Annex I

List of the names, pharmaceutical forms, active substance, strengths of the veterinary medicinal products, animal species, marketing authorisation holders in the Member States

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
Austria	**Richter Pharma AG** Feldgasse 19 A-4600 Wels AUSTRIA	Pulmotil G 100 g/kg Arzneimittel-Vormischung zur Herstellung von Fütterungsarzneimitteln für Schweine und Kaninchen	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Austria	**Richter Pharma AG** Feldgasse 19 A-4600 Wels AUSTRIA	Pulmotil G 200 g/kg Arzneimittel-Vormischung zur Herstellung von Fütterungsarzneimitteln für Schweine und Kaninchen	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Belgium	**Eli Lilly Benelux N.V.** **Elanco Animal Health** Rue de l'Etuve 52 Stoofstraat 52 1000 Brussel BELGIUM	Pulmotil 40 VET Pre-mix	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Belgium	**Eli Lilly Benelux N.V.** **Elanco Animal Health** Rue de l'Etuve 52 Stoofstraat 52 1000 Brussel BELGIUM	Pulmotil 100 VET Pre-mix	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Belgium	**Eli Lilly Benelux N.V.** **Elanco Animal Health** Rue de l'Etuve 52 Stoofstraat 52 1000 Brussel BELGIUM	Pulmotil 100 Granules	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
Belgium	**Eli Lilly Benelux N.V.** **Elanco Animal Health** Rue de l'Etuve 52 Stoofstraat 52 1000 Brussel BELGIUM	Pulmotil 200 VET Pre-mix	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Cyprus	**Eli Lilly Regional Operations GmbH** Elanco Animal Health Kolblgasse 8-10 1030 Wien AUSTRIA	Pulmotil pre-mix 200 g/kg ,πρόμιγμα για φαρμακούχο ζωοτροφή,για χοίρους και κονίκλους.	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Czech Republic	**Eli Lilly Regional Operations GmbH** Elanco Animal Health Kolblgasse 8-10 1030 Wien AUSTRIA	Pulmotil 200 mg/g pre-mix pro medikaci krmiva	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Germany	**Lilly Deutschland GmbH** Abt. Elanco Animal Health Werner-Reimers-Str. 2-4 D-61352 Bad Homburg GERMANY	Pulmotil G 40	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Germany	**Lilly Deutschland GmbH**Abt. Elanco Animal Health Werner-Reimers-Str. 2-4 D-61352 Bad Homburg GERMANY	Pulmotil G 100	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Germany	**Lilly Deutschland GmbH** Abt. Elanco Animal Health Werner-Reimers-Str. 2-4 D-61352 Bad Homburg GERMANY	Pulmotil G 20% AMV	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
Denmark	**Elanco Animal Health Eli Lilly Danmark A/S** Nybrovej 110 DK-2800 Kongens Lyngby DENMARK	Pulmotil Vet.	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Denmark	**Elanco Animal Health Eli Lilly Danmark A/S** Nybrovej 110 DK-2800 Kongens Lyngby DENMARK	Pulmotil Vet.	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Denmark	**Elanco Animal Health Eli Lilly Danmark A/S** Nybrovej 110 DK-2800 Kongens Lyngby DENMARK	Pulmotil Vet.	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Greece	**Eli Lilly Regional Operations GmbH** Elanco Animal HealthKolblgasse 8-10 1030 Wien AUSTRIA	PULMOTIL 200	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Spain	**ELANCO VALQUÍMICA, S.A.** Avda. de la Industria 30 28108 Alcobendas Madrid SPAIN	PULMOTIL G 40	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Spain	**ELANCO VALQUÍMICA, S.A.** Avda. de la Industria 30 28108 Alcobendas Madrid SPAIN	PULMOTIL G 100	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
Spain	**ELANCO VALQUÍMICA, S.A.** Avda. de la Industria 30 28108 Alcobendas Madrid SPAIN	PULMOTIL G 200	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
