TECHNICAL Brief

Information for Animal Health Professionals

AIVLOSIN®

Rationale, Regulations, and Product Characteristics Supporting Judicious Antibiotic Use in Food Animals

Antibiotics and Resistance Concerns

The introduction of antibiotics in the 1940s revolutionized medicine, saving the lives of millions of people afflicted with a range of infectious diseases. Today, antibiotics remain as the primary tools for treating bacterial infectious diseases, and many modern medical practices (e.g., organ transplantation, chemotherapy, orthopedic surgery) would be classified as extremely high-risk procedures without the availability of antibiotics.

Soon after the introduction of antibiotic drugs from multiple chemical classes, antimicrobial resistance evolved in some bacteria and the efficacy of some drugs was reduced. The epidemiology of antibiotic resistance is complicated not only by the ability of bacteria to spread but also by the ability of genes responsible for resistance to transfer between bacteria. The spread of resistance has been attributed to people, animals, animal products, or environmental contamination, though much of the evidence for such transmission is only circumstantial. However, the spread of zoonotic bacteria (e.g., *Salmonella, Campylobacter*) from animals to man via the food supply is clearly beyond argument.

For many years the World Health Organization (WHO) has recognized antibiotic resistance as a significant and increasing international public health problem.[1] Because of antibiotic resistance, some pathogens that formerly responded to antibiotic treatment have become difficult and sometimes impossible to cure, thereby increasing morbidity, mortality, and societal costs. The development of resistance to different classes of antibiotics is steadily increasing among different types of bacteria, and in different ecological settings and environments. Thus, previously effective antibiotics are losing their power and health care is approaching a situation similar to the pre-antibiotic era. Today, people often remain seriously ill for longer periods or even die from infections with resistant organisms that defy treatment.

Because the ominous trend of rising antibiotic resistance is unabated and few new antibiotics are in the development pipeline, WHO believes that urgent, cooperative efforts are needed to preserve the effectiveness of antibiotics. WHO argues that health professionals must focus on:

- reducing unnecessary use of antibiotics and promoting their prudent use, to minimize development of resistance;
- interrupting the spread of antibiotic-resistant strains between individuals and communities through improved infection control and measures for prevention (including vaccinations), hygiene, and biosecurity.

PharmGate Animal Health

Food-Animal Antibiotics in Europe

Antibiotics were introduced into veterinary medicine in the 1950s and used for therapy, disease prevention (prophylaxis), and growth promotion. Initially, all available chemical classes of antibiotics could be used as antimicrobial growth promoters (AGP), typically at sub-therapeutic dose levels. However, concerns about the possible adverse effects of veterinary antibiotic use on human health led to the 1968 appointment in the United Kingdom of the *Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine* (chaired by Dr. M. Swann). The subsequent report recommended that antibiotics should not be used as AGP if the same drugs were used as therapeutic agents in human or animal medicine, or if the agents were associated with the development of cross-resistance to antibiotics used in people. Thus, the 'Swann Report' became the foundation for a policy of *prudent* use of antibiotics and for regulations regarding antibiotic use in many western European countries.

The global use of AGP continued after release of the Swann Report, but Sweden subsequently banned all AGP in 1986 and soon after Denmark and Norway withdrew market authorizations of individual antibiotics as AGP. These actions also prompted withdrawal of the market authorization of avoparcin in the EU in 1997 though this withdrawal was based on precautionary principles rather than definitive scientific data. The trend toward regulatory action culminated in 2006 with the complete ban of all AGP in the EU. Despite data showing that in some cases the moratorium has resulted in a reduction in antimicrobial resistance in the animal population, there is no evidence that the AGP ban has favorably impacted antimicrobial resistance patterns in the EU human population.

Antibiotics & Public Health Research

Multiple risk-assessments have been conducted since the early 1990s that investigated the impact of antimicrobial use in veterinary medicine on public health, and none have demonstrated a significant risk. Indeed, the links between the use of antimicrobials in veterinary medicine and resistance development in human medicine are somewhat tenuous,[2-6] although this assessment has been contested by other workers.[7-10]

Irrespective of whatever view is held, all users of antimicrobial compounds should examine the ways in which society deploys these valuable resources. It is also important that we understand the overall context in which veterinary medicinal products contribute to resistance development. Veterinary use is merely one of a number of contributory factors and must be viewed alongside the use of antimicrobials in humans, especially considering there are no clinically important bacteria that have not developed some type of antibiotic resistance.[11]

US Regulatory Review Process

As part of the approval process for pharmaceutical drugs for use in animals (whether companion animals or food animals), the US Food and Drug Administration Center for Veterinary Medicine (FDA/CVM) must evaluate a New Animal Drug Application (NADA prepared by the sponsor company) to determine that the drug is safe and effective for its intended use in the animal. 'Effectiveness' must be verified to show that the drug does what the label says, and 'safety' includes safety to the animal, humans if the animal is consumed, and the environment.

