SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Pulmovet 250 mg/ml solution for use in drinking water/milk for cattle, pigs, chickens and turkeys

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Tilmicosin (as tilmicosin phosphate): 250 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Propyl gallate (E310)	0.2 mg
Disodium edetate	2.0 mg
Phosphoric acid, concentrated (for pH adjustment)	
Purified water	

Clear yellow to brown solution.

3. CLINICAL INFORMATION

3.1 Target species

Cattle (pre-ruminant), pigs, chickens (except hens producing eggs for human consumption) and turkeys.

3.2 Indications for use for each target species

Calves: For the treatment and metaphylaxis of bovine respiratory disease, associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma bovis* and *M. dispar* susceptible to tilmicosin.

Pigs: For the treatment and metaphylaxis of respiratory disease associated with *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* and *Mycoplasma hyopneumoniae* susceptible to tilmicosin.

Chickens: For the treatment and metaphylaxis of respiratory disease associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin.

Turkeys: For the treatment and metaphylaxis of respiratory disease associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin.

The presence of the disease in the group/flock must be established before the veterinary medicinal product is used.

3.3 Contraindications

Do not allow horses and other equines access to drinking water containing tilmicosin.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

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 the veterinary medicinal product has to be adapted in a way that the recommended 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 veterinary medicinal product should be avoided by improving management practices and thorough cleansing and disinfection.

Use of the veterinary medicinal product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to tilmicosin and may decrease the effectiveness of treatment with other macrolides, lincosamides and streptogramin B due to the potential for cross-resistance.

3.5 Special precautions for use

Special precautions for safe use in the target species:

For oral use only. Contains disodium edetate; do not inject.

Use of the veterinary medicinal product should be based 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 the target bacteria.

Official, national and regional antimicrobial policies should be taken into account when the veterinary medicinal 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 or milk replacer, wear overalls, safety glasses, and impervious gloves. Do not eat, drink or smoke when handling this veterinary medicinal product. Wash hands after use.

In case of accidental ingestion, wash out mouth immediately with water, seek medical advice and show the package leaflet or the label to the physician. 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 veterinary medicinal product if you are allergic to ingredients in the veterinary medicinal 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.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle, pigs, chickens and turkeys:

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Decreased drinking

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 the national competent authority via the national reporting system. See the label for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy, lactation and lay:
The safety of the veterinary medicinal product has not been established during pregnancy, lactation or lay. Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 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 antimicrobial agents.

3.9 Administration routes and dosage

For oral use only. The veterinary medicinal 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 veterinary medicinal product per 20 kg BW), twice daily, for 3-5 consecutive days.

Pigs: 15-20 mg tilmicosin/kg body weight/day (i.e. 6-8 ml of veterinary medicinal product per 100 kg of BW per day), for 5 consecutive days, which may be achieved by the inclusion of 200 mg of tilmicosin per litre (80 ml of veterinary medicinal product per 100 litres).

Chickens: 15-20 mg tilmicosin/kg body weight/day (i.e. 6-8 ml of veterinary medicinal product per 100 kg of BW per day), for 3 consecutive days, which may be achieved by the inclusion of 75 mg of tilmicosin per litre (30 ml of veterinary medicinal product per 100 litres).

Turkeys: 10-27 mg tilmicosin/kg body weight/day (i.e. 4-11 ml of veterinary medicinal product per 100 kg of BW per day), for 3 consecutive days, which may be achieved by the inclusion of 75 mg of tilmicosin per litre (30 ml of veterinary medicinal product per 100 litres).

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:
ml veterinary medicinal product per litre of drinking water = [ml veterinary medicinal product per kg body weight per day x average body weight (kg) of animals to be treated] / average daily water intake (l/animal).

One 960 ml bottle of veterinary medicinal product is sufficient to medicate 1200 litres of drinking water for pigs or 3200 litres of drinking water for chickens or turkeys. One 5040 ml can is sufficient to medicate 6300 litres of drinking water for pigs or 16800 litres of drinking water for chickens or turkeys.

One 960 ml bottle and 5040 ml can of veterinary medicinal product are sufficient to medicate in milk replacer respectively 48 to 80 and 252 to 420 veal calves each of 40 kg body weight depending on the duration of treatment.

