

## **Annex I**

**List of the names, pharmaceutical forms, strengths of the veterinary medicinal product, animal species, route of administration, marketing authorisation holders in the Member States**

| <b>Member State<br/>EU/EEA</b> | <b>Marketing<br/>authorisation holder</b>  | <b>Name</b>  | <b>INN</b> | <b>Strength</b> | <b>Pharmaceutical<br/>form</b> | <b>Animal species</b> | <b>Route of<br/>administration</b> |
|--------------------------------|--|--|------------|-----------------|--------------------------------|-----------------------|------------------------------------|
| Austria                        | Richter Pharma AG<br>Feldgasse 19<br>4600 Wels<br>AUSTRIA  | Micotil 300 mg/ml -<br>Injektionslösung für<br>Rinder                    | Tilmicosin | 300 mg/ml       | Solution for<br>injection      | Cattle                | Subcutaneous<br>injection          |
| Belgium                        | ELI LILLY BENELUX N.V.<br>Division Elanco Animal<br>Health<br>Stoofstraat 52<br>1000 Brussel<br>BELGIUM      | Micotil 300 mg/ml  | Tilmicosin | 300 mg/ml       | Solution for<br>injection      | Cattle, sheep         | Subcutaneous<br>injection          |
| Czech Republic                 | Eli Lilly Regional<br>Operations GmbH<br>Elanco Animal Health<br>Kölblgasse 8-10<br>1030 Wien<br>AUSTRIA     | Micotil 300 mg/ml<br>injekční roztok pro<br>skot (telata, mladý<br>skot) | Tilmicosin | 300 mg/ml       | Solution for<br>injection      | Cattle                | Subcutaneous<br>injection          |
| Germany                        | Lilly Deutschland GmbH<br>Teichweg 3<br>35396 Gießen<br>GERMANY  | Micotil 300  | Tilmicosin | 300 mg/ml       | Solution for<br>injection      | Cattle                | Subcutaneous<br>injection          |
| France                         | LILLY FRANCE<br>13 Rue Pages<br>92158 Suresnes Cedex<br>FRANCE   | MICOTIL 300  | Tilmicosin | 300 mg/ml       | Solution for<br>injection      | Cattle                | Subcutaneous<br>injection          |
| Greece                         | Eli Lilly Regional<br>Operations GesmbH<br>Elanco Animal Health<br>Kölblgasse 8-10<br>1030 Vienna<br>AUSTRIA | MICOTIL 300  | Tilmicosin | 300 mg/ml       | Solution for<br>injection      | Cattle, sheep         | Subcutaneous<br>injection          |

| Member State EU/EEA | Marketing authorisation holder   | Name                                       | INN        | Strength  | Pharmaceutical form    | Animal species          | Route of administration |
|---------------------|--|--|------------|-----------|------------------------|-------------------------|-------------------------|
| Spain               | ELANCO VALQUÍMICA S.A,<br>Avenida de la Industria 30<br>28108 Alcobendas<br>Madrid<br>SPAIN  | Micotil 300                                | Tilmicosin | 300 mg/ml | Solution for injection | Cattle                  | Subcutaneous injection  |
| Hungary             | Eli Lilly Regional Operations GmbH<br>Elanco Animal Health<br>Kölblgasse 8-10<br>1030 Vienna<br>AUSTRIA                              | Micotil 300 injekció                       | Tilmicosin | 300 mg/ml | Solution for injection | Cattle                  | Subcutaneous injection  |
| Ireland             | Eli Lilly and Company Ltd<br>Priestley Road<br>Basingstoke<br>Hampshire<br>RG24 9NL<br>UNITED KINGDOM                                | Micotil 300mg/ml<br>Solution for Injection | Tilmicosin | 300 mg/ml | Solution for injection | Cattle, sheep           | Subcutaneous injection  |
| Italy               | ELI LILLY ITALIA S.p.A.<br>Via A. Gramsci, 731/733<br>Sesto Fiorentino<br>ITALY  | Micotil 300                                | Tilmicosin | 300 mg/ml | Solution for injection | Cattle, sheep<br>rabbit | Subcutaneous injection  |
| The Netherlands     | Eli Lilly Nederland<br>B.V./Elanco AnimalHealth<br>Grootslag 1-5<br>3991 RA Houten<br>THE NETHERLANDS                                | MICOTIL 300<br>INJECTIE                    | Tilmicosin | 300 mg/ml | Solution for injection | Cattle, sheep           | Subcutaneous injection  |
| Portugal            | Lilly Portugal – Produtos Farmacêuticos, Lda.<br>Rua Cesário Verde, 5 –<br>piso 4<br>Linda-a-Pastora<br>2790-326 QUEIJAS<br>PORTUGAL | Micotil 300 mg/ml<br>solução injectável    | Tilmicosin | 300 mg/ml | Solution for injection | Cattle                  | Subcutaneous injection  |

