ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE VETERINARY MEDICINAL PRODUCTS, ANIMAL SPECIES, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATE

40 g tilmicosin per 1000 g

Member State	Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Route of administration
Belgium	Eli Lilly Benelux N.V. Elanco Animal Health Rue de l'Etuve 52 Stoofstraat 52 1000 Brussel Belgium	Pulmotil 40 VET Premix	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen Germany	Pulmotil G 40 AMV	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen Germany	Pulmotil G 40 Granulat	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral
Denmark	Eli Lilly Danmark A/S Elanco Animal Health Nybrovej 110 2800 Lyngby Denmark	Pulmotil Vet	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral
Spain	Elanco Valquímica, S.A. Avenida de la Industría, 30 28108 – Alcobendas Madrid Spain	PULMOTIL 40	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral
France	Lilly France SA Département Elanco Santé Animale 13 Rue Pagès 92158 Suresnes Cedex France	Pulmotil Tilmicosine 40 Porcins	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral

Ireland	Elanco Animal Health Eli Lilly and Company Ltd Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Pulmotil G40 Premix	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral
The Netherlands	Eli Lilly Nederland B.V. Elanco Animal Health Grootslag 1-5 3991 RA Houten The Netherlands	Pulmotil G40 premix	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral
Portugal	Lilly Portugal - Produtos Farmacêuticos, Lda Rua Dr. António Loureiro Borges, 1-piso 1, Arquiparque, Miraflores 1495-016 Algés Portugal	PULMOTIL G40 Pré Mistura para alimento medicamentoso	Premix for medicated feeding stuff	40g tilmicosin per 1000g	Pigs	Oral

100 g tilmicosin per 1000 g

Member State	Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Route of administration
Austria	Richter Pharma AG Feldgasse 19 4600 Wels Austria	PULMOTIL Prämix 10% - Granulat für Schweine	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Belgium	Eli Lilly Benelux N.V. Elanco Animal Health Rue de l'Etuve 52 Stoofstraat 52 1000 Brussel Belgium	Pulmotil 100 VET Premix	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Belgium	Eli Lilly Benelux N.V. Elanco Animal Health Rue de l'Etuve 52-Bte Stoofstraat 52 1000 Brussel Belgium	Pulmotil 100 Granules	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen Germany	Pulmotil G 100 AMV	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen Germany	Pulmotil G 100	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Denmark	Eli Lilly Danmark A/S Elanco Animal Health Nybrovej 110 2800 Lyngby Denmark	Pulmotil Vet	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral

Denmark	Eli Lilly Danmark A/S Elanco Animal Health Nybrovej 110 2800 Lyngby Denmark	Pulmotil Vet Oralt pulver	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Spain	Elanco Valquímica, S.A. Avenida de la Industría, 30 28108 – Alcobendas Madrid Spain	PULMOTIL 100	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Ireland	Elanco Animal Health Eli Lilly and Company Ltd Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Pulmotil G100 Premix	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Italy	Eli Lilly Italia Elanco Animal Health Via A. Gramsci, 731-733 50019 Sesto Fiorentino Florence Italia	PULMOTIL G100 PREMIX	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
Luxembourg	Eli Lilly Benelux N.V. Elanco Animal Health Rue del'Etuve 52-Bte 1Stoofstraat 52 1000 Brussel Belgium	Pulmotil 100 Vet Premix	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
The Netherlands	Eli Lilly Nederland B.V. Elanco Animal Health Grootslag 1-5 3991 RA Houten The Netherlands	Pulmotil G100 premix	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral

Portugal	Lilly Portugal - Produtos Farmacêuticos, Lda Rua Dr. António Loureiro Borges, 1-piso 1, Arquiparque, Miraflores 1495-016 Algés Portugal	PULMOTIL G100 Pré Mistura para alimento medicamentoso	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral
United Kingdom	Elanco Animal Health Eli Lilly and Company Ltd Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Pulmotil G100 Premix	Premix for medicated feeding stuff	100g tilmicosin per 1000g	Pigs	Oral

