SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tilmicosol

250 mg/ml Solution for Use in Drinking Water/ Milk

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:
Active substance:
Tilmicosin (as phosphate) 250 mg

Excipients:
Propyl gallate (E 310) 0.2 mg
Disodium edetate 2.0 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for use in drinking water/ milk.
Clear yellow to dark yellow solution.

4. CLINICAL PARTICULARS

4.1 Target species

Chickens (except hens producing eggs for human consumption),
Turkeys,
Pigs,
Calves (pre-ruminant cattle)

4.2 Indications for use, specifying the target species

Pigs: For the treatment and metaphylaxis of respiratory disease in pig herds, associated with *Mycoplasma hyopneumoniae, Pasteurella multocida, Actinobacillus pleuropneumoniae* susceptible to tilmicosin.
Chickens: For the treatment and metaphylaxis of respiratory disease in chicken flocks, associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin.
Turkeys: For the treatment and metaphylaxis of respiratory disease in turkey flocks, associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin.
Calves: For the treatment and metaphylaxis of bovine respiratory disease, associated with *Mannheimia haemolytica, Pasteurella multocida, Mycoplasma bovis, M. dispar* susceptible to tilmicosin.
The presence of the disease in the group/flock must be established before the product is used.

4.3 Contraindications

Do not allow horses and other equines access to drinking water containing tilmicosin.
Do not use in case of hypersensitivity to tilmicosin or to any of the excipients.
Do not administer to ruminating animals with active rumen function.

4.4 Special warnings for each target species

Important: Must be diluted before administration to animals
Pigs, chickens and turkeys: Water consumption should be monitored in order to guarantee adequate dosing. In case water consumption does not match quantities for which recommended concentrations were calculated, the concentration of product has to be adapted in a way that the recommend dosage will be taken up by the animals or different medication should be considered.
The uptake of medication by animals can be altered as a consequence of illness. In case of insufficient uptake of water or milk replacer, animals should be treated parenterally using an appropriate injectable product.
Repeated use of the product should be avoided by improving management practices and thorough cleansing and disinfection.

4.5 Special precautions for use

Special precautions for use in animals
For oral use only. Contains disodium edetate; do not inject.
Inappropriate use of the product may increase the prevalence of bacteria resistant to tilmicosin and may decrease the effectiveness of treatment with tilmicosin-related substances. The use of the product should be based on susceptibility tests.

Official, national and regional antimicrobial policies should be taken into account when the product is used.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Tilmicosin may induce irritation. Macrolides, such as tilmicosin, may also cause hypersensitivity (allergy) following injection, inhalation, ingestion or contact with skin or eye. Hypersensitivity to tilmicosin may lead to cross reactions to other macrolides and vice versa. Allergic reactions to these substances may occasionally be serious and therefore direct contact should be avoided.
To avoid exposure during preparation of the medicated drinking water, wear overalls, safety glasses, and impervious gloves. Do not eat, drink or smoke when handling this product. Wash hands after use.
In the case of accidental ingestion, wash out mouth immediately with water and seek medical advice. In the event of accidental skin contact, wash thoroughly with soap and water. In case of accidental eye contact, flush the eyes with plenty of clean, running water.
Do not handle the product if you are allergic to ingredients in the product.
If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases (less than 1 animal in 10,000 animals, including isolated reports), a decrease in water intake has been observed.

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay. Use only accordingly to the benefit/risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

Tilmicosin may lessen the antibacterial activity of beta-lactam antibiotics.
Do not use simultaneously with bacteriostatic antimicrobials.

4.9 Amounts to be administered and administration route

In drinking water/milk use
The product must be diluted in drinking water (pigs, chickens, turkeys) or milk replacer (calves) before administration.

Calves: 12.5 mg tilmicosin/kg body weight (i.e.1 ml of product per 20 kg body weight), twice daily, for 3-5 consecutive days.

Pigs: 15-20 mg tilmicosin/kg body weight/day (i.e. 6-8 ml of product per 100 kg of body weight per day), for 5 consecutive days, which may be achieved by the inclusion of 150-200 mg of tilmicosin per litre (60-80 ml of product per 100 litres based on a water consumption of 10 % of bodyweight).