| <b>Member State<br/>EU/EEA</b> | <b>Marketing<br/>authorisation holder</b>   | <b>Name</b>                                    | <b>INN</b> | <b>Strength</b> | <b>Pharmaceutical<br/>form</b> | <b>Animal species</b> | <b>Route of<br/>administration</b> |
|--------------------------------|---|--|------------|-----------------|--------------------------------|-----------------------|------------------------------------|
| United<br>Kingdom              | Eli Lilly & Company Ltd<br>Elanco Animal Health<br>Lilly House<br>Priestley Road<br>Basingstoke<br>RG24 9NL<br>UNITED KINGDOM | Micotil 300 mg/ml<br>Solution for<br>Injection | Tilmicosin | 300 mg/ml       | Solution for<br>injection      | Cattle, sheep         | Subcutaneous<br>injection          |

## **Annex II**

**Scientific conclusions and grounds for amendment of the summary of product characteristics, labelling and package leaflet**

# Overall summary of the scientific evaluation of Micotil 300 mg/ml Injectie and its associated names (see annex I)

## 1. Introduction

Micotil 300 Injectie is a solution for injection containing tilmicosin with a strength of 300 mg per ml. Tilmicosin is a macrolide antibiotic synthesized from tylosin which has an antibacterial spectrum similar to tylosin with enhanced activity against *Pasteurella multocida* and *Mannheimia haemolytica*. Micotil 300 Injectie and its associated names are veterinary medicinal products authorised for use in the target species cattle, sheep and rabbits for treatment of various infections caused by microorganisms susceptible to tilmicosin.

On 24 April 2012, the Netherlands sent a referral notification under Article 34(1) of Directive 2001/82/EC, as amended, to the CVMP/European Medicines Agency for Micotil 300 mg/ml Injectie and its associated names. The Netherlands referred the issue due to divergent national decisions having been taken by the EU Member States resulting in discrepancies in the product information for Micotil 300 mg/ml Injectie and its associated names.

The main areas of disharmony in the existing SPCs relate to:

- Target species;
- Indications;
- Posology;
- Withdrawal period.

## 2. Discussion of data available

### Cattle

Tilmicosin *in vitro* microbiological data of European isolates from respiratory disease in bovines were presented for several periods (2002-2004; 2004-2006 and 2009-2013). MIC measured in these isolates did not show an increase in MIC levels for *Pasteurella multocida* (97% of the isolates were susceptible to tilmicosin), therefore from the data provided no trend in resistance increase could be observed for one of the major pathogens for respiratory diseases in cattle. A slight increase in MIC levels could be observed for *Mannheimia haemolytica* isolates over the last decade, most of isolates (83%) were clinically susceptible to tilmicosin. The MIC<sub>90</sub> data from recently isolated European strains should be included in SPC section 5.1 Pharmacodynamic properties.

Numerous field studies using naturally infected calves of various ages with pneumonia, conducted over 20 years ago, indicated that tilmicosin is not inferior towards other positive controls, being long acting antibiotics or combinations of two antibiotics. Bacteriology from nasal swabs and lung tissues in these studies revealed *M. haemolytica* and *P. multocida* as major causes of pneumonia in calves.

The Committee considered that the proposed indication "treatment of respiratory tract infections caused by *M. haemolytica* and *P. multocida*" had been sufficiently substantiated by data.

Regarding the *Haemophilus (Actinobacillus)* and *Mycoplasma* the Committee considered that the data to substantiate these two pathogens were insufficient and the MAHs agreed to remove *Haemophilus (Actinobacillus)* and *Mycoplasma* from the respiratory indication for cattle.