200 g tilmicosin per 1000 g

Member State	Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Route of administration
Austria	Richter Pharma AG Feldgasse 19 4600 Wels Austria	Pulmotil Prämix 20%	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs, Rabbit	Oral
Belgium	Eli Lilly Benelux N.V. Elanco Animal Health Rue de l'Etuve 52 Stoofstraat 52 1000 Brussel Belgium	Pulmotil 200 VET Premix	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs, Rabbits	Oral
Czech Republic	Eli Lilly Regional Operation Ges.m.b.H. Elanco Animal Health Kölblgasse 8-10 1030 Vienna Austria	PULMOTIL 200 prm. ad us. vet.	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Cyprus	Eli Lilly Regional Operation Ges.m.b.H. Elanco Animal Health Kölblgasse 8-10 1030 Vienna Austria	Pulmotil G200 Premix	Premix for medicated feeding stuff	200g tilmicosin per 100g	Pigs	Oral
Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen Germany	Pulmotil G 20% AMV	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral

Germany	Lilly Deutschland GmbH Teichweg 3 35396 Gießen Germany	Pulmotil G 20%	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Denmark	Eli Lilly Danmark A/S Elanco Animal Health Nybrovej 110 2800 Lyngby Denmark	Pulmotil Vet	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Greece	Eli Lilly Regional Operation Ges.m.b.H. Elanco Animal Health Kölblgasse 8-10 1030 Vienna Austria	Pulmotil 200 medicated premix	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Spain	Elanco Valquímica, S.A. Avenida de la Industría, 30 28108 – Alcobendas Madrid Spain	PULMOTIL 200	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Hungary	Eli Lilly Regional Operation Ges.m.b.H. Elanco Animal Health Kölblgasse 8-10 1030 Vienna Austria	Pulmotil G 200 premix	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Ireland	Elanco Animal Health Eli Lilly and Company Ltd Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Pulmotil G200 Premix	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral

Italy	Eli Lilly Italia Elanco Animal Health Via A. Gramsci, 731-733 50019 Sesto Fiorentino Florence Italia	PULMOTIL G200 PREMIX	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs, Rabbits	Oral
Latvia	Eli Lilly Regional Operation Ges.m.b.H. Elanco Animal Health Kölblgasse 8-10 1030 Vienna Austria	Pulmotil 200 premix	Premix for medicated feeding stuff	200 g tilmicosin per 1000 g	Pigs	Oral
Luxembourg	Eli Lilly Benelux N.V. Elanco Animal Health Rue del'Etuve 52-Bte 1Stoofstraat 52 1000 Brussel Belgium	Pulmotil 200 Vet Premix	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs, Rabbits	Oral
The Netherlands	Eli Lilly Nederland B.V. Elanco Animal Health Grootslag 1-5 3991 RA Houten The Netherlands	Pulmotil G200 premix	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Poland	Eli Lilly Regional Operation Ges.m.b.H. Elanco Animal Health Kölblgasse 8-10 1030 Vienna Austria	Pulmontil 200	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Portugal	Lilly Portugal - Produtos Farmacêuticos, Lda Rua Dr. António Loureiro Borges, 1-piso 1, Arquiparque, Miraflores 1495-016 Algés Portugal	PULMOTIL G200 Pré Mistura para alimento medicamentoso	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral

Romania	Eli Lilly Regional Operation Ges.m.b.H. Elanco Animal Health Kölblgasse 8-10 1030 Vienna Austria	Pulmotil 200 Vet Premix	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral
Slovak Republic	Eli Lilly Regional Operation Ges.m.b.H. Elanco Animal Health Kölblgasse 8-10 1030 Vienna Austria	PULMOTIL G 200	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Fattening pigs	Oral
United Kingdom	Elanco Animal Health Eli Lilly and Company Ltd Priestley Road Basingstoke Hampshire RG24 9NL United Kingdom	Pulmotil G200 Premix	Premix for medicated feeding stuff	200g tilmicosin per 1000g	Pigs	Oral

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND LABELLING

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF PULMOTIL VET PREMIX

1. Introduction

Pulmotil VET Premix for medicated feeding stuff is currently registered in 19 EU Member States with three different strengths (40g, 100g and 200g per kg) available. The majority of the marketing authorisations have been approved via national procedures. However, marketing authorisations were also granted via two separate Mutual Recognition Procedures with Italy and Ireland as the Reference Member States.

This referral was related to the divergent national decisions taking by member states in relation with the SPC of the products Pulmotil 40 VET Premix, Pulmotil 100 VET Premix, Pulmotil 200 VET Premix and associated name, raised by Belgium.

The main sections of disharmony of the existing SPCs (non exhaustive) are:

4.2 Indications for Use, Specifying the Target Species: in some Member States the product is indicated for rabbits and in others not.

4.9 Amount to be administered and administered route: the recommended amount to be administered and the treatment duration vary amount the Member States.

4.11 Withdrawal period(s): for pigs the withdrawal period granted for the product varies among the Member States from 7 to 21 days before slaughter

2. Discussion

The Marketing Authorisation Holders submitted at the request of CVMP:
- an exhaustive list of differences between the SPCs of the product authorized in the member states;
- a proposal for a harmonised product information (SPC, labelling and package leaflet), taking into account the latest guidance;
- the available relevant data substantiating such proposed harmonised product information.

Efficacy in pigs

The CVMP has assessed for the preventive use a pilot study, four dose determination studies and 12 field trial reports. For the treatment use, the field trial reports included in the two European Clinical Field Trials Programme (9 field trial in the first phase and 10 field trial in the second phase) and two additional field trial reports were assessed.

The CVMP accepts that a claim for efficacy at a dose of 8 to 16 mg/kg bw/day of tilmicosin (equivalent to 200 to 400 ppm in the feed) for a period of 15 to 21 days for prevention and treatment of respiratory infections in pigs has been demonstrated.

In relation to the pathogens involved the microorganism *Haemophilus parasuis* should be removed. The following indication can be accepted: Prevention and treatment of respiratory disease caused by *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae, Pasteurella multocida* and other organisms sensitive to tilmicosin in pigs.

Efficacy in rabbits

Rabbits were approved as target species only in Austria, Belgium, Italy and Luxembourg for Pulmotil 200 Vet premix. The CVMP has assessed a PK/PD approach to support use in respiratory disease in rabbit and one clinical trial, as well as bibliographic and pharmacovigilance data provided by the

Marketing Authorisation Holders. As to where the SPC in Austria and Italy include indications that cover enteric disease caused by Clostridia, CVMP concludes that no data have been provided in support of this claim.

In respect of the benefit/risk balance for target species rabbit, the CVMP considers that benefit/risk balance is positive:

- notwithstanding the fact that the clinical field study using dosage of the product have some shortcomings, the pre-clinical studies and the recent MICs data suggest the effective dosage in feed is 12.5 mg/kg for 7 days in the prevention and treatment of respiratory disease caused by *Pasteurella multocida and Bordetella bronchiseptica* in rabbits;
- rabbit is minor species, with specific problems on availability of authorised veterinary products;
- the history of use and the various management steps now set out in the harmonised SPC (bacteriological sampling and susceptibility testing are recommended).

The CVMP can accept:

a) The indication for use in rabbits: prevention and treatment of respiratory disease caused by *Pasteurella multocida and Bordetella bronchiseptica* susceptible to tilmicosin.

b) The amounts to be administered and administration route: administered in the feed at 12 mg/kg bodyweight/day of tilmicosin (equivalent to 200 ppm in the feed) for 7 days.

Withdrawal periods

The Marketing Authorisation Holders' proposal to harmonise the withdrawal period for both species, on the basis of the pivotal residue studies presented can be accepted:

Pigs: 21 days
Rabbits: 4 days

Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: the proposed 2 years is acceptable.

Shelf life after first opening the immediate packaging: 3 months is not included in the Marketing Authorisation Holders' proposal, but it is part of the marketing authorisation in 3 Member States.

In relation to 'shelf life after incorporation into meal or pelleted feed', CVMP cannot accept the Marketing Authorisation Holders' proposal " 3 months, except for medicated feed containing 30% wheat in which case the validity is reduced to 1 month". Although tilmicosin appears to have an acceptable stability through 3 months at 25 ºC in meal type feeds, in pelleted feeds the behaviour is not the same. The sudden decline in potency after one month at 25 ºC for tilmicosin in pelleted feeds with levels of wheat higher than 30% is troubling. It would give warning that there could be other components (such as other cereals) that could produce the same effect, since the reason for this loss of activity has not been explained in the submission and remained unknown. In conclusion, the recommended shelf life after incorporation into meal or pelleted feed for both target species is 1 month.

SPC harmonisation

Where the indications in rabbits are restricted to respiratory infections, the CVMP can accept this claim. CVMP can also accept the proposed dose in both pigs and rabbits as these are in accordance with those used in the experimental and field studies.

The CVMP recommends that further changes to the SPC proposed by the Marketing Authorisation Holders are made:

- Indication for pigs: delete the microorganism *Haemophilus parasuis;*
- Contraindications: include a new statement in relation to the hypersensitivity to tilmicosin;
- Include a new statement in relation to the prudent use: due to the likely variability (time, geographical) in the occurrence of the resistance of bacteria for tilmicosin, bacteriological sampling and susceptibility testing are recommended;
- Modify the special precautions to be taken by the person administering the veterinary medicinal product to animals;
- Two sentences should be added in point 4.9: in accordance with the information provided, it has been observed that before incorporation into the finished feed, it was performed a previous mix with a suitable amount of feed. Besides, temperature in the pelleting conditions have not exceeded 75 ºC;
- The inclusion rate in feed established at the tables (4.9) would differ on each product strength;
- The reference to rice hulls should be removed from the SPC. It is noted in relation to the list of excipients, that the difference in formulations of the different product strengths should be resolved by the use of separate SPCs per product strength;
- The shelf life after first opening of the immediate packaging should be added;
- The shelf life after incorporation into meal or pelleted feed: 1 month;
- The description of the nature and composition of immediate packaging should be harmonised.

Having considered the grounds for referral and the response provided by the Marketing Authorisation Holders, the CVMP concludes that the benefit/risk balance of the products is positive for use in both pigs and rabbits subject to the recommended changes of Summary of the Product Characteristics and product information (Annex III).

GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND LABELLING

Whereas:

- The efficacy against infections caused by *Haemophilus parasuis* in pigs has not been substantiated;
- Contraindications should include a statement in relation to the hypersensitivity to tilmicosin;
- Due to the likely variability (time, geographical) in the occurrence of the resistance of bacteria for tilmicosin, bacteriological sampling and susceptibility testing are recommended;
- The special precautions to be taken by the person administering the veterinary medicinal product to animals need modification;
- Information should be provided on pre-mixing before pelleting and pelleting temperature;
- The inclusion rate in feed established would differ for each product strength;
- The reference to rice hulls should be removed;
- The shelf life after first opening of the immediate packaging should be added;
- The proven shelf life after incorporation into meal or pelleted feed is 1 month;
- The description of the nature and composition of immediate packaging should be harmonised;
- The complete SPC should be harmonised in the framework of this referral procedure,

the CVMP has recommended the amendment of the Marketing Authorisations for which the Summary of Product Characteristics is set out in Annex III for Pulmotil 40 VET Premix, Pulmotil 100 VET Premix, Pulmotil 200 VET Premix and associated names.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Tilmicosin (as phosphate) 40 g/kg
Active substance:
Tilmicosin (as phosphate) 100 g/kg
Active substance:
Tilmicosin (as phosphate) 200 g/kg

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff.

A yellowish tan to reddish tan free-flowing granular material.

4. CLINICAL PARTICULARS

4.1 Target species

Pigs and rabbits

4.2 Indications for use, specifying the target species

Pigs: Prevention and treatment of respiratory disease caused by *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae, Pasteurella multocida* and other organisms sensitive to tilmicosin

Rabbits: Prevention and treatment of respiratory disease caused by *Pasteurella multocida and Bordetella bronchiseptica,* susceptible to tilmicosin.

4.3 Contraindications

Horses or other *Equidae*, must not be allowed access to feeds containing tilmicosin. Horses fed with tilmicosin medicated feeds may present signs of toxicity with lethargy, anorexia, reduction of feed consumption, loose stools, colic, distension of the abdomen and death.

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

4.4 Special warnings for each target species

Under practical conditions, the management of respiratory disease outbreaks recognises that acutely ill animals are inappetant and require parenteral therapy.

4.5 Special precautions for use

Special precautions for use in animals

Inappropriate use of the product may increase the prevalence of bacteria resistant to tilmicosin and may decrease the effectiveness of treatment with tilmicosin related substances.

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

Due to the likely variability (time, geographical) in the occurrence of the resistance of bacteria for tilmicosin, bacteriological sampling and susceptibility testing are recommended

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 feed, wear overalls, safety glasses, impervious gloves and wear either a disposable half mask respirator conforming to European Standard EN149 or a non-disposable respirator to European Standard EN140 with a filter to EN143. 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.

4.6 Adverse reactions (frequency and seriousness)

In very rare cases, feed intake may decrease (including feed refusal) in animals receiving medicated feed. This effect is transient.

4.7 Use during pregnancy, lactation or lay

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

4.8 Interaction with other medicinal products and other forms of interaction

None known.

4.9 Amounts to be administered and administration route

The uptake of medicated feed depends on the clinical condition of the animals. In order to obtain a correct dosage the concentration of tilmicosin has to be adjusted accordingly.

