SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Apotil 300 mg/ml Solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active Substance:
Tilmicosin 300 mg

Excipients:
For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for injection
Clear, yellowish to brown-yellowish 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 (bovine pododermatitis, foul in the foot).

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

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

Treatment of ovine mastitis associated with *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 pigs.

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

4.4. Special warnings for each target species

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

A bacteriological cure of acute ovine mastitis caused by *Staphylococcus aureus* and *Mycoplasma agalactiae* has not been demonstrated by a clinical trial.

4.5. Special precautions for use

i) Special precautions for use in animals

Use of the 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.

ii) 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 APOTIL 300 MG/ML SOLUTION FOR INJECTION 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 APOTIL 300 MG/ML SOLUTION FOR INJECTION.
- 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 eyes.

- 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:0844 892 0111.

4.6. Adverse reactions (frequency and seriousness)

Occasionally, a soft diffuse swelling may occur at the injection site, but this disappears within five to eight days.

Deaths of cattle have been observed following a single intravenous dose of 5 mg/kg, and following the subcutaneous injection of doses of 150 mg/kg at 72 hour intervals. In pigs, intramuscular injection at 20 mg/kg has caused deaths. Sheep have died following a single intravenous injection of 7.5 mg/kg.

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 have been 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 Apotil 300 mg/ml per 30 kg body weight).

Cattle: method of administration
Withdraw the required dose from the vial and remove the syringe from the needle. When a group of animals is to be treated, leave the needle in the vial to remove the subsequent doses. Restrain the animal and insert a separate needle subcutaneously into the injection site, preferablyin 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 20 ml per injection site.

Sheep: method of administration

Accurate weighing of lambs is important to avoid overdosing. The use of a 2-ml or smaller syringe 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 skinfold. 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 the 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

The acute manifestations of multiple injections of large subcutaneous doses (150 mg/kg) in cattle included moderate electrocardiographic changes accompanied by mild focal necrosis, marked injection site oedema and death.

Single subcutaneous administration injection of 30 mg/kg in sheep produced increased respiratory rate, and at higher levels (150 mg/kg) ataxia, lethargy and drooping of the head.

4.11. Withdrawal periods

Cattle:
Meat & 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 & 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

ATCVet code: QJ01FA91
Pharmacotherapeutic group: Macrolides

5.1. Pharmacodynamic properties

Tilmicosin is a semi-synthetic antibiotic of the macrolide group, and is believed to affect bacterial protein synthesis. It is bacteriostatic but at high concentrations it may be bactericidal. This antibacterial activity is predominantly against Gram-positive microorganisms with activity against certain Gram-negative ones and Mycoplasma of bovine and ovine origin. In particular its activity has been demonstrated against the following micro-organisms:
Mannheimia, *Pasteurella, Actinomyces (Corynebacterium), Fusobacterium, Dichelobacter, Staphylococcus,* and *Mycoplasma* organisms of bovine and ovine origin.

Minimum inhibitory concentration measured in recently (2009-2012) isolated European field strains, derived from bovine respiratory 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 inotrophic 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 caused increased respiration, emesis and convulsions; 20 mg/kg resulted in mortality in 3 of 4 pigs, and 30 mg/kg caused the death of all 4 pigs tested. Intravenous injection of 4.5 to 5.6 mg tilmicosin/kg 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 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 Feedlot cattle	 10 mg/kg 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 10 mg/kg	 8 hours 8 hours	 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. In calves, lung concentrations of tilmicosin remain above 3.12 µg/ml for at least 72 hours after injection. In lambs, lung concentration was found to be approximately 3.7 µg/ml three days after a single subcutaneous injection of 10 mg/kg. In lactating ewes, its concentration in remained ≥1µg/ml for at least 72 hours after injection.

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, concentrated (for pH adjustment)
Water for injection

6.2. 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: 3 years
Shelf-life after first opening the immediate packaging: 28 days

6.4. Special precautions for storage

Do not store above 30 °C.
Protect from light.

6.5. Nature and composition of immediate packaging

50 ml, 100 ml and 250 ml Type-II glass amber vials, in boxes of 1, 6, 10 or 12 vials.

50 ml and 100 ml: closed with grey bromobutyl rubber stopper and an aluminium overseal.

250 ml: Closed with pink bromobutyl rubber stopper and aluminium overseals.

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 product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Nimrod Nederland B.V.
Doetinchemseweg 59
7007 Doetinchem
Netherlands

8. MARKETING AUTHORISATION NUMBER

Vm 61571/5000

9. DATE OF FIRST AUTHORISATION

14 April 2011

10. DATE OF REVISION OF TEXT

October 2025

Gavin Hall
Approved: 27 October 2025