To ensure a correct dosage, body weight should be determined as accurately as possible.
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 veterinary medicinal product should be diluted with water or milk replacer prior to its use and the concentration of the prediluted solution should not exceed 200 ml of veterinary medicinal product/litre (i.e. 1 in 5). The lowest concentrations of the veterinary medicinal product at which stability can be assured are 0.3 ml veterinary medicinal product/litre drinking water and 0.7 ml veterinary medicinal product/litre milk replacer.

The intake of medicated water/milk replacer depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of tilmicosin may need to be adjusted accordingly.

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

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.

When pigs are offered drinking water containing 300 or 400 mg tilmicosin/litre (equivalent to 22.5-40 mg tilmicosin/kg body weight 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 tilmicosin/kg body weight or 5 times the recommended dose) for 5 days; daily treatment with 75 mg tilmicosin/litre (equivalent to the maximum recommended dose) for 10 days resulted in a reduction 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 tilmicosin/kg body weight or 5 times the recommended dose) for 3 days; daily treatment with 75 mg tilmicosin/litre (equivalent to the maximum recommended dose) for 6 days also produced no symptoms of overdose.

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

Not applicable.

3.12 Withdrawal periods

Calves: meat and offal: 42 days.
Pigs: meat and offal: 14 days.
Chickens: meat and offal: 12 days.
Turkeys: meat and offal: 19 days.

Not authorised for use in animals producing milk for human consumption.
Not for use in birds producing eggs for human consumption. Do not use within 2 weeks before the start of the laying period.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01FA91

4.2 Pharmacodynamics

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.

Tilmicosin is primarily active against Gram-positive bacteria, although some Gram-negative bacteria and mycoplasmas are also affected by this drug. In particular, activity has been demonstrated against the following microorganisms:
- Calves: *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma bovis* and *M. dispar*.
- Pigs: *Pasteurella multocida, Actinobacillus pleuropneumoniae* and *Mycoplasma hyopneumoniae*
- Chickens and turkeys: *Mycoplasma gallisepticum* and *Mycoplasma synoviae*

NCCLS breakpoints	resistant	intermediate	susceptible
Bovine Pasteurella spp	≥ 32 µg/ml	16 µg/ml	≤ 8 µg/ml
Porcine Pasteurella multocida	≥ 32 µg/ml		≤ 16 µg/ml
Porcine Actinobacillus pleuropneumoniae	≥ 32 µg/ml		≤ 16 µg/ml

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.
Macrolides inhibit protein synthesis by reversibly binding to the 50S ribosomal subunit. Bacterial growth is inhibited by induction of the separation of peptidyl transfer RNA from the ribosome during the elongation phase.
Ribosomal methylase, encoded by the erm gene, can precipitate resistance to macrolides by alteration of the ribosomal binding site.

The gene that encodes for an efflux mechanism, mef, also brings about a moderate degree of resistance.
Resistance is also brought about by an efflux pump that actively rids the cells of the macrolide. This efflux pump is chromosomally mediated by genes referred to as acrAB genes.

4.3 Pharmacokinetics

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

Calves: As early as 6 hours after oral administration of 25 mg tilmicosin/kg body weight/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.

Pigs: After oral administration of 200 mg tilmicosin/l drinking water, the average active substance concentrations detected in lung tissue, alveolar macrophages and bronchial epithelium 5 days after the start of treatment were 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/l 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 treatment, the tilmicosin concentrations in lung and alveolar tissue were 2.3 µg/g and 3.29 µg/g respectively.

Turkeys: After oral administration of 75 mg tilmicosin/l 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.

Environmental properties

The active ingredient tilmicosin is persistent in soils.

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: 3 months.
Shelf life after dilution in drinking water: 24 hours.
Shelf life after dilution in milk replacer: 6 hours.

5.3 Special precautions for storage

Store below 25ºC. Do not refrigerate or freeze. Protect from frost. Protect from light.

5.4 Nature and composition of immediate packaging

- High-density polyethylene bottles with low-density polyethylene screw cap containing 960 ml of veterinary medicinal product;

- High-density polyethylene can with high-density polyethylene screw cap containing 5040 ml of veterinary medicinal product.

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

Dopharma Research B.V.

7. MARKETING AUTHORISATION NUMBER

Vm 28365/3003

8. DATE OF FIRST AUTHORISATION

14 May 2018

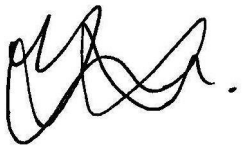
9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

September 2023

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).



Approved: 14 February 2024