Package Insert: Aivlosin Water Soluble

FOR USE ON ANIMALS ONLY

AIVLOSIN WATER SOLUBLE
Reg. No. G1598 (Act 36 of 1947)
Namibia S0 V02/17.1.4/1144

CAUTION

STORAGE INSTRUCTIONS
Do not store above 25°C

DOSAGE FORM
Granules for use in drinking water for Pigs and Poultry.

COMPOSITION
Each gram contains 625 mg Tylvalosin (as tylvalosin tartrate) as active substance

INDICATIONS
Chickens:
Treatment and prevention of respiratory infections caused by *Mycoplasma gallisepticum* in chickens. The presence of the disease in the flock should be established before metaphylactic treatment.

As an aid in reducing the development of clinical signs and mortality from respiratory disease in flocks, where infection *in ovum* with *Mycoplasma gallisepticum* is likely because the disease is known to exist in the parent generation. The strategy should include efforts to eliminate the infection from the parent generation.
AIVLOSIN proved effective in the treatment of artificial mycoplasma infection in chickens by *Mycoplasma synoviae*.
Turkeys:
Treatment of respiratory disease associated with tylvalosin sensitive strains of *Ornithobacterium rhinotracheale* in turkeys.
Pigs:
Treatment and prevention of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis*.

WARNINGS
- **Withdrawal periods:**
  Meat and offal: Pigs – 1 day
  Poultry – 2 days
  Eggs (chicken): zero days
  Not authorised for use in turkeys producing eggs for human consumption. Turkeys: do not use within 21 days of the onset of lay.
- Keep out of reach of children, uninformed persons and animals
- Although this remedy has been extensively tested under a large variety of conditions, failure thereof may ensue as a result of a wide range of reasons. If this is suspected, seek veterinary advice and notify the distributor

PRECAUTIONS
For each target species
Chickens and Turkeys
None

Pigs
In severely diseased pigs, if water intake is reduced, pigs should be treated with a suitable injectable veterinary medicinal product.

Special precautions for use

Special precautions for use in animals
Good management and hygiene practices should be introduced to reduce the risk of re-infection.
It is sound clinical practice to base treatment on susceptibility testing of the bacteria isolated from the animal. If this is not possible, therapy should be based on local (regional, farm level) epidemiological information about susceptibility of target bacteria.
Use of the veterinary medicinal product deviating from the instructions may increase the risk of development and selection of resistant bacteria and decrease the effectiveness of treatment with other macrolides due to the potential for cross-resistance.
Special precautions to be taken by the person administering the veterinary medicinal product to animals
Tylvalosin has been shown to cause hypersensitivity (allergic) reactions in laboratory animals; therefore, people with known hypersensitivity to tylvalosin should avoid contact with this product.
When mixing the veterinary medicinal product and handling the medicated water, direct contact, with eyes, skin and mucous membranes should be avoided. Personal protective equipment consisting of impervious gloves and mask should be worn when mixing the product. Wash contaminated skin.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.

Adverse reactions (frequency and seriousness)

None known.

Use during pregnancy, lactation or lay

Chicken and Turkeys
The product can be used in chickens laying eggs for human consumption as it has been shown to have no adverse effects on egg formation or the laying process at the recommended treatment dose.
The safety of the veterinary medicinal product has not been established during lay in turkeys.
Use only in accordance with risk/benefit assessment by the responsible veterinarian
Pigs
The safety of the veterinary medicinal product has not been established during pregnancy and lactation in pigs.
Use only in accordance with benefit-risk assessment by the responsible veterinarian.
Laboratory studies in animals have not produced any evidence of a teratogenic effect. Maternal toxicity in rodents has been observed at doses of 400 mg tylvalosin per kg bodyweight and above. In mice, a slight reduction in the foetal bodyweight was seen at doses causing maternal toxicity.

Interaction with other medicinal products and other forms of interaction

None known.

DOSE AND DIRECTIONS FOR USE

Use only as directed

FOR USE IN DRINKING WATER

Chickens
For treatment of respiratory disease associated with *Mycoplasma spp:* The dose is 25 mg tylvalosin per kg bodyweight per day in drinking water for 3 consecutive days.
When used as an aid in reducing the development of clinical signs and mortality (where infection *in ovum* with *Mycoplasma gallisepticum* is likely): The dose is 25 mg tylvalosin per kg bodyweight per day in drinking water for 3 consecutive days at 1 day old. This is followed by a second treatment with 25 mg tylvalosin per kg bodyweight per day in drinking water for 3 consecutive days at the period of risk, i.e., at times of management stress such as administration of vaccines (typically when birds are 2–3 weeks old).
Determine the combined bodyweight (in kg) of all the chickens to be treated. Select the correct number of sachets according to the amount of product required:

- One sachet of 40 g is sufficient to treat a total of 1,000 kg of chickens (e.g. 20,000 birds with an average bodyweight of 50 g).
- The 160 g sachet is sufficient to treat a total of 4,000 kg of chickens (e.g. 10,000 birds with an average body weight of 400 g).
- One sachet of 400 g is sufficient to treat a total of 10,000 kg of chickens (e.g. 20,000 birds with an average bodyweight of 500 g).