No data to support the term "control" were provided. Furthermore, the text in the proposed indication "...and other microorganisms sensitive to tilmicosin" is not in accordance with recommendations in the CVMP reflection paper on macrolides, lincosamides and streptogramins

(EMA/CVMP/SAGAM/741087/2009)<sup>1</sup> and not in line with the CVMP guideline on the SPC for antimicrobials (EMA/CVMP/SAGAM/383441/2005)<sup>2</sup>.

Thus, based on the available data, the Committee considered the acceptable and more accurately described respiratory indication for cattle at the recommended dose of 10 mg/kg body weight should be: "Treatment of bovine respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida*".

Regarding treatment of interdigital necrobacillosis in cattle, the *in vitro* studies demonstrated that the MIC values (MIC<sub>50</sub> <0.25-0.5 µg/ml) of most major pathogens strains causing interdigital necrobacillosis in cattle, with the exception of *treponeme* infections, can be reached in the subcutaneous fat after a single subcutaneous injection with tilmicosin at a dose of 10 mg/kg body weight.

The clinical studies used naturally infected cattle with interdigital necrobacillosis without a bacteriological diagnosis. The recommended dose rate of 5 to 10 mg/kg body weight seems justified based on the available data, however pharmacokinetic studies combined with *in vitro* MIC studies imply that a dose of 10 mg/kg body weight would be preferable for curing the major pathogens in interdigital necrobacillosis in cattle.

Thus, based on the available data, the Committee considered the indication "treatment of interdigital necrobacillosis in cattle" is acceptable at the recommended dose of 10 mg/kg body weight.

Residue depletion data were made available and supported a cattle meat and offal withdrawal period of 70 days following a subcutaneous injection at the recommended dose of 10 mg/kg body weight.

Residue depletion data were made available and supported a cattle milk withdrawal period of 36 days following a subcutaneous injection at the recommended dose of 10 mg/kg body weight. There may be a concern that if the product is administered to an animal during the dry period, residues may continue to be present in milk for several days after parturition. Therefore, the Committee considered that the following warning sentence should be added in SPC section 4.11 Withdrawal period(s): "If the product is administered to cows during the dry period (in accordance with section 4.7 of the SPC), milk should not be used for human consumption until 36 days after calving".

## Sheep

Tolerance studies clearly demonstrate that a dosage of 20 mg/kg body weight subcutaneous tilmicosin injection in lambs (7-11 kg) was toxic, leading to deaths. Sheep weighing 40 kg were more resistant and survived a subcutaneous dose of 150 mg/kg body weight, showing ataxia and lethargy. A dose of 30 mg/kg body weight resulted in increased respiratory rate. Sometimes (1 in 12) a pain reaction was seen after subcutaneous injection of tilmicosin.

Pharmacokinetic studies demonstrate that concentrations of tilmicosin in the lung can exceed 2 µg/ml for more than 3 days which would be therapeutic for *M. haemolytica*, *Trueperella pyogenes* (formerly known as *Actinomyces pyogenes*), *Staphylococcus aureus* and *Mycoplasma ovipneumonia* according to *in vitro* studies conducted in 1992. During an artificial respiratory infection study with *M. haemolytica*, a single subcutaneous injection at 10 mg/kg body weight resulted in a significant overall improvement compared to the control group. Studies with naturally infected sheep, diagnosed with *M. haemolytica*, resulted in a clear reduction of body temperature, dyspnea scores and demeanour scores at day 3 after

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<sup>1</sup> CVMP Reflection paper on the use of macrolides, lincosamides and streptogramins (MLS) in food-producing animals in the European Union: development of resistance and impact on human and animal health (EMA/CVMP/SAGAM/741087/2009) - [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2011/11/WC500118230.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/11/WC500118230.pdf)

<sup>2</sup> CVMP guideline on the SPC for antimicrobials (EMA/CVMP/SAGAM/383441/2005) - [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Scientific\\_guideline/2010/02/WC500070670.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/02/WC500070670.pdf)

a single subcutaneous injection with tilmicosin at a dose of 10 mg/kg body weight. No inferiority was seen between the tilmicosin groups and positive controls, being long acting antibiotics.

The Committee considered that the proposed indication "treatment of respiratory tract infections caused by *M. haemolytica*" had been sufficiently substantiated by data. With regard to *P. multocida* it can be concluded that based on the information available for cattle this pathogen should remain in the indication.

