1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Tilmovet 300 mg/ml solution for injection for cattle and sheep

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Tilmicosin 300 mg

Excipient:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Propylene glycol (E1520)	250 mg
Phosphoric acid, concentrated (for pH adjustment)	
Water for injections	

Clear amber yellow liquid.

3. CLINICAL INFORMATION

3.1 Target species

Cattle and sheep.

3.2 Indications for use for each target species

Cattle
Treatment of bovine respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida*.

Treatment of interdigital necrobacillosis.

Sheep
Treatment of respiratory tract infections caused by *Mannheimia haemolytica* and *Pasteurella multocida*.

Treatment of foot rot in sheep caused by *Dichelobacter nodosus* and *Fusobacterium necrophorum.*

Treatment of acute ovine mastitis caused by *Staphylococcus aureus* and *Mycoplasma agalactiae*.

3.3 Contraindications

Do not administer intravenously.
Do not administer intramuscularly
Do not administer to lambs weighing less than 15 kg.
Do not administer to primates.

Do not administer to pigs.
Do not administer to horses and donkeys.
Do not administer to goats.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

Sheep
The clinical trials did not demonstrate a bacteriological cure in sheep with acute mastitis caused by *Staphylococcus aureus* and *Mycoplasma agalactiae.*

Accurate weighing of lambs is important to avoid overdose.

3.5 Special precautions for use

Special precautions for safe use in the target species:

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.

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.

The feeding of waste milk containing residues of tilmicosin to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria.

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

Do not administer to lambs weighing less than 15 kg since there is a risk of overdose toxicity.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Operator Safety Warnings:

INJECTION OF TILMICOSIN IN HUMANS CAN BE FATAL – EXERCISE EXTREME CAUTION TO AVOID ACCIDENTAL SELF-INJECTION AND FOLLOW THE ADMINISTRATION INSTRUCTIONS AND THE GUIDANCE BELOW, PRECISELY

- This veterinary medicinal product should only be administered by a veterinary surgeon.
- Never carry a syringe loaded with the veterinary medicinal product with the needle attached. The needle should be connected to the syringe only when filling the syringe or administering the injection. Keep the syringe and needle separate at all other times.
- Do not use automatic injection equipment.
- Ensure that animals are properly restrained, including those in the vicinity.
- Do not work alone when using the veterinary medicinal product.
- In case of self-injection SEEK IMMEDIATE MEDICAL ATTENTION and take the vial or the package leaflet with you. Apply a cold pack (not ice directly) to the injection site.

Additional operator safety warnings:

- Avoid contact with skin and eyes. Rinse any splashes from skin and eyes immediately with water.
- May cause sensitisation by skin contact. Wash hands after use.

NOTE TO THE PHYSICIAN
INJECTION OF TILMICOSIN IN HUMANS HAS BEEN ASSOCIATED WITH FATALITIES.
The cardiovascular system is the target of toxicity, and this toxicity may be due to calcium channel blockade. Administration of intravenous calcium chloride should only be considered if there is positive confirmation of exposure to tilmicosin.
In dog studies, tilmicosin induced a negative inotropic effect with consequent tachycardia, and a reduction in systemic arterial blood pressure and arterial pulse pressure.
DO NOT GIVE ADRENALIN OR BETA-ADRENERGIC ANTAGONISTS SUCH AS PROPRANOLOL.
In pigs, tilmicosin-induced lethality is potentiated by adrenalin.
In dogs, treatment with intravenous calcium chloride showed a positive effect on the left ventricular inotropic state and some improvements in vascular blood pressure and tachycardia.
Pre-clinical data and an isolated clinical report suggest that calcium chloride infusion may help to reverse tilmicosin induced changes in blood pressure and heart rate in humans.
Administration of dobutamine should also be considered due to its positive inotropic effects although it does not influence tachycardia.
As tilmicosin persists in tissues for several days, the cardiovascular system should be closely monitored and supportive treatment provided.
Physicians treating patients exposed to this compound are advised to discuss clinical management with the National Poison Information Service on: 018379964