In order to achieve a correct dose, the preparation of a concentrated (stock) solution might be required (e.g., to treat a total of 500 kg total bird weight, only 50% of the prepared stock solution prepared from the 40 g sachet should be used).
The product should be added to a volume of water that the chickens will consume in one day. No other source of drinking water should be available during the medication period.

Turkeys

For treatment of respiratory disease associated with *Ornithobacterium rhinotracheale:* The dose is 25 mg tylvalosin per kg bodyweight per day in drinking water for 5 consecutive days.
Determine the combined bodyweight (in kg) of all the turkeys to be treated. Select the correct number of sachets according to the amount of product required:

- One sachet of 40 g is sufficient to treat a total of 1,000 kg of turkeys (e.g. 10,000 birds with an average bodyweight of 100 g).
- The 160 g sachet is sufficient to treat a total of 4,000 kg of turkeys (e.g. 10,000 birds with an average bodyweight of 400 g).
- One sachet of 400 g is sufficient to treat a total of 10,000 kg of turkeys (e.g. 10,000 birds with an average bodyweight of 1 kg).

In order to achieve a correct dose, the preparation of a concentrated (stock) solution might be required (e.g. to treat a total of 500 kg total bird weight, only 50% of the prepared stock solution prepared from the 40 g sachet should be used). The product should be added to a volume of water that the turkeys will consume in one day. No other source of drinking water should be available during the medication period.

Mixing instructions:

The veterinary medicinal product may be mixed directly into the drinking water system or first mixed as a stock solution into a smaller amount of water, which is then added into the drinking water system.
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 thoroughly until a clear solution is produced (usually within 3 minutes).
When preparing a stock solution, the maximum concentration should be 40 g per 1,500 ml or 400 g of product per 15 litres and it is necessary to mix the solution for 10 minutes. After this time, any remaining cloudiness will not affect efficacy of the product.
Only a sufficient amount of medicated drinking water should be prepared to cover the daily requirements.
Medicated drinking water should be replaced every 24 hours.

Pigs

For use in drinking water.
The dose is 5 mg tylvalosin per kg bodyweight per day in drinking water for 5 consecutive days. Calculate the total amount of product required with the following formula:
Total weight of product in grams = total bodyweight of pigs to be treated in kg x 5 / 625.
Select the correct number of sachets according to the amount of product required.

- The 40 g sachet is sufficient to treat a total of 5,000 kg of pigs (e.g. 250 pigs with an average bodyweight of 20 kg).
- The 160 g sachet is sufficient to treat a total of 20,000 kg of pigs (e.g. 400 pigs with an average bodyweight of 50 kg).
- The 400 g sachet is sufficient to treat a total of 50,000 kg of pigs (e.g. 1000 pigs with an average body weight of 50 kg).

In order to achieve a correct dose, the preparation of a concentrated (stock) solution might be required (e.g. to treat a total of 2,500 kg total pig weight, only 50% of the prepared stock solution prepared from the 40 g sachet should be used).
The product should be added to a volume of water that the pigs will consume in one day. No other source of drinking water should be available during treatment.
Mixing instructions:
The veterinary medicinal product may be mixed directly into the drinking water system or first mixed as a stock solution into a smaller amount of water, which is then added into the drinking water system.
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 thoroughly until a clear solution is produced (usually within 3 minutes).
When preparing a stock solution, the maximum concentration should be 40 g of product per 1,500 ml, 160 g of product per 6,000 ml or 400 g of product per 15, 000 ml and it is necessary to mix the solution for 10 minutes. After this time, any remaining cloudiness will not affect the efficacy of the veterinary medicinal product.
Only a sufficient amount of medicated drinking water should be prepared to cover the daily requirements.
Medicated drinking water should be replaced every 24 hours.

Overdose (symptoms, emergency procedures, antidotes), if necessary

No signs of intolerance have been observed in poultry species at up to 150 mg tylvalosin per kg bodyweight per day for 5 days. The effects of overdose on egg formation and the egg laying process have not been established in chickens.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.