Regarding the *Haemophilus (Actinobacillus)* and *Mycoplasma* the Committee considered that the data to substantiate these two pathogens were insufficient and the MAHs agreed to remove *Haemophilus (Actinobacillus)* and *Mycoplasma* from the respiratory indication for sheep.

No data to support the term "control" were provided. Furthermore, the text in the proposed indication "...and other microorganisms sensitive to tilmicosin" is not in accordance with recommendations in the CVMP reflection paper on macrolides, lincosamides and streptogramins (EMA/CVMP/SAGAM/741087/2009)<sup>1</sup> and not in line with the CVMP guideline on the SPC for antimicrobials (EMA/CVMP/SAGAM/383441/2005)<sup>2</sup>.

Thus, based on the available data the Committee considered the acceptable respiratory indication for sheep at the recommended dose of 10 mg/kg body weight should be: "Treatment of respiratory tract infections caused by *Mannheimia haemolytica* and *Pasteurella multocida*".

Regarding treatment of foot rot in sheep associated with *Dichelobacter nodosus* and *Fusobacterium necrophorum*, the *in vitro* studies demonstrated that the MIC values (MIC<sub>50</sub> <0.25-0.5 µg/ml) of several bacteria, causing foot rot in sheep, indicate sensitivity for tilmicosin, however some strains were resistant. Pharmacokinetic data showed that tilmicosin was well distributed into the skin of sheep following subcutaneous injection at doses of 5 mg/kg body weight or 10 mg/kg body weight. In a clinical field study including severe cases, treatment with tilmicosin at doses of either 5 mg/kg body weight or 10 mg/kg body weight resulted in a better cure rate as compared to the positive control group (amoxicillin 15 mg/kg body weight). The percentage of relapses was lowest in the 10 mg/kg body weight tilmicosin group, suggesting that this dose would be preferable.

Thus, based on the available data the Committee considered the indication "treatment of foot rot in sheep associated with *Dichelobacter nodosus* and *Fusobacterium necrophorum*" was acceptable at the recommended dose of 10 mg/kg body weight.

Regarding the treatment of acute ovine mastitis associated with *Staphylococcus aureus* and *Mycoplasma agalactiae*, the pathogens *Staphylococcus aureus* and *Mycoplasma agalactiae* appear to be sensitive for tilmicosin according to the measured MIC values (*S. aureus* MIC <0.25-1 µg/ml, *M. agalactiae* MIC=0.5 µg/ml). In milk, a concentration of tilmicosin of 1.2 µg/ml at day 3 has been measured indicating a concentration above most MIC values of the pathogens. In *Staphylococcus aureus* challenge study, tilmicosin treatment (10 mg/kg body weight as a single subcutaneous injection) in ewes resulted in significantly less mortality, and more normal udders at day 10 although milk samples were still bacteriologically positive in treated animals at day 10. In a field study, involving sheep with mastitis due to natural infection with *Mycoplasma agalactiae*, a single subcutaneous administration with tilmicosin at a dose of 10 mg/kg body weight resulted in significantly lower milk scores and overall udder scores compared to long-acting oxytetracycline. At day 10 tilmicosin still appeared to have lower udder scores although no longer significant. The CVMP concluded that, due to limited availability of alternative veterinary medicinal products for this indication and in the absence of reports on suspected lack of efficacy, the indication "for treatment of ovine mastitis associated with *Staphylococcus aureus* and *Mycoplasma agalactiae*" should be maintained, but in a modified manner to better reflect the study results, to "treatment of acute ovine mastitis associated with *Staphylococcus*



*aureus* and *Mycoplasma agalactiae*". The absence of bacteriological cure demonstration in the clinical study should be stated in the SPC in section 4.4 Special warnings for each target species.

The indication "as an aid in the control of outbreaks of enzootic abortion in ewes caused by *Chlamydia psittaci*" was only supported by positive control data. The treatment appears to be intended to be preventive, which is not in line with the principles of prudent use of antibiotics. Further to the serious concerns expressed by the CVMP about the proposed indication "as an aid in the in the control of outbreaks of enzootic abortion in ewes caused by *Chlamydia psittaci*" the MAHs agreed to remove all reference to this indication from the product information.

Residue depletion data was made available and supported a sheep meat and offal withdrawal period of 42 days following a subcutaneous injection at the recommended dose of 10 mg/kg body weight.