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Cattle and sheep:

Rare (1 to 10 animals / 10,000 animals treated):	Recumbency, incoordination, convulsions
Undetermined frequency (cannot be estimated from the available data):	Injection site swelling[1] Death[2]

[1] Soft and diffuse. Disappears within five to eight days.
[2] Deaths of cattle have been observed following a single intravenous dose of 5 mg/kg body weight, and following the subcutaneous injection of doses of 150 mg/kg body weight at 72 hour intervals. In pigs, intramuscular injection at 20 mg/kg body weight has caused deaths. Sheep have died following a single intravenous injection of 7.5 mg/kg body weight.

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

3.8 Interaction with other medicinal products and other forms of interaction

Interactions between macrolides and ionophores could be observed in some species.
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 subcutaneous use only.
Use a single treatment of 10 mg tilmicosin per kg body weight (corresponding to 1 ml of the veterinary medicinal product per 30 kg body weight).

Cattle
Method of administration:
To ensure the correct dosage, the body weight must be determined as accurately as possible in order to avoid underdosing.

Withdraw the required dose from the vial and remove the syringe from the needle, leaving the needle in the vial. When a group of animals has to be treated, leave the needle in the vial to remove the subsequent doses. Restrain the animal and insert a separate needle subcutaneously at the injection site, preferably in a skinfold over the rib cage behind the shoulder. Attach the syringe to the needle and inject into the base of the skinfold. Do not inject more than 20 ml per injection site.

Sheep
Method of administration:
Accurate weighing of lambs is important to avoid overdosing. The use of a 2 ml syringe or smaller improves accurate dosing.

Withdraw the required dose from the vial and remove the syringe from the needle, leaving the needle in the vial. Restrain the sheep whilst leaning over the animal and insert a separate needle subcutaneously into the injection site, which should be in a skinfold over the rib cage behind the shoulder. Attach the syringe to the needle and inject into the base of the skin fold. Do not inject more than 2 ml per injection site.

If no improvement is noted within 48 hours, the diagnosis should be confirmed.

Avoid introduction of contamination into vial during use. The vial should be inspected visually for any foreign particulate matter and/or abnormal physical appearance. In the event of either being observed, discard the vial.

The closure should not be broached more than 15 times. In order to prevent excessive broaching of the stopper, a suitable multiple dosing device should be used.

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

In cattle subcutaneous injections of 10, 30 and 50 mg/kg body weight, repeated three times with a 72 hours interval, did not cause death. As expected, oedema developed at the site of injection. The only lesion observed at autopsy was a necrosis of the myocardium in the group treated with 50 mg/kg body weight.

Doses of 150 mg/kg body weight, administered subcutaneously with an interval of 72 hours caused death. Oedema at the site of injection was observed and at autopsy a light necrosis of the myocardium was the only lesion determined. Other symptoms observed were: difficulty in moving, reduced appetite and tachycardia.

In sheep single injections (approximately 30 mg/kg body weight) may cause a slight increase of the rate of respiration. Higher doses (150 mg/kg body weight) caused ataxia, lethargy and the inability to raise the head.
Deaths occurred after one single intravenous injection of 5 mg/kg body weight in cattle and 7.5 mg/kg in sheep body weight.

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

For administration only by a veterinarian.

3.12 Withdrawal periods

Cattle
Meat and offal: 70 days.
Milk: 36 days.

If the veterinary medicinal product is administered to cows during the dry period or to pregnant dairy heifers (in accordance with section 3.7 above), milk should not be used for human consumption until 36 days after calving.

Sheep
Meat and offal: 42 days.
Milk: 18 days.

If the veterinary medicinal product is administered to ewes during the dry period or to pregnant ewes (in accordance with section 3.7 above), milk should not be used for human consumption until 18 days after lambing.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QJ01FA91

4.2 Pharmacodynamics

Tilmicosin is a mainly bactericidal semi-synthetic antibiotic of the macrolide group. It 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 and ovine origin. In particular its activity has been demonstrated against the following micro-organism:
Mannheimia, Pasteurella, Actinomyces (Corynebacterium), Fusobacterium, Dichelobacter, Staphylococcus, and *Mycoplasma* organisms of bovine and ovine origin.