Chickens: 15-20 mg tilmicosin/kg body weight/day (i.e. 6-8 ml of product per 100 kg of body weight per day), for 3 consecutive days, which may achieved by the inclusion of 75-100 mg of tilmicosin per litre (30-40 ml of product per 100 litres based on a water consumption of 20 % of bodyweight).

Turkeys: 10-27 mg tilmicosin/kg body weight/day (i.e. 4-11 ml of product per 100 kg of body weight per day), for 3 consecutive days, which may achieved by the inclusion of 143-386 mg of tilmicosin per litre (57-154 ml of product per 100 litres based on a water consumption of 7 % of bodyweight).
If signs of disease do not significantly improve within 3-5 days, the diagnosis should be re-evaluated and treatment changed.

The exact concentration of the veterinary medicinal product required can be calculated according to the following formula:
ml product per litre drinking water per day = [ml product per kg bodyweight per day x average bodyweight (kg)] / average daily water intake (litre).

Bodyweight should be determined as accurately as possible to avoid under-dosing. The required dose should be measured using suitably calibrated measuring equipment. Only sufficient medicated drinking water should be prepared to cover the daily requirements. The medicated water should be the only source of drinking water for the animals for the entire duration of the treatment period. Water intake should be monitored at frequent intervals during medication. After the end of the medication period, the water supply system should be cleaned appropriately to avoid intake of sub-therapeutic amounts of the active substance.

Medicated drinking water should be prepared fresh every 24 hours. Medicated milk replacer should be prepared fresh every 6 hours.

The medicinal product should be diluted with water or milk replacer prior to its use. When preparing a stock solution, the maximum concentration should not exceed 200 ml of product/litre. The lowest concentrations of the product at which stability can be assured are 0.3 ml product/litre drinking water and 0.8 ml product/litre milk replacer.

The uptake of medicated drinking water/milk replacer depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of the product should be adjusted accordingly.

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

When pigs are offered drinking water containing 300 or 400 mg tilmicosin/litre (equivalent to 22.5-40 mg/kg bodyweight or 1.5-2 times the recommended concentration) commonly animals exhibit a reduced water intake. Although this has a self-limiting effect on tilmicosin intake, it could, in extreme circumstances, result in dehydration. This can be corrected by the removal of the medicated drinking water and replacement with fresh unmedicated water.
No symptoms of overdose have been seen in chickens given drinking water containing levels of tilmicosin up to 375 mg/litre (equivalent to 75-100 mg/kg bodyweight or 5 times the recommended dose) for 5 days, daily treatment with 75 mg/litre (equivalent to the maximum recommended dose) for 10 days resulted in a decrease in faecal consistency.
No symptoms of overdose have been seen in turkeys given drinking water containing levels of tilmicosin up to 375 mg/litre (equivalent to 50-135 mg/kg bodyweight or 5 times the recommended dose) for 3 days, daily treatment with 75 mg/litre (equivalent to the maximum recommended dose) for 6 days also produced no symptoms of overdose.
No symptoms of overdose, with exception of a slight decrease in the milk consumption, have been seen in calves given twice daily doses 5 times the maximum recommended dose or for twice the maximum recommended duration of treatment.

4.11 Withdrawal period(s)

Pigs
Meat and offal: 14 days

Chicken
Meat and offal: 12 days
Not authorised for use in birds producing eggs for human consumption. Do not use within 14 days of the start of the laying period.

Turkeys
Meat and offal: 19 days

Calves
Meat and offal: 42 days
Not authorised for use in animals producing milk for human consumption.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides

ATC vet code: QJ01FA91

5.1 Pharmacodynamic properties

Tilmicosin is a semi-synthetic antibiotic of the macrolide group, and is believed to affect protein synthesis. It has bacteriostatic action but at high concentrations it may be bactericidal.