Use the following formula:

$$\text{Kg Premix/tonne feed} = \frac{\text{Dose rate (mg/kg bodyweight) x bodyweight (kg)}}{\text{Daily feed intake (kg) x premix strength (g/kg)}}$$

Pigs
Administer in the feed at a dose of 8 to 16 mg/kg body weight/day of tilmicosin (equivalent to 200 to 400 ppm in the feed) for a period of 15 to 21 days.

Indication	Dose of tilmicosin	Duration of treatment	Inclusion rate in feed
Prevention and treatment of respiratory disease	8-16 mg/kg bodyweight/day	15 to 21 days	1-2 kg Pulmotil 200 Vet Premix /tonne 2-4 kg Pulmotil 100 Vet Premix /tonne 5-10 kg Pulmotil 40 Vet Premix/tonne

Rabbits
Administer in the feed at 12 mg/kg body weight/day of tilmicosin (equivalent to 200 ppm in the feed) for 7 days.

Indication	Dose of tilmicosin	Duration of treatment	Inclusion rate in feed
Prevention and treatment of respiratory disease	12 mg/kg bodyweight/day	7 days	1 kg Pulmotil 200 Vet Premix /tonne 2 kg Pulmotil 100Vet Premix/tonne 5kg Pulmotil 40 Vet Premix /tonne

To ensure thorough dispersion of the product, it should first be mixed with a suitable quantity of feed before incorporation into the finished feed.

This product can be incorporated into pelleted feed, preconditioned for the minimum time-period at a temperature not exceeding 75°C

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary
No symptoms of overdose have been seen in pigs fed a ration containing levels of tilmicosin up to 80 mg/kg bodyweight (equivalent to 2000 ppm in the feed or ten times the recommended dose) for 15 days.

4.11 Withdrawal period(s)

Pigs: 21 days
Rabbits: 4 days

5. PHARMACOLOGICAL PROPERTIES

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

5.1 Pharmacodynamic properties

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. This antibacterial activity is predominantly against Gram-positive microorganism with activity against certain gram-negative ones and Mycoplasma of a bovine, porcine, ovine and avian origin. In particular its activity has been demonstrated against the following micro-organism:
Pigs: Mycoplasma hyopneumoniae, Pasteurella multocida, Actinobacillus pleuropneumoniae.
Rabbits: Pasteurella multocida, Staphylococcus aureus and Bordetella bronchoseptica

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.

5.2 Pharmacokinetic particulars

Pigs:
Absorption: When administered to pigs via the oral route at a dose of 400 mg tilmicosin/kg feed (equivalent to approximately 21.3 mg tilmicosin/kg bodyweight/day), tilmicosin moves rapidly out of the serum into areas of low pH. The highest concentration in the serum (0.23 ±0.08 µg/ml) was recorded on day 10 of medication, but concentrations above the limit of quantification (0.10 µg/ml) were not found in 3 out of 20 animals examined. Lung concentrations increased rapidly between days 2 and 4 but no significant changes were obtained following four days of dosing. The maximum concentration in lung tissue (2.59±1.01 µg/ml) was recorded on day 10 of medication.

When administered at a dose of 200 mg tilmicosin/kg feed (equivalent to approximately 11.0 mg/kg/day), plasma concentrations above the limit of quantification (0.10 µg/ml) were found in 3 out of 20 animals examined. Quantifiable levels of tilmicosin were found in lung tissue with the maximum concentration (1.43±1.13 µg/ml) being recorded on day 10 of medication.

Distribution: Following oral administration, tilmicosin is distributed throughout the body with especially high levels found in the lung and in lung tissue macrophages. It is also distributed in the liver and kidney tissues.

Rabbits:
Absorption: When administered orally to rabbits at a dose of 12 mg tilmicosin/kg b.w. as a single dose there is a quick absorption. Maximum concentrations were reached in 30 minutes, being the Cmax obtained of 0.35 µg/ml. Tilmicosin plasma concentrations decreased to 0.1 µg/ml within 2 hours and to 0.02 µg/ml after 8 hours. The elimination half-life was 22 hours.

Distribution: Following oral administration, tilmicosin is distributed throughout the body with especially high levels found in lungs. After 5 days of treatment with medicated feed at a dosage of 200 ppm of Pulmotil, tilmicosin concentrations in lung tissues were of 192 ± 103 µg/g.

Applicable to both species:
Biotransformation: Several metabolites are formed, the predominant one being identified as T1. However the bulk of tilmicosin is excreted unchanged.