Minimum inhibition concentration measured in recently (2009-2012) isolated European field strains, derived from respiratory bovine disease.

Bacteria spp	MIC (µg/ml) range	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
P. multocida	0.5- > 64	4	8
M. haemolytica	1 - 64	8	16

The Clinical and Laboratory Standards Institute (CLSI) has set the interpretive criteria for tilmicosin against *M. haemolyica* of bovine origin and specifically for bovine respiratory disease, as ≤8µg/ml = susceptible, 16 µg/ml = intermediate and ≥ 32 µg/ml = resistant. The CLSI at the present time have no interpretive criteria for *P. multocida* of bovine origin, however they have interpretive criteria for *P. multocida* of swine origin, specifically swine respiratory disease, as ≤16 µg/ml = susceptible and ≥ 32 µg/ml = resistant.

Scientific evidence suggests that macrolides act synergistically with the host immune system. Macrolides appear to enhance phagocyte killing of bacteria.

Following oral or parenteral administration of tilmicosin the main target organ for toxicity is the heart. The primary cardiac effects are increased heart rate (tachycardia) and decreased contractility (negative inotrophy). Cardiovascular toxicity may be due to calcium channel blockade.

In dogs, $CaCl_2$ treatment showed a positive effect on the left ventricular inotrophic state after tilmicosin administration and some changes in vascular blood pressure and heart rate.

Dobutamine partially offset the negative inotropic effects induced by tilmicosin in dogs. Beta adrenergic antagonists such as propanolol exacerbated the negative inotrophy of tilmicosin in dogs.

In pigs, intramuscular injection of 10 mg tilmicosin/kg body weight caused increased respiration, emesis and convulsions; 20 mg/kg body weight resulted in mortality in 3 of 4 pigs, and 30 mg/kg body weight caused the death of all 4 pigs tested. Intravenous injection of 4.5 to 5.6 mg tilmicosin/kg body weight followed by intravenous injection of 1 ml epinephrine (1/1000) 2 to 6 times resulted in death of all 6 injected pigs. Pigs given 4.5 to 5.6 mg tilmicosin/kg body weight intravenously with no epinephrine all survived. These results suggest that intravenous epinephrine may be contraindicated.

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

Absorption: Several studies have been conducted. The results show that, when administered as recommended to calves and sheep by subcutaneous injection over the dorso-lateral chest, the main parameters are:

	Dose Rate	**Tmax**	**Cmax**
Cattle:			
Neonatal calves	10 mg/kg body weight	1 hour	1.55 µg/ml
Feedlot cattle	10 mg/kg body weight	1 hour	0.97 µg/ml

Sheep:			
40 kg animals	10 mg/kg body weight	8 hours	0.44 µg/ml
28-50 kg animals	10 mg/kg body weight	8 hours	1.18 µg/ml

Distribution: Following subcutaneous injection, tilmicosin is distributed throughout the body, but especially high levels are found in the lung.

Biotransformation: Several metabolites are formed, the predominant one being identified as T1 (N-demethyl tilmicosin). However the bulk of the tilmicosin is excreted unchanged.

Elimination: Following subcutaneous injection, tilmicosin is excreted mainly via the bile into the faeces, but a small proportion is excreted via the urine. The half-life following subcutaneous injection in cattle is 2-3 days.

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: 24 months.
Shelf life after first opening the immediate packaging: 28 days.

5.3 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

5.4 Nature and composition of immediate packaging

25 ml Type I amber glass vials, 50 ml, 100 ml, and 250 ml Type II amber glass vials sealed with Type I bromobutyl stoppers and aluminium caps, supplied in cardboard boxes. One vial per box.
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

Huvepharma NV

7. MARKETING AUTHORISATION NUMBER(S)

VPA10782/032/001

8. DATE OF FIRST AUTHORISATION

24/05/2019

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

16/04/2025

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).