Following Europe's example, regulatory changes have also occurred in the US, most notably the introduction of *Guidance for Industry #152* in 2003.[12] As a result of this directive, *food-animal* drugs have *additional* requirements as part of the NADA approval process. Such drugs include a whole range of uses and include antibiotics for control and treatment of diseases caused by bacteria (*target* organisms). CVM must determine that new animal drugs are safe with regard to human health[13] by evaluating their potential effects on bacteria of human health concern (*non-target* organisms) carried by food-producing animals.

CVM uses a *risk-assessment* approach to accomplish this microbial food-safety evaluation of new antimicrobial animal drugs. The process assesses the risk of transmitting antibiotic-resistant bacteria to humans via food products derived from animals. The FDA believes that animal-derived foods represent the

most significant pathway for human exposure to resistant bacteria that have emerged as a consequence of antimicrobial drug use in animals.

The risk analysis evaluation is comprised of the following elements:

- hazard characterization (drug properties, microbiology, and resistance information);
- release assessment (estimation of emergence or selection of resistant bacteria in the food animal);
- exposure assessment (likelihood of human exposure to foodborne bacteria of human health concern through animal-derived food products);
- consequence assessment (the human medical importance of the antimicrobial drug);
- risk estimation (integrates the results from the release, exposure, and consequence assessments into an overall risk estimation associated with the proposed use of the drug).

The risk-estimation phase provides an overall conclusion, a qualitative indication of the potential risk to human health of the proposed use of the antimicrobial animal drug. The FDA then uses the overall risk estimation ranking, along with other relevant data and information submitted in support of the NADA, to determine whether the drug is approvable under specific risk-management conditions. This process helps to identify steps necessary to manage the risks associated with the proposed use of an antimicrobial drug in animals.

More recently, the FDA released a number of documents concerning uses of medically important antibiotics in animal agriculture, with the intent of preventing unnecessary use and promoting prudent use. Implementation of this new US policy requires that such antibiotics be used only for *therapeutic purposes*: disease treatment, control, and prevention, and *under the supervision of a licensed veterinarian*. This policy will assure that medically important medicines are used in animal health similar to how they are used in human health, under the supervision of a licensed professional and only to address disease challenges at various stages. As a result, use of AGP will eventually be phased-out in the US.

AIVLOSIN® Supports Judicious Use

AIVLOSIN Water Soluble Granules, from Pharmgate Animal Health, is a new water-soluble formulation containing tylvalosin, a novel macrolide antibiotic with potent activity against *Lawsonia intracellularis,* the cause of swine ileitis. AIVLOSIN is indicated for control of porcine proliferative enteropathy (ileitis) when administered at 50 ppm in drinking water of swine for 5 consecutive days (no pre-slaughter withdrawal needed in the US).

AIVLOSIN fully complies with the concept of judicious antimicrobial use. To receive FDA approval, AIVLOSIN satisfied all elements of the FDA risk-assessment model. When used according to label instructions, AIVLOSIN is the ideal medication for the judicious and effective control of ileitis due to its low effective therapeutic dose rate and short duration of treatment that targets a specific infection in swine. Furthermore, AIVLOSIN is only available for use by or on the order of a licensed veterinarian.