Residue depletion data was made available and supported a sheep milk withdrawal period of 18 days following a subcutaneous injection at the recommended dose of 10 mg/kg body weight. There may be a concern that if the product is administered to an animal during the dry period, residues may continue to be present in milk for days after parturition. Therefore, the Committee considered that the following warning sentence should be added in SPC section 4.11 Withdrawal period(s): "If the product is administered to ewes during the dry period (in accordance with section 4.7 of the SPC), milk should not be used for human consumption until 18 days after lambing".

### **Rabbits**

In a clinical trial, treatment of Pasteurellosis was performed with a dose of 25 mg/kg body weight. Since no dose-finding studies in rabbits were provided it cannot be concluded from the data available that Pasteurellosis can be treated with the recommended tilmicosin dosage of 10 mg/kg body weight. *Bordetella bronchiseptica* was not isolated in any clinical or preclinical study and no *in vitro* study has been performed with this bacteria. *Staphylococcus aureus* was not isolated in any preclinical study or clinical trial.

The second clinical trial which studied efficacy of tilmicosin against reproductive diseases showed no inferiority towards the positive control (penicillin combined with an aminoglycoside) however no negative controls were included. Therefore it is difficult to assess the efficacy of tilmicosin since no bacteriological diagnosis was conducted and both tilmicosin as well as the positive control were administered as a preventive therapeutic, five days before parturition.

Overall it can be concluded that data to substantiate the proposed indications in rabbits is minimally reported or lacking.

Furthermore, the safety of margin of the product is not in line with a safe use of the product in the rabbit species given the very small volume to administer. When administered by injection, tilmicosin has a narrow safety of margin. This led the CVMP in 2005 to limit the use of Micotil to sheep weighing more than 15 kg and to be administered by veterinary surgeons only (referral procedure under Article 35 of Directive 2001/82/EC, for Micotil 300 (EMA/V/A/010)). This restriction in sheep seems difficult to "coexist" with an authorisation in rabbits whose weight is less than 5 kg (rabbits are generally slaughtered around 2.5 kg). The posology is 10 mg tilmicosin per kg body weight which corresponds to 1 ml of product per 30 kg body weight. A rabbit doe of 5 kg body weight would require a dose of 0.1 ml of product and a growing rabbit a volume around 0.05 ml. An overdosage is likely to happen for such a small amount of product.

Further to the assessment of the above mentioned data and the serious concerns expressed by the CVMP about the use of the product in the target species rabbits the MAHs agreed to remove all references to rabbits from the product information.

### 3. Benefit-Risk assessment

Numerous studies revealed that 10 mg tilmicosin/kg body weight is effective against respiratory disease due to *M. haemolytica* and *P. multocida* in cattle and sheep.

Since the MIC values of *M. haemolytica* tended to increase over the last decade the MIC<sub>90</sub> data from recently isolated European strains should be included in SPC section 5.1 Pharmacodynamic properties.

The available data demonstrated that tilmicosin is efficacious at the proposed dose of 10 mg tilmicosin/kg body weight against interdigital necrobacillosis in cattle and foot rot in sheep.

Studies demonstrated that tilmicosin at 10 mg tilmicosin/kg body weight has efficacy against acute mastitis in sheep caused by *Staphylococcus aureus* and *Mycoplasma agalactiae* although no bacterial cure was established. The absence of bacteriological cure demonstration in the clinical study should appear in SPC section 4.4 Special warnings for each target species.

Further to the serious concerns expressed by the CVMP regarding the use of the product in the target species rabbits and as "aid in the control of outbreaks of enzootic abortion in ewes caused by *Chlamydia psittaci*" the MAHs agreed to remove all references to rabbits and enzootic abortion in ewes from the product information.

Regarding the cattle and sheep withdrawal periods there may be a concern that if the product is administered to an animal during the dry period, residues may continue to be present in milk for days after parturition. Therefore the following warning sentences should be added in SPC section 4.11 Withdrawal period(s): (i) "If the product is administered to cows during the dry period (in accordance with section 4.7 of the SPC), milk should not be used for human consumption until 36 days after calving" and (ii) "If the product is administered to ewes during the dry period (in accordance with section 4.7 of the SPC), milk should not be used for human consumption until 18 days after lambing".

