

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

TILMINJECT 300 mg/ml Solution for Injection for Cattle and Sheep.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

### Active substance:

Tilmicosin 300 mg

### Excipients:

Propylene Glycol (E 1520) 250 mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection.

Clear yellow-orange 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 *Staphylococcus aureus* and *Mycoplasma agalactiae*.

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 this veterinary medicinal product should only be used based on susceptibility testing.

Use of the 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 macrolide antimicrobials, due to the potential for cross-resistance.

##### 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 Tilminject 300 mg/ml Solution for injection for cattle and ovine 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 Tilminject 300 mg/ml Solution for injection for cattle and ovine.
- 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:

The product is slightly irritant to the skin and eye. Avoid splashes on the skin and eyes. Personal protective equipment consisting of impervious gloves and

protective glasses should be worn when handling the veterinary medicinal product. In the event of accidental contact with the skin or eyes, rinse thoroughly with water. If irritation persists, seek medical advice. 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: .....

#### **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. In rare cases recumbency, incoordination and convulsions have been observed.

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.

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 and lactation**

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 a single dose of 10 mg tilmicosin per kg body weight (corresponding to 1 ml Tilminject per 30 kg body weight).

To ensure a correct dosage body weight should be determined as accurately as possible to avoid underdosing.

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.

##### **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 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.

#### **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 periods

**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

**ATCVet code:** QJ01FA91

#### 5.1. Pharmacodynamic properties

Tilmicosin is mainly a bactericidal semi-synthetic antibiotic of the macrolide group. Their antibacterial action is produced by an inhibition of protein synthesis by reversibly binding to 50S subunits of the ribosome. It has bacteriostatic action but at high concentrations it may be bactericidal. Tilmicosin is active against the following microorganisms which are involved in respiratory diseases in cattle and sheep: *Pasteurella multocida* and *Mannheimia haemolytica*. Tilmicosin is also active against the following microorganisms which cause foot rot in sheep: *Dichelobacter nodosus* and *Fusobacterium necrophorum*, and acute ovine mastitis in sheep: *Staphylococcus aureus* and *Mycoplasma agalactiae*.

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

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

Bacteria can develop resistance to macrolides through three basic mechanisms: 1) Natural resistance, 2) Acquired resistance or 3) Horizontally transferable resistance.

The Clinical and Laboratory Standards Institute CLSI has set the interpretative criteria for tilmicosin against *M. haemolytica* of bovine origin and specifically for bovine respiratory disease, as  $\leq 8 \mu\text{g/ml}$  susceptible,  $16 \mu\text{g/ml}$  intermediate, and  $\geq 32 \mu\text{g/ml}$  resistant (CLSI, (2018)).

## 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 <sub>max</sub>	C <sub>max</sub>
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.

### Environmental properties

Tilmicosin is persistent in soils.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1. List of excipients

Propylene glycol (E 1520)  
Phosphoric acid, concentrated (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: 18 months  
Shelf life after first opening of the immediate packaging: 28 days.

### 6.4. Special precautions for storage

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

### 6.5. Nature and composition of immediate packaging

Amber glass vials (Type II) sealed with a bromobutyl rubber stopper and Flip-off aluminium capsules.

Package sizes:

Carton box with 1 vial of 100 ml  
Carton box with 1 vial of 250 ml

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**

Laboratorios Calier, S.A.  
Barcelonès, 26  
08520 Les Franqueses del Vallès  
Barcelona (Spain)

**8. MARKETING AUTHORISATION NUMBER**

**9. DATE OF FIRST AUTHORISATION**

Date of first authorisation:> <{DD/MM/YYYY}><{DD month YYYY}>.

**10. DATE OF REVISION OF THE TEXT**

**PROHIBITION OF SALE, SUPPLY AND/OR USE**

For animal treatment only to be supplied only on veterinary prescription.  
For use by veterinary surgeons only