SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Micotil 300 mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml contains:

Active substance:
Tilmicosin 300 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear solution.

4. CLINICAL PARTICULARS

4.1 Target species

Cattle and sheep

4.2 Indications for use, specifying the 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*.

4.3 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.

4.4 Special warnings for each target species

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

Do not administer to lambs weighing less than 15 kg since there is a risk of overdose toxicity.
Accurate weighing of lambs is important to avoid overdose. The use of a 2 ml or smaller syringe will facilitate accurate dosing.

4.5 Special precautions for use

Special precautions for use in animals

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

To avoid self-injection do not use automatic injection equipment.
Wherever possible, the use of the product should be based on susceptibility testing.

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 product should only be administered by a veterinary surgeon. Never carry a syringe loaded with Micotil 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 Micotil. 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 or 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: ... relevant national number stated (*to be completed nationally*)

4.6 Adverse reactions (frequency and seriousness)

A soft diffuse swelling may occur at the injection site very rarely but this disappears within five to eight days. Recumbency, incoordination and convulsions have been observed in rare cases.

Hypersensitivity reactions may occur in very rare cases. Such reactions may include anaphylaxis, which may be life-threatening. If such reactions occur appropriate treatment is recommended. Death may occur in very rare cases.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

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.

4.8 Interaction with other medicinal products and other forms of interaction

Interactions between macrolides and ionophores could be observed in some species.

4.9 Amounts to be administered and administration route

For subcutaneous injection only.
Use 10 mg tilmicosin per kg body weight (corresponding to 1 ml Micotil per 30 kg body weight).

Cattle:
Method of administration:
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 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.

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

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.

4.11 Withdrawal period(s)

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

If the product is administered to cows during the dry period or to pregnant dairy heifers (in accordance with section 4.7 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 product is administered to ewes during the dry period or to pregnant ewes (in accordance with section 4.7 above), milk should not be used for human consumption until 18 days after lambing.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, macrolides.
ATC vet code: QJ01FA91

5.1 Pharmacodynamic properties

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.

5.2 Pharmacokinetic particulars

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	T_{max}	C_{max}
Cattle: Neonatal calves	10 mg/kg body weight 10 mg/kg	1 hour 1 hour	1.55 µg/ml 0.97 µg/ml
Sheep 40 kg animals 28-50 kg animals	10 mg/kg body weight 10 mg/kg body weight	8 hours 8	0.44 µg/ml 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Propylene glycol
Phosphoric acid (for pH adjustment)
Water for injections

6.2 Major incompatibilities

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

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years for the 25 ml presentation. 3 years for the 50 ml, 100 ml and 250 ml presentations.
Shelf life after first opening the immediate packaging: 28 days

6.4 Special precautions for storage

Protect from direct sunlight.

6.5 Nature and composition of immediate packaging

50 ml, 100 ml or 250 ml amber glass vials (Type I or Type II) sealed with a rubber stopper and aluminium overseal. Each vial is packed into a carton.

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.

Veterinary medicinal product must not be disposed of via waste water or the drainage systems.

7. MARKETING AUTHORISATION HOLDER

Elanco Europe Ltd.
Form 2, Bartley Way
Bartley Wood Business Park
Hook
RG27 9XA
United Kingdom

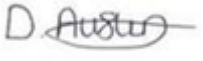
8. MARKETING AUTHORISATION NUMBER

Vm 00879/4203

9. DATE OF FIRST AUTHORISATION

21 August 1991

10. DATE OF REVISION OF THE TEXT

January 2022

Approved: 05/01/22