The overall benefit-risk balance of the product for use in cattle and sheep was deemed positive subject to the recommended changes in the product information (see annex III).

### Grounds for amendment of the summary of product characteristics, labelling and package leaflet

Whereas

- the CVMP considered the scope of the referral was the harmonisation of the summary of product characteristics, labelling and package leaflet;
- the CVMP reviewed the summary of product characteristics, labelling and package leaflet proposed by the marketing authorisation holders and considered all the overall submitted data;

the CVMP has recommended the amendment of the marketing authorisations for which the summary of product characteristics, labelling and package leaflet are set out in annex III for Micotil 300 Injectie and associated names (see annex I).

## **Annex III**

### **Summary of product characteristics, labelling and package leaflet**

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally.

## 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 case 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*.

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 “product name (to be completed nationally)” 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 “product name (to be completed nationally)”. 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)**

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.

#### **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 "*product name (to be completed nationally)*") 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 ( $\mu\text{g/ml}$ ) range | MIC <sub>50</sub> ( $\mu\text{g/ml}$ ) | MIC <sub>90</sub> ( $\mu\text{g/ml}$ ) |
|-----------------------|--------------------------------|--|--|
| <i>P. multocida</i>   | 0.5- > 64                      | 4                                      | 8                                      |
| <i>M. haemolytica</i> | 1 - 64                         | 8                                      | 16                                     |

The Clinical and Laboratory Standards Institute (CLSI) has set the interpretive 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. 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  $\leq 16\mu\text{g/ml}$  = susceptible and  $\geq 32\mu\text{g/ml}$  = 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 inotropy). Cardiovascular toxicity may be due to calcium channel blockade.

In dogs,  $\text{CaCl}_2$  treatment showed a positive effect on the left ventricular inotropic 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 propranolol 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:

|                  | <b>Dose Rate</b>     | <b>T<sub>max</sub></b> | <b>C<sub>max</sub></b> |
|------------------|----------------------|------------------------|------------------------|
| 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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

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

### **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: 2 years  
Shelf life after first opening of the immediate packaging: 28 days

### **6.4 Special precautions for storage**

Protect from direct sunlight.

### **6.5 Nature and composition of immediate packaging**

25 ml, 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 national requirements.

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

**7. MARKETING AUTHORISATION HOLDER**

*To be completed nationally.*

**8. MARKETING AUTHORISATION NUMBER(S)**

*To be completed nationally.*

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

*To be completed nationally.*

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

*To be completed nationally.*

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

*To be completed nationally.*

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGE**

Cardboard carton

**1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

*To be completed nationally.*

**2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES**

Tilmicosin 300 mg/ml

**3. PHARMACEUTICAL FORM**

Solution for injection

**4. PACKAGE SIZE**

25 ml  
50 ml  
100 ml  
250 ml

**5. TARGET SPECIES**

Cattle and sheep

**6. INDICATION(S)**

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*.

**7. METHOD AND ROUTE(S) OF ADMINISTRATION**

FOR SUBCUTANEOUS INJECTION ONLY.

Read the fold out label or package leaflet before use.

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.

The use of the product should be based on susceptibility tests.

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.

Use 10 mg tilmicosin per kg body weight (corresponding to 1 ml “*product name (to be completed nationally)*” per 30 kg body weight).

Do not treat lamb weighing less than 15 kg, since there is a risk of overdose toxicity.

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

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

## 8. WITHDRAWAL PERIOD

### Cattle:

Meat and offal: 70 days

Milk: 36 days

### Sheep:

Meat and offal: 42 days

Milk: 18 days

## 9. SPECIAL WARNING(S), IF NECESSARY

Do not administer intravenously. Intravenous injection in cattle and sheep has been fatal.

Do not administer intramuscularly.

Do not administer to lambs weighing less than 15 kg.

Do not administer to horses, donkeys, pigs, goats or primates. Injection of the product in goats and pigs has been fatal.

Do not use in case of hypersensitivity to the active substance or to any of the excipients.

### 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 “*product name (to be completed nationally)*” 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 “*product name (to be completed nationally)*”.
- 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.

**NOTE TO PHYSICIAN:** please see inside of label or package leaflet for details.

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.

**10. EXPIRY DATE**

EXP

Once broached use within 28 days.