Elimination: Following oral administration, tilmicosin is excreted mainly via the bile into the faeces but a small proportion is excreted via the urine.

Environmental properties

The primary route of environmental exposure is from manure applied to agricultural land as fertilizer. Tilmicosin degrades/declines slowly in the soil. Therefore, to protect soil and ground water, pig manure not to be spread onto the grass land and when spread onto arable land plough to a depth of 30 cm. Environmental assessments have demonstrated that the use of Pulmotil Premix as indicated is not expected to have any impact on the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

For products containing 40 and 100g tilmicosin/kg:	For products containing 200g tilmicosin/kg:
Ground corn cobs	Ground corn cobs
Soya-bean oil (as stated in the Ph.Eur)	Soya-bean oil
Soya-bean mill run	

6.2 Incompatibilities

Not to be incorporated into feeds containing Bentonite.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 3 months.
Shelf life after incorporation into meal or pelleted feed: 1 month.

6.4. Special precautions for storage

Store in a dry place.
Do not store above 25 ºC.
Protect from direct sunlight.

6.5 Nature and composition of immediate packaging

Products containing 40 and 100g tilmicosin/kg are packed in either:
1. Polyethylene/polyamide/polyethylene (inner layer) bags containing 10 kg of product, or,
2. Paper/polyethylene/aluminium/polyethylene/paper bags containing 2 kg, 5 kg or 10 kg of product.

Product containing 200g tilmicosin/kg is packed in either:
1. Polyethylene/polyamide/polyethylene (inner layer) bag containing 10 kg of product, or,
2. A preformed block bottomed 1 kg bag constructed using a paper/polyethylene/aluminium/polyethylene/paper laminate either stitched closed or heat-sealed

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.

See the environmental properties section.

7. MARKETING AUTHORISATION HOLDER

{For national implementation}

8. MARKETING AUTHORISATION NUMBER(S)

{For national implementation}

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

LABELLING

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

To be completed nationally

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Active substance:
Tilmicosin (as phosphate) 40 g/kg
Active substance:
Tilmicosin (as phosphate) 100 g/kg
Active substance:
Tilmicosin (as phosphate) 200 g/kg

3. PHARMACEUTICAL FORM

Premix for medicated feeding stuff

4. PACKAGE SIZE

40 g/kg Premix:
2 kg, 5 kg and 10 kg
100 g/kg Premix:
2 kg, 5 kg and 10 kg
200g/kg: 1 kg and 10 kg

5. TARGET SPECIES

Pigs
Rabbits

6. INDICATION(S)

Pigs: Prevention and treatment of respiratory disease caused by *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae, Pasteurella multocida* and other organisms sensitive to tilmicosin.

Rabbits: Prevention and treatment of respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica,* susceptible to tilmicosin.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

In-feed use.

Read the package leaflet on reverse of the bag before use.

Pigs
Administer in the feed at a dose of 8 to 16 mg/kg body weight/day of tilmicosin activity (equivalent to 200 to 400 ppm in the feed) for a period of 15 to 21 days.

Rabbits
Administer in the feed at 12 mg/kg body weight/day of tilmicosin (equivalent to 200 ppm in the feed) for 7 days.

Not to be incorporated into feeds containing Bentonite.

To ensure thorough dispersion of the product, it should first be mixed with a suitable quantity of feed before incorporation into the finished feed.

This product can be incorporated into pelleted feed, preconditioned for the minimum time-period at a temperature not exceeding 75°C.

8. WITHDRAWAL PERIOD

Pigs: 21 days
Rabbits: 4 days

9. SPECIAL WARNING(S), IF NECESSARY

Do not allow horses and other equines access to medicated feed containing tilmicosin.

People with known hypersensitivity to tilmicosin should avoid contact with the product.

When mixing the veterinary medicinal product and handling the medicated feed, direct contact with eyes, skin and mucous membranes should be avoided. Personal protective equipment should be worn.

In case of accidental ingestion seek medical advice immediately and show the label to the physician.

10. EXPIRY DATE

EXP Once opened, use within 3 months
Once incorporated into meal or pelleted feed, use within 1 month

11. SPECIAL STORAGE CONDITIONS

Store in a dry place.
Do not store above 25 °C.
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 products 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 reach and sight of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{For national implementation}

16. MARKETING AUTHORISATION NUMBER(S)

{For national implementation}

17. MANUFACTURER'S BATCH NUMBER

Lot