Pharmacodynamic properties

Tylvalosin is a macrolide antibiotic. Macrolides are metabolites or derivatives of metabolites of soil organisms obtained by fermentation. They interfere with protein synthesis by reversibly binding to the 50S ribosome subunit. They are generally considered bacteriostatic. Tylvalosin has activity against pathogenic organisms isolated from a range of animal species-mainly Gram-positive organisms and mycoplasma but also some Gram-negative organisms.
Macrolides (including tylvalosin) have been shown to have effects on the innate immune system, which may augment the direct effects of the antibiotic on the pathogen and aid the clinical situation.
Chickens
Tylvalosin has activity against the following mycoplasma species found in chickens: *Mycoplasma gallisepticum* and *Mycoplasma synoviae.*
The minimal inhibitory concentration (MIC) of tylvalosin for *M. gallisepticum* ranges from 0.007 to 0.25 µg/ml.
Turkeys
Tylvalosin has activity against *Ornithobacterium rhinotracheale*, a Gram-negative organism found in turkeys and chickens.
The MIC of tylvalosin for *Ornithobacterium rhinotracheale* ranges from 0.016 to 32 µg/ml. Efficacy of tylvalosin against *O. rhinotracheale* in turkeys was demonstrated in a challenge model using co-infection with avian metapneumovirus and a single strain of *O.rhinotracheale* under strictly controlled conditions. These studies demonstrated a modest but statistically significant reduction in the incidence of lower respiratory lesions (lung and air sac) and clinical signs in turkeys treated with tylvalosin compared with negative controls. Efficacy studies under field conditions have not been conducted.
Bacteria can develop resistance to antimicrobial substances. There are multiple mechanisms responsible for resistance development to macrolide compounds.
Cross-resistance within the macrolide group of antibiotics cannot be excluded. Reduced susceptibility for tylvalosin was generally noted in tylosin resistant strains.
Pigs
Macrolides in general and tylvalosin in particular are unlikely to benefit from the application of conventional pharmacokinetic-pharmacodynamic (PK-PD) approaches to the determination of appropriate dosage schedules for clinical use in the pig; all have in common a high level of tissue uptake, including uptake into gastrointestinal

mucosal cells, leading to significantly higher tissue levels than those obtained in plasma. The effectiveness of the antibiotic is best determined in the clinical situation using challenge models and field trials.
The minimal inhibitory concentration (MIC) of tylvalosin for *L. intercellularis* was 32 µg/ml.

Pharmacokinetic properties

Tylvalosin tartrate is rapidly absorbed after oral administration of the veterinary medicinal product. Tylvalosin is widely distributed in tissues with the highest concentrations found in the respiratory tissues, bile, intestinal mucosa, spleen, kidney and liver. Tylvalosin has been shown to concentrate in phagocytic cells and gut epithelial cells. Concentrations (up to 12 times) were achieved in the cells (intracellular), compared to the extracellular concentration. *In vivo* studies have shown tylvalosin to be present in higher concentrations in the mucous lining of the respiratory and gut tissues compared to the plasma.
The major metabolite of tylvalosin is 3-acetyltylosin (3-AT), which is also microbiologically active.
The terminal half-lives for the elimination of tylvalosin and its active metabolite 3-AT range from 1 to 1.45 hours in the chicken. Six hours after treatment, the concentration of tylvalosin in the gastrointestinal tract mucosa has a mean concentration of 133 ng/g and in the gastrointestinal contents of 1,040 ng/g. The active metabolite 3-AT has a mean concentration of 57.9 ng/g and 441 ng/g, respectively.
The following pharmacokinetic data have been obtained for tylvalosin in pigs after a single oral dose at an elevated dose of 50 mg/kg body weight: $t_{1/2}$ (plasma half-life) of 2.20 hour, AUC (area under the plasma concentration time curve) 17.11 µg hours per mL, C_{max} (maximum plasma concentration) of 2.86 µg per mL and T_{max} (time to Cmax) 2.23 hours.

PHARMACEUTICAL PARTICULARS

Shelf life

Shelf life of the veterinary medicinal product as packaged for sale:
40 g sachet: 3 years.
160 g and 400 g sachet: 2 years.
Shelf life after first opening of the immediate packaging: 5 weeks
Shelf life of the medicated drinking water: 24 hours.

Nature and composition of immediate packaging

M12 three layer laminate of polyester, aluminium, and low density polyethylene
Pack sizes: 40g, 160g or 400g.
Not all pack sizes may be marketed.

Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with the National Environmental Management: Waste Act, 2008 (Act No. 59 of 2008). .

REGISTRATION HOLDER

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