1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Aivlosin 42.5 mg/g premix for medicated feeding stuff for pigs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Tylvalosin (as tylvalosin tartrate) 42.5 mg/g

Excipients:

Qualitative composition of excipients and other constituents
Hydrated magnesium silicate (sepiolite)
Wheat flour
Hydroxypropyl cellulose
Non-fat soyabean powder

A beige granular powder.

3. CLINICAL INFORMATION

3.1 Target species

Pigs

3.2 Indications for use for each target species

The presence of the disease in the group must be established before the product is used.

- Treatment and metaphylaxis of swine enzootic pneumonia caused by *Mycoplasma hyopneumoniae* in pigs. At the recommended dose, lung lesions and weight loss are reduced but infection with *Mycoplasma hyopneumoniae* is not eliminated.
- Treatment of porcine proliferative enteropathy (ileitis) caused by *Lawsonia intracellularis* in groups where there is a diagnosis based on clinical history, post-mortem findings and clinical pathology results.
- Treatment and metaphylaxis of swine dysentery, caused by *Brachyspira hyodysenteriae* in groups where the disease has been diagnosed.

3.3 Contraindications

Do not use in cases of hypersensitivity to macrolide antibiotics or to any of the excipients.

3.4 Special warnings

Acute cases and severely diseased pigs with reduced food or water intake should be treated with a suitable injectable product.

Generally, strains of *B. hyodysenteriae* have higher minimal inhibitory concentration (MIC) values in cases of resistance against other macrolides, such as tylosin. The clinical relevance of this reduced susceptibility is not fully explored. Cross-resistance has been shown between tylvalosin and other macrolides. Use of the veterinary medicinal product should be carefully considered when susceptibility testing has shown resistance to tylvalosin because its effectiveness may be reduced.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use of the product should be in accordance with official, national and regional antimicrobial policies.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

Good management and hygiene practices should be followed to reduce the risk of re-infection.

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

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 premix, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment consisting of impervious gloves and a half-mask respirator conforming to European Standard EN 149 or a non- disposable respirator conforming to European Standard EN 140 with a filter conforming to European Standard EN 143 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.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

None known.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy and lactation

. Use only according to the benefit-risk assessment by the responsible veterinarian.
No signs of adverse effects were observed in sows or their offspring when tylvalosin was administered orally and continuously for 195 days to sows, from before insemination to weaning, at an inclusion rate of 150 mg tylvalosin per kg water, corresponding to an average of 4.6 mg tylvalosin per kg body weight per day.

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.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

In-feed use.
For incorporation into dry feed only.

For treatment and metaphylaxis of swine enzootic pneumonia
The dose is 2.125 mg tylvalosin per kg bodyweight per day in-feed for 7 consecutive days.

Secondary infection by organisms such as Pasteurella multocida and Actinobacillus pleuropneumoniae may complicate enzootic pneumonia and require specific medication.

For treatment of porcine proliferative enteropathy (ileitis)
The dose is 4.25 mg tylvalosin per kg bodyweight per day in-feed for 10 consecutive days.

For treatment and metaphylaxis of swine dysentery
The dose is 4.25 mg tylvalosin per kg bodyweight per day in-feed for 10 consecutive days.

Indication	**Dose of active substance**	**Duration of treatment**	**In feed inclusion rate**
Treatment and metaphylaxis of swine enzootic pneumonia	2.125 mg/kg bodyweight/day	7 days	1 kg/tonne*
Treatment of PPE (ileitis)	4.25 mg/kg bodyweight/day	10 days	2 kg/tonne*
Treatment and metaphylaxis of swine dysentery	4.25 mg/kg bodyweight/day	10 days	2 kg/tonne*

* **Important**: these inclusion rates assume a pig eats the equivalent of 5% bodyweight per day.

In older pigs, or in pigs with reduced appetite, or on restricted feed intake, inclusion levels may need to be increased to achieve target dose. Where feed intake is reduced, use the following formula:

$$\text{kg veterinary medicinal product/tonne feed} = \frac{\text{Dose rate (mg/kg bodyweight)} \times \text{Bodyweight (kg)}}{\text{Daily feed intake (kg)} \times \text{veterinary medicinal product strength (mg/g)}}$$

As an adjunct to medication, good management and hygiene practices should be introduced in order to reduce the risk of infection and to control the build-up of resistance.