**11. SPECIAL STORAGE CONDITIONS**

Protect from direct sunlight.

**12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY**

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with national requirements.

**13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable**

For animal treatment only.  
To be supplied only on veterinary prescription.

**14. THE WORDS “KEEP OUT OF THE REACH AND SIGHT OF CHILDREN”**

Keep out of the sight and reach of children.

**15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

*To be completed nationally*

**16. MARKETING AUTHORISATION NUMBER(S)**

*To be completed nationally*

**17. MANUFACTURER’S BATCH NUMBER**

Lot



**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE**

Glass vial – base label (fold out label details are the same as the package leaflet)

**1. NAME OF THE VETERINARY MEDICINAL PRODUCT**

*To be completed nationally.*

**2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES**

Tilmicosin 300 mg/ml

**3. PHARMACEUTICAL FORM**

Solution for injection

**4. PACKAGE SIZE**

25 ml  
50 ml  
100 ml  
250 ml

**5. TARGET SPECIES**

Cattle and sheep

**6. INDICATION(S)**

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*.

**7. METHOD AND ROUTE(S) OF ADMINISTRATION**

FOR SUBCUTANEOUS INJECTION ONLY.

Read the fold out label or package leaflet before use.

**8. WITHDRAWAL PERIOD**

See fold out label or package leaflet for details.

**9. SPECIAL WARNING(S), IF NECESSARY**

**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 “*product name (to be completed nationally)*” 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 “*product name (to be completed nationally)*”.
- 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.

**NOTE TO PHYSICIAN:** please see inside of label or package leaflet for details.

**10. EXPIRY DATE**

EXP

Once broached use within 28 days.  
Discard date.....

**11. SPECIAL STORAGE CONDITIONS**

Protect from direct sunlight.

**12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY**

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with national requirements.

**13. THE WORDS “FOR ANIMAL TREATMENT ONLY” AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE**

For animal treatment only.  
To be supplied only on veterinary prescription.

**14. THE WORDS “KEEP OUT OF THE SIGHT AND REACH OF CHILDREN”**

Keep out of the reach and sight of children.

**15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

*To be completed nationally.*

**16. MARKETING AUTHORISATION NUMBER(S)**

*To be completed nationally.*

**17. MANUFACTURER'S BATCH NUMBER**

Lot

**B. PACKAGE LEAFLET**

## PACKAGE LEAFLET

*Product name (to be completed nationally)*

### 1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:

*To be completed nationally*

Manufacturer responsible for batch release:

*To be completed nationally*

### 2. NAME OF THE VETERINARY MEDICINAL PRODUCT

*To be completed nationally*

### 3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Tilmicosin 300 mg/ml

### 4. INDICATIONS

#### 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*.

### 5. 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 case of hypersensitivity to the active substance or to any of the excipients.

## 6. ADVERSE REACTIONS

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.

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

## 7. TARGET SPECIES

Cattle and sheep.

## 8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

FOR SUBCUTANEOUS INJECTION ONLY.

Use 10 mg tilmicosin per kg body weight (corresponding to 1 ml “*product name (to be completed nationally)*” 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.

## 9. ADVICE ON CORRECT ADMINISTRATION

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.

The use of the product should be based on susceptibility tests.

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

Avoid introduction of contamination into vial during use. Do not use “*product name (to be completed nationally)*” if you notice any foreign particulate matter and/or abnormal physical appearance.

## 10. WITHDRAWAL PERIOD

### **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, 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, milk should not be used for human consumption until 18 days after lambing.

## 11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Protect from direct sunlight

Do not use this veterinary medicinal product after the expiry date which is stated on the label after EXP.

Shelf-life after first opening the container: 28 days

Do not use “*product name (to be completed nationally)*” if you notice any foreign particulate matter and/or abnormal physical appearance.

## 12. SPECIAL WARNING(S)

### **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*.

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.

### **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 “*product name (to be completed nationally)*” 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 “*product name (to be completed nationally)*”.
- 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*)**

**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.

**Overdose (symptoms, emergency procedures, 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.

### **Incompatibilities**

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

### **13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY**

Medicines should not be disposed of via wastewater or household waste.

Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

### **14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED**

*To be completed nationally.*

### **15. OTHER INFORMATION**

“*product name (to be completed nationally)*” is contained in 25 ml, 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.