion scores. The analysis included 95 tylvalosin-treated pigs and 93 nonmedicated control pigs. There was a statistically significant ($P<0.0001$) improvement in pen mean *M. hyopneumoniae* lung lesion scores in the 50 ppm tylvalosin treated pigs (5.1%) compared to negative control (10.9%).

ANIMAL SAFETY:
Margin of safety: Aivlosin® Water Soluble Granules given orally in drinking water at 0, 50, 150 and 250 ppm tylvalosin (0, 1X, 3X and 5X the labeled dose, respectively) to 8 healthy pigs per treatment group over 15 days (3X the labeled duration) did not result in drug-induced clinical signs, gross pathologic lesions, histopathologic lesions or clinically-relevant clinical pathology abnormalities.
Sow Reproductive Safety: A reproductive safety study was conducted to evaluate the effect of Aivlosin® Water Soluble Granules administered to reproducing sows in drinking water. Fourteen multiparous sows (parity 2 to 9; average 4.6) were administered tylvalosin at a targeted inclusion rate of 150 ppm (3X the labeled inclusion rate) in drinking water. Medicated water was supplied ad libitum through a minimum of two estrous cycles, breeding, gestation, farrowing, lactation, and weaning (174 to 195 days total, depending on farrowing date). Piglets were weaned at 21 days post-farrowing. Fourteen multiparous sows (parity 2 to 9; average 3.7) were included in a non-treated control group. Conception rate, farrowing rate, total number of piglets born per sow, total number of piglets born alive per sow, percentage of mummified piglets, percentage of stillborn piglets, sex ratio, 1-day survival rate, 5-day survival rate, 21-day survival rate (weaning index), average live piglet weight per litter, and sow health were evaluated. Piglets were assessed for congenital abnormalities, body weight, and general health until weaning (21 days post-farrowing). Treatment with tylvalosin had no adverse effect on the evaluated variables (values reported are medians unless otherwise noted). There were no statistically significant differences in total number of piglets born per sow (control group: 24.0; treated group: 21.0), percentage of mummified piglets (control group: 0%, range 0-14.8%; treated group: 0%, range 0-9.1%), or percentage of stillborn piglets (control group: 7.0%, range 0-37.5%; treated group: 10.5%, range 0-35.7%). At a significance level of 0.10, the total number piglets born alive per sow was statistically different between the control group (20.0) and the treated group (16.0). However, the proportion of piglets born alive was not significantly different between the control group (89.2%) and the treated group (85.7%). Sows treated with tylvalosin had reduced water intake at the start of treatment. One sow refused to drink the tylvalosin treated water, became dehydrated, and was removed from the study. Otherwise, no negative health effects due to the transient reduction in water consumption were observed. There were no congenital abnormalities in piglets attributed to tylvalosin. Piglet body weights, survival rates, and general health were consistent with values reported in literature and indicated that tylvalosin did not have a negative effect on piglet growth or viability. The difference in sex ratio between groups was not clinically significant.

STORAGE:
Store in a cool dry place at or below 25°C (77°F).

HOW SUPPLIED: Aivlosin® Water Soluble Granules is packaged in 160- and 400-gram sachets supplied in boxes holding 10 and 5 sachets respectively.

LOT NO.: Printed on label.
EXPIRY: Printed on label.

Distributed in the USA by:
Pharmgate Animal Health LLC.
14040 Industrial Road,
Omaha, NE 68144.
www.pharmgate.com

For technical assistance or to obtain a Safety Data Sheet, call Pharmgate Animal Health LLC. at 1-800-380-6099

Aivlosin® is a registered trademark of ECO Animal Health Ltd.

Revised 12/2023 US04PIM-10

1. Data on file. ECO Animal Health.
2. Stuart et al. Pig J 2007; 60:26-35.

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