France	**LILLY France** 13 Rue Pages 92158 Suresnes Cedex FRANCE	PULMOTIL TILMICOSINE 40 PORC-LAPIN	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
France	**QALIAN** 34 Rue Jean Monnet Zi D'Etriche 49500 Serge FRANCE	SANTAMIX TILMICOSINE 40 PORCINS - LAPINS	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
France	**SOGEVAL** 200 Route de Mayenne Zi des Touches 53000 Laval FRANCE	CONCENTRAT VO 08 TILMICOSINE PORCIN-LAPIN	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Hungary	**Eli Lilly Regional Operations GmbH** Elanco Animal Health Kolblgasse 8-10 1030 Wien AUSTRIA	Pulmotil G 200 gyógypre-mix	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Ireland	**Eli Lilly and Company Ltd Elanco Animal Health** Lilly House Priestly Road Basingstoke Hampshire RG24 9NL UNITED KINGDOM	Pulmotil G40 Pre-mix for medicated feedingstuff	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
Ireland	**Eli Lilly and Company Ltd Elanco Animal Health** Lilly House Priestly Road Basingstoke Hampshire RG24 9NL UNITED KINGDOM	Pulmotil G100 Pre-mix for medicated feedingstuff	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Ireland	**Eli Lilly and Company Ltd Elanco Animal Health** Lilly House Priestly Road Basingstoke Hampshire RG24 9NL UNITED KINGDOM	Pulmotil G200 Pre-mix for medicated feedingstuff	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Italy	**ELI LILLY ITALIA SPA** VIA GRAMSCI 731/733 - SESTO FIORENTINO - FI ITALY	PULMOTIL G 200 PRE-MIX	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Italy	**CEVA VETEM SpA** via Colleoni 15 20041 Agrate Brianza (MB) ITALY	MICLOZAN 200 PRE-MIX	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Netherlands	**Eli Lilly Nederland B.V.** Elanco Animal Health Grootslag 1-5 3991 RA Houten THE NETHERLANDS	PULMOTIL® G40 pre-mix voor gemedicineerd voer voor varkens	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Netherlands	**Eli Lilly Nederland B.V.** Elanco Animal Health Grootslag 1-5 3991 RA Houten THE NETHERLANDS	PULMOTIL® G100 pre-mix voor gemedicineerd voer voor varkens	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
Netherlands	**Eli Lilly Nederland B.V.**Elanco Animal Health Grootslag 1-5 3991 RA Houten THE NETHERLANDS	PULMOTIL® G200 pre-mix voor gemedicineerd voer voor varkens	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Portugal	**Lilly Portugal – Produtos Farmacêuticos, Lda.** Rua Cesário Verde, nº5- piso 4 Linda-a-Pastora 2790 – 326 QUEIJAS PORTUGAL	Pulmotil G40 Pré-mistura medicamentosa para alimento medicamentoso para suínos e coelhos	Tilmicosin (as phosphate)	40 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Portugal	**Lilly Portugal – Produtos Farmacêuticos, Lda.** Rua Cesário Verde, nº5- piso 4 Linda-a-Pastora 2790 – 326 QUEIJAS PORTUGAL	Pulmotil G100 Pré-mistura medicamentosa para alimento medicamentoso para suínos e coelhos	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Portugal	**Lilly Portugal – Produtos Farmacêuticos, Lda.** Rua Cesário Verde, nº5- piso 4 Linda-a-Pastora 2790 – 326 QUEIJAS PORTUGAL	Pulmotil G200 Pré-mistura medicamentosa para alimento medicamentoso para suínos e coelhos	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Romania	**Eli Lilly Regional Operations GmbH** Elanco Animal Health Kolblgasse 8-10 1030 Wien AUSTRIA	PULMOTIL 200g/kg pre-mix	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
Slovak Republic	**Elli Lilly and Company Limited**.Speke OperationsFleming RoadSpeke Liverpool L24 9LN UNITED KINGDOM	Pulmotil G 200 pre-mix ad us.vet.	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits

Member State EU/EEA	Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Animal species
United Kingdom	**Eli Lilly and Company Ltd Elanco Animal Health** Lilly House Priestly Road Basingstoke Hampshire RG24 9NL UNITED KINGDOM	Pulmotil G100 Pre-mix for Medicated Feedingstuff	Tilmicosin (as phosphate)	100 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits
United Kingdom	**Eli Lilly and Company Ltd Elanco Animal Health** Lilly House Priestly Road Basingstoke Hampshire RG24 9NL UNITED KINGDOM	Pulmotil G200 Pre-mix for Medicated Feedingstuff	Tilmicosin (as phosphate)	200 g tilmicosin per kg pre-mix	Pre-mix for medicated feedingstuff	Pigs, Rabbits

Annex II

Scientific conclusions and grounds for amendment of the Summary of Product Characteristics and labelling

Overall summary of the scientific evaluation of all pre-mixes for medicated feedingstuff containing 40, 100 or 200 g tilmicosin per kg pre-mix and administered to rabbits (*see Annex I*)

1. Introduction

The pre-mixes for medicated feedingstuffs containing 40 g, 100 g or 200 g of tilmicosin per kg pre-mix, are veterinary medicinal products which are indicated in pigs for the prevention and treatment of respiratory disease caused by *Actinobacillus pleuropneumoniae, Mycoplasma hyopneumoniae, Pasteurella multocida* and other organisms sensitive to tilmicosin. Additionally, these veterinary medicinal products are indicated in rabbits for the prevention and treatment of respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica,* susceptible to tilmicosin.

On 8 April 2011, the European Commission initiated a referral under Article 35 of Directive 2001/82/EC, as amended, for all pre-mixes for medicated feedingstuff containing 40, 100 or 200 g tilmicosin per kg pre-mix and administered to rabbits. The CVMP was requested to give its opinion on the recommended dose and inclusion rates in feed for pre-mixes for medicated feedingstuffs containing 40, 100 or 200 g tilmicosin per kg pre-mix and administered to rabbits. The Committee was also asked to recommend whether the marketing authorisations should be maintained, varied, suspended or withdrawn.

The marketing authorisation holders were requested to provide the following:

1. Justification and relevant supporting data for the recommended dose and inclusion rates in feed for pre-mixes for medicated feedingstuffs containing 40, 100 or 200 g tilmicosin per kg pre-mix and administered to rabbits.
2. The CVMP's Note for guidance on additional quality requirements for products intended for incorporation into animal feedingstuffs (medicated pre-mixes) (EMEA/CVMP/080/95)[1] states that the daily dose of the medicated pre-mix must be contained in at least half the daily ration of the animals under treatment. Confirmation should be provided that this requirement will be fulfilled by all of the pack sizes for all the different strengths.
3. As outlined in the CVMP's Note for guidance (EMEA/CVMP/080/95) a description should be provided of how the pre-mix is to be incorporated into the feedingstuff. The relevant advice given in the product literature should be provided along with a discussion of whether this is in line with CVMP's Note for guidance (EMEA/CVMP/080/95). This discussion should be supported with the appropriate data, i.e. data confirming the pelleting conditions suitability and demonstrating that these conditions do not affect the shelf-life granted for the medicated feedingstuff (1 month). If the existing advice is not considered sufficient a proposal for revised text should be submitted.

[1] CVMP Note for Guidance on additional quality requirements for products intended for incorporation into animal feedingstuffs (mediciated premixes) - http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004466.pdf

2. Discussion of the data available

Supporting data for the recommended dose

During the previous referral procedure under Article 34 of Directive 2001/82/EC (EMEA/V/A/037)[2] the CVMP assessed the efficacy of tilmicosin in rabbits and considered that, notwithstanding the fact that the clinical field study using dosage of the product had some shortcomings, the pre-clinical studies and the minimal inhibitory concentration (MICs) data suggested the effective dosage in feed is 12.5 mg/kg bw/day for 7 days in the prevention and treatment of respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica* in rabbits. The CVMP also considered that rabbits are minor species, with specific problems concerning availability of authorised veterinary products for this species and considered the history of use and the various management steps now set out in the harmonised SPC (bacteriological sampling and susceptibility testing are recommended).

The use of tilmicosin in rabbits orally at 12.5 mg/kg bw/day for 7 days showed that from the second day of treatment, tilmicosin concentrations attained in lung tissue and pulmonary alveolar macrophages exceeded those in plasma by 7 and 400 fold, respectively, and high levels were maintained in lung tissues during the entire treatment duration. The pharmacokinetic parameters confirm the effective dose of tilmicosin. This dose should be maintained by a proper mixing of medicated pre-mixes of different concentrations into feedingstuffs.

The pharmakokinetic/pharmