ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

TILMICOSIN CALIER 250 mg/ml Solution for use in drinking water/milk (DE, EL, ES, HU, PT)
TILMICOSINA CALIER 250 mg/ml Solution for use in drinking water/milk (IT)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Tilmicosin (as phosphate)..... 250 mg
(Equivalent to tilmicosin phosphate..... 278.2 mg)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Disodium edetate	2 mg
Propyl gallate (E 310)	0.2 mg
Phosphoric acid, concentrated	
Purified water	

Light amber clear solution.

3. CLINICAL INFORMATION

3.1 Target species

Chickens (except hens producing eggs for human consumption),
Turkeys
Pigs
Calves (non-ruminant)

3.2 Indications for use for each target species

Pigs: For the treatment and metaphylaxis of respiratory disease in pig herds, associated with *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae* and *Pasteurella multocida.*

The presence of the disease in the group/flock must be established before the product is used.

Chickens (except hens producing eggs for human consumption): For the treatment and metaphylaxis of respiratory disease in chicken flocks, associated with *Mycoplasma gallisepticum* and *M. synoviae.*

The presence of the disease in the group/flock must be established before the product is used.

Turkeys: For the treatment and metaphylaxis of respiratory disease in turkey flocks, associated with *Mycoplasma gallisepticum* and *M. synoviae..*

The presence of the disease in the group/flock must be established before the product is used.

Calves: For the treatment and metaphylaxis of bovine respiratory disease, associated with *Mannheimia haemolytica, Mycoplasma bovis, M. dispar* and *Pasteurella multocida.*

The presence of the disease in the group/flock must be established before the product is used.

3.3 Contraindications

Do not allow horses and other equines access to drinking water containing tilmicosin.

Do not use in cases of hypersensitivity to tilmicosin or to any of the excipients.

3.4 Special warnings

Important: Must be diluted before administration to animals.

Pigs, chickens and turkeys: Water consumption should be monitored in order to guarantee adequate dosing. In case water consumption does not match quantities for which recommended concentrations were calculated, the concentration of the veterinary medicinal product has to be adapted in a way that the recommended dosage will be taken up by the animals or different medication should be considered.

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

3.5. Special precautions for use

Special precautions for safe use in the target species:

For oral use only. Contains disodium edetate; do not inject

Severely ill individuals tend to drink less and may need simultaneous treatment, preferably by parenteral medication.

Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level.

Use of the product should be in accordance with official, national and regional antimicrobial policies.

An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach.

Do not exceed the stated dose or duration of treatment.

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

Tilmicosin may induce irritation. Macrolides, such as tilmicosin, may also cause hypersensitivity (allergy) following injection, inhalation, ingestion or contact with skin or eye. Hypersensitivity to tilmicosin may lead to cross reactions to other macrolides and vice versa. Allergic reactions to these substances may occasionally be serious and therefore direct contact should be avoided.

To avoid exposure during preparation of the medicated drinking water, wear overalls, safety glasses, and impervious gloves. Do not eat, drink or smoke when handling this product. Wash hands after use.

In the case of accidental ingestion, wash out mouth immediately with water and seek medical advice. In the event of accidental skin contact, wash thoroughly with soap and water. In case of accidental eye contact, flush the eyes with plenty of clean, running water.

Do not handle the product if you are allergic to ingredients in the product.

If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.

Special precautions for the protection of the environment:

Tilmicosin is toxic to cyanobacteria.

3.6 Adverse events

Chickens (except hens producing eggs for human consumption), Turkeys, Pigs, Calves (non-ruminant):

Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Decreased drinking

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian,

to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See also the last section of the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of tilmicosin has not been established in animals used for breeding purposes.

3.8 Interaction with other medicinal products and other forms of interaction

None known.

3.9 Administration routes and dosage

In drinking water/milk use
The product must be diluted in drinking water (pigs, chickens, turkeys) or milk replacer (calves) before the administration

Pigs: To be included in the drinking water to provide a daily dose of 15-20 mg/kg bodyweight for 5 days.

Chickens and Turkeys (except hens producing eggs for human consumption): To be included in the drinking water at a daily dose of 15-20 mg/kg bodyweight in chickens and 10-27 mg/kg bodyweight in turkeys for 3 days.

Calves: To be included in milk replacer only, at a dose of 12.5 mg/kg bodyweight and given twice daily for 3-5 consecutive days, which may be achieved by the inclusion of 1 ml of product every 20 kg bodyweight.

To ensure a correct dosage, body weight should be determined as accurately as possible.

Medicated water should be the only source of drinking. Medicated water must be renewed every 24 hours. Medicated milk replacer should be prepared freshly every 6 hours.

The uptake of medicated water/milk replacer depends on the clinical condition of the animals. In order to obtain the correct dosage, the concentration of the tilmicosinmay need to be adjusted accordingly.

The use of suitably calibrated measuring equipment is recommended.

Based on the recommended dose and the number and weight of animals to be treated, the exact daily concentration of the veterinary medicinal product should be calculated according to the following formula:

Dose (mg veterinary medicinal product per kgX body weight per day)	mean body weight (kg) of animals to be treated	= mg veterinary medicinal product per litre drinking water

Average daily water intake (l/animal)

Animals with acute or severe clinical conditions that cannot drink, should receive adequate parenteral treatment.

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

When pigs are offered drinking water containing 300 or 400 mg/litre (equivalent to 22.5-40 mg/kg bodyweight or 1.5-2 times the recommended concentration) commonly animals exhibit a reduced water intake. Although this has a self-limiting effect on tilmicosin intake, it could, in extreme circumstances, result in dehydration. This can be corrected by the removal of the medicated drinking water and replacement with fresh unmedicated water.

No symptoms of overdose have been seen in chickens given drinking water containing levels of tilmicosin up to 375 mg/litre (equivalent to 75-100 mg/kg bodyweight or 5 times the recommended dose) for 5 days; daily treatment with 75 mg/litre (equivalent to the maximum recommended dose) for 10 days resulted in a reduction in faecal consistency.

No symptoms of overdose have been seen in turkeys given drinking water containing levels of tilmicosin up to 375 mg/litre (equivalent to 50-135 mg/kg bodyweight or 5 times the recommended dose) for 3 days; daily treatment with 75 mg/litre (equivalent to the maximum recommended dose) for 6 days also produced no symptoms of overdose.

No symptoms of overdose, with exception of a slight decrease in the milk consumption, have been seen in calves given twice daily doses 5 times the maximum recommended dose or for twice the maximum recommended duration of treatment.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

This veterinary medicinal product is intended to be used for the preparation of medicated water/milk.

Administration by a veterinary surgeon or under their direct responsibility.

3.12 Withdrawal period(s)

Meat and offal:

Pigs: 14 days
Chickens: 12 days
Turkeys: 19 days
Calves: 42 days

Not for use in birds producing or intended to produce eggs for human consumption. Do not use within 14 days of the start of the laying period.

Not authorised for use in animals producing milk for human consumption.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QJ01FA91

4.2 Pharmacodynamics

Tilmicosin is a semi-synthetic antibiotic of the macrolide group and is believed to affect protein synthesis. It has bacteriostatic action but at high concentrations it may be bactericidal.

Tilmicosin is active against the following microorganisms:

- *Pigs: Mycoplasma hyopneumoniae, Pasteurella multocida and Actinobacillus pleuropneumoniae*
- *Chickens and turkeys: Mycoplasma gallisepticum and Mycoplasma synoviae*
- *Calves: Mannheimia haemolytica, Pasteurella multocida, Mycoplasma bovis and M. dispar.*

NCCLS breakpoints	resistant	intermediate	susceptible
Bovine Pasteurella spp	≥ 32 µg/ml	16 µg/ml	≤ 8 µg/ml
Porcine Pasteurella multocida	≥ 32 µg/ml		≤ 16 µg/ml
Porcine Actinobacillus pleuropneumoniae	≥ 32 µg/ml		≤ 16 µg/ml

Scientific evidence suggests that macrolides act synergistically with the host immune system. Macrolides appear to enhance phagocyte killing of bacteria. Tilmicosin has been shown to inhibit *in vitro* the replication of the Porcine Reproductive and Respiratory Syndrome virus in alveolar macrophages in a dose dependent fashion.

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

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

4.3 Pharmacokinetics

Whilst blood concentrations of tilmicosin are low, there is pH-dependent macrophage accumulation of tilmicosin in inflamed tissues.

Pigs: After oral administration of 200 mg tilmicosin/l drinking water, the average active substance concentrations detected in lung tissue, alveolar macrophages and bronchial epithelium 5 days after the start of treatment were 1.44 µg/ml, 3.8 µg/ml and 7.4 µg/g respectively.

Poultry: As early as 6 hours after oral administration of 75 mg tilmicosin/l drinking water, the average active substance concentrations detected in lung and alveolar tissue were 0.63 µg/g and 0.30 µg/g respectively. 48 hours after the start of treatment, the tilmicosin concentrations in lung and alveolar tissue were 2.3 µg/g and 3.29 µg/g respectively.

Calves: As early as 6 hours after oral administration of 25 mg tilmicosin/kg body weight/day in milk replacer, an average active substance concentration of 3.1 µg/g was detected in lung tissue. 78 hours after the start of treatment, the tilmicosin concentration in lung tissue was 42.7 µg/g. Therapeutically effective concentrations of tilmicosin were measured up to 60 hours after treatment.

Turkeys: After oral administration of 75 mg tilmicosin/l drinking water, the average active substance concentrations detected in lung tissue, air sac tissue and plasma 5 days after the start of treatment were 1.89 µg/ml, 3.71 µg/ml and 0.02 µg/g respectively. The highest mean tilmicosin concentration detected for lung tissues was 2.19 µg/g at 6 days; for air sac tissue it was 4.18 µg/g at 2 days and in the plasma it was 0.172 µg/g at 3 days.

Environmental properties

Tilmicosin is very persistent and toxic to cyanobacteria.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

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

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 18 months
Shelf life after first opening the immediate packaging: 6 months
Shelf life after dilution in drinking water according to directions: 24 hours
Shelf life after reconstitution in milk replacer according to directions: 6 hours

5.3 Special precautions for storage

As packaged for sale:
This veterinary medicinal product does not require any special temperature storage conditions.
Protect from light.

After first opening the immediate packaging:
Do not store above 25ºC.
Protect from light.

5.4 Nature and composition of immediate packaging

White opaque high-density polyethylene bottles closed with white high density polyethylene screw cap with strapping and removable polyethylene sealing disk.

Package sizes:
Bottle of 1 L
Bottle of 5 L
Not all pack sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

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

The veterinary medicinal product should not enter water courses as tilmicosin phosphate may be dangerous for fish and other aquatic organisms.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Laboratorios Calier, S.A.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: DD month YYYY

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

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database.