This antibacterial activity is predominantly against Gram-positive microorganism with activity against certain gram-negative ones and Mycoplasma of a bovine, porcine and avian origin. In particular, its activity has been demonstrated against the following microorganism:

- Pigs: *Mycoplasma hyopneumoniae, Pasteurella multocida and Actinobacillus pleuropneumoniae*
- Chickens and turkeys*: Mycoplasma gallisepticum and Mycoplasma synoviae*
- Calves*: Mannheimia haemolytica, Pasteurella multocida, Mycoplasma bovis, M. dispar*

Scientific evidence suggests that macrolides act synergistically with the host immune system. Macrolides appear to enhance phagocyte killing of bacteria. Tilmicosin has been shown to inhibit *in vitro* the replication of the Porcine Reproductive and Respiratory Syndrome virus in alveolar macrophages in a dose dependent fashion.

Cross-resistance between tilmicosin and other macrolides and lincomycin has been observed.

CLSI breakpoints for tilmicosin *	resistant	intermediate	susceptible
Porcine *Pasteurella multocida*	≥ 32 µg/ml	-	≤ 16 µg/ml
Porcine *Actinobacillus pleuropneumoniae*	≥ 32 µg/ml	-	≤ 16 µg/ml

***** VET08, 4th ed. June 2018

5.2 Pharmacokinetic particulars

Whilst blood concentrations of tilmicosin are low, there is pH-dependent macrophage accumulation of tilmicosin in inflamed tissue.

Pigs: After oral administration of 200 mg tilmicosin/litre drinking water, the average active substance concentrations detected in lung tissue, alveolar macrophages and bronchial epithelium 5 days after the start of treatment were reported 1.44 µg/ml, 3.8 µg/ml and 7.4 µg/g respectively.

Poultry: As early as 6 hours after oral administration of 75 mg tilmicosin/litre drinking water, the average active substance concentrations detected in lung and alveolar tissue were 0.63 µg/g and 0.30 µg/g respectively. 48 hours after the start of the treatment, the tilmicosin concentrations in lung and alveolar tissue were 2.3 µg/g and 3.29 µg/g respectively.

Calves: As early as 6 hours after oral administration of 25 mg tilmicosin/kg bodyweight/day in milk replacer, an average active substance concentration of 3.1 µg/g was detected in lung tissue. 78 hours after the start of treatment, the tilmicosin concentration in lung tissue was 42.7 µg/g. Therapeutically effective concentrations of tilmicosin were measured up to 60 hours after treatment.

Turkeys: After oral administration of 75 mg tilmicosin/litre drinking water, the average active substance concentrations detected in lung tissue, air sac tissue and plasma 5 days after the start of treatment were 1.89 µg/ml, 3.71 µg/ml and 0.02 µg/g respectively. The highest mean tilmicosin concentration detected for lung tissues was 2.19 µg/g at 6 days; for air sac tissue it was 4.18 µg/g at 2 days and in the plasma it was 0.172 µg/g at 3 days.

5.3 Environmental properties:

The active ingredient tilmicosin is persistent in soils. Tilmicosin is known to be toxic to aquatic organisms, including cyanobacteria, with potentially long lasting effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Propyl gallate, E 310
Phosphoric acid, concentrated (for pH adjustment)
Purified water

6.2 Major incompatibilities

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

6.3 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years
Shelf-life after first opening the immediate packaging: 3 months
Shelf-life after dilution or reconstitution in drinking water according to directions: 24 hours
Shelf-life after reconstitution in milk replacer: 6 hours.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original container in order to protect from light. Do not freeze.

6.5 Nature and composition of immediate packaging

250 ml in white high density polyethylene bottle with polypropylene screw cap
1000 ml in white high density polyethylene bottle with polypropylene screw cap and calibrated polypropylene measuring cup
Not all pack sizes may be marketed.

6.6 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 products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Lavet Pharmaceuticals Ltd.
H-2143 Kistarcsa
Batthyány u. 6.
Hungary

8. MARKETING AUTHORISATION NUMBER

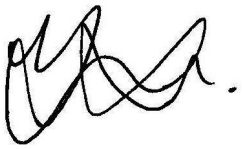
Vm 32823/4003

9. DATE OF FIRST AUTHORISATION

11 February 2011

10. DATE OF REVISION OF THE TEXT

November 2020



Approved: 06 November 2020