References

1. World Health Organization. Tackling antibiotic resistance from a food safety perspective in Europe. 2011.
2. Casewell M, Friis C, Marco E, McMullin P, Phillips I. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. *J Antimicrobial Chemotherapy* 2003; 52:159-161.
3. Cox LA, Copeland D, Vaughn M. Ciprofloxacin resistance does not affect duration of domestically acquired campylobacteriosis. *J Infectious Diseases* 2005; 191:1565-1566.
4. Phillips I. Withdrawal of growth-promoting antibiotics in Europe and its effects in relation to human health. *Int J Antimicrobial Agents* 2007; 30:101-107.
5. Phillips I, Casewell M, Cox T, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. *J Antimicrobial Chemotherapy* 2004; 53:28-52.
6. Wassenaar TM, Kist M, de Jong A. Re-analysis of the risks attributed to ciprofloxacin-resistant *Campylobacter jejuni* infections. *Int J Antimicrobial Agents* 2007; 30:195-201.
7. Mølbak K. Human health consequences of antimicrobial drug-resistant *Salmonella* and other foodborne pathogens. *Clinical Infectious Diseases* 2005; 41:1613-1620.
8. Smith KE, Besser JM, Hedberg CW, et al. Quinolone-resistant *Campylobacter jejuni* infections in Minnesota, 1992-1998 Investigation Team. *New England J Medicine* 1999; 340:1525-1532.
9. Nelson JM, Smith KE, Vugia DJ, et al. Prolonged diarrhea due to ciprofloxacin-resistant *Campylobacter* infection. *J Infectious Diseases* 2004; 190:1150-1157.
10. Engberg J, Neimann J, Nielsen EM, et al. Quinolone-resistant *Campylobacter* infections: risk factors and clinical consequences. *Emerging Infectious Diseases* 2004; 10:1056-1063.
11. Rehm SJ, Weber JT. The far-reaching impact of antimicrobial resistance. *Clinical Infectious Diseases* 2007; 45(Supplement 2):S97-S98.
12. US FDA/CVM. *Guidance for Industry #152.* Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. October 23, 2003.
13. FDA regulation: *Code of Federal Regulations,* 21 CFR 514.1(b)(8).

Important Safety Information: For use only in the drinking water of pigs. Not for use in lactating or pregnant females, or males and females 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.

NADA 141-336 **Approved by FDA.**

AIVLOSIN®

(62.5% w/w Tylvalosin as Tylvalosin Tartrate)

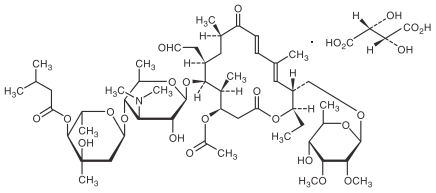
Water Soluble Granules

Use only as directed.
For use only in the drinking water of pigs.
Not for use in lactating or pregnant females, or males and females 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.

TYLVALOSIN TARTRATE CHEMICAL NOMENCLATURE AND STRUCTURE:
(4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-{[(6-deoxy-2,3-di-*O*-methyl-β-D-allopyranosyl)oxy]methyl}-6-({3,6-dideoxy-4-*O*-[2,6-dideoxy-3-C-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl}oxy)-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate (2*R*,3*R*)-2,3-dihydroxybutanedioate.



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

INDICATIONS:
Swine:
Control of porcine proliferative enteropathy (PPE) associated with *Lawsonia intracellularis* infection in groups of swine in buildings experiencing an outbreak of PPE.

DOSAGE AND ADMINISTRATION:
Swine:
Control of Porcine Proliferative Enteropathy

Prepare drinking water medicated with 50 parts per million Tylvalosin as shown in the following table.

Aivlosin® Water Soluble Granules sachet size	40 grams	160 grams	400 grams
Tylvalosin content of sachet (grams)	25	100	250
Volume of drinking water (liters)	500	2000	5000
Volume of drinking water (US gallons)	132	528	1320
Tylvalosin inclusion rate in 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 40-gram sachet per US gallon, or one 160-g sachet per four (4) US gallons or one 400-gram 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:
NOT FOR HUMAN USE.
KEEP OUT OF REACH OF CHILDREN.

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:
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. If irritation persists, seek medical attention.

Avoid eating, chewing gum and smoking during handling.

Wash contaminated skin.

The Material Safety Data Sheet contains more detailed occupational safety information.

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

PRECAUTIONS:
Not for use in lactating or pregnant females, or males and females intended for breeding. The effects of Tylvalosin on swine reproductive performance, pregnancy and lactation have not been determined. The safety and efficacy of this formulation in species other than swine have not been determined.

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 the ASPCA Animal Product Safety Service at 1-800-345-4735 or the FDA at 1-888-FDA-VETS.

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: Swine:
Control of Porcine Proliferative Enteropathy (PPE): A multi-location challenge model study was conducted to confirm the effectiveness of AIVLOSIN® 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.

ANIMAL SAFETY: Swine:
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.

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

HOW SUPPLIED: Aivlosin® Water Soluble Granules is packaged in 40-, 160- and 400-gram sachets supplied in boxes holding 20, 10 and 5 sachets respectively.

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

Distributed in the USA by:
Pharmgate Animal Health.
161 North Franklin Turnpike,
Ramsey, NJ 07446
www.pharmgateah.com

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

To report suspected adverse drug events, contact the ASPCA Animal Product Safety Service at 1-800-345-4735 or FDA at 1-888-FDA-VETS.

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

NDC 51429-10-002

US04PIM-1

PharmGate Animal Health

161 North Franklin Turnpike
Ramsey, NJ 07446
201.327.3800 **www.pharmgateAH.com**