A horizontal ribbon mixer should be used to incorporate the product into the feeding stuff. It is recommended that the veterinary medicinal product is first mixed into 10 kg of the feeding stuff, followed by the rest of the feeding stuff and mixed well. Medicated feed may then be pelleted. Pelleting conditions involve a single pre-conditioning step with steam for 5 minutes and pelleting at not more than 70 °C under normal conditions.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

No signs of intolerance have been observed in growing pigs at up to 10 times the recommended dose.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

This veterinary medicinal product is intended to be used for the preparation of medicated feed.

Do not use for prophylaxis.

3.12 Withdrawal periods

Meat and offal: 2 days.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01FA92

4.2 Pharmacodynamics

Tylvalosin tartrate is a macrolide antibiotic that has antibacterial activity against Gram-positive, some Gram-negative organisms and mycoplasma. It acts by inhibiting protein synthesis in the bacterial cell.

Macrolide antibiotics are metabolites or semi-synthetic derivatives of metabolites of soil organisms obtained by fermentation. They have differently sized lactone rings and are basic due to the dimethylamino group. Tylvalosin has a sixteen-membered ring.

Macrolides interfere with protein synthesis by reversibly binding to the 50S ribosome subunit. They bind to the donor site and prevent the translocation necessary for keeping the peptide chain growing. Their effect is essentially confined to rapidly dividing organisms. Macrolides are generally considered bacteriostatic and mycoplasmastatic.

It is considered that there are multiple mechanisms responsible for resistance development to macrolide compounds, namely alteration of the ribosomal target site, utilisation of active efflux mechanisms and production of inactivating enzymes.

Resistance to tylvalosin by *Mycoplasma hyopneumoniae* and *Lawsonia intracellularis* has not been reported or found in the field to date. No breakpoint for Brachyspira hyodysenteriae has been established.

Generally, strains of *B. hyodysenteriae* have higher MIC values in cases of resistance against other macrolides, such as tylosin. The clinical relevance of this reduced susceptibility is not fully explored. Cross-resistance between tylvalosin and other macrolide antibiotics cannot be excluded.

In addition to their antimicrobial properties, immunomodulating and anti-inflammatory effects have been described for some macrolides in experimental studies. Tylvalosin has been shown to induce apoptosis of porcine neutrophils and macrophages, promote efferocytosis and inhibit proinflammatory CXCL-8, IL1α and LTB4 production, while inducing the release of pro-resolving Lipoxin A4 and Resolvin D1 in vitro.

4.3 Pharmacokinetics

Tylvalosin tartrate is rapidly absorbed after oral administration of the veterinary medicinal product.

After administration of the recommended dose, lung concentrations of 0.060–0.066 mcg/ml were found at 2 and 12 hours post-treatment. The parent compound is widely distributed in the tissues with the highest concentrations found in the lungs, bile, intestinal mucosa, spleen, kidney and liver.

There is evidence that the concentration of macrolides is higher at the site of infection than in plasma, in particular in neutrophils, alveolar macrophages and alveolar epithelial cells.

In vitro metabolism studies have confirmed that the parent compound is rapidly metabolised to 3-O-acetyltylosin. In a trial with ^{14}C-labeled veterinary medicinal product administered at 2.125 mg/kg to pigs for 7 days, over 70% of the dose was excreted in the faeces, with urinary excretion accounting for 3 to 4% of the dose.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 4 weeks.
Shelf life after incorporation into feed: 1 month in meal or pellets.

5.3 Special precautions for storage

Store below 30 °C.
Store in the original container.
Keep the bag tightly closed.

5.4 Nature and composition of immediate packaging

One aluminium foil/polyester laminated bag containing 2 kg, 5 kg or 20 kg.

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

ECO Animal Health Europe Limited

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/04/044/001 – 20 kg
EU/2/04/044/002 – 5 kg
EU/2/04/044/020 – 2 kg

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 09/09/2004

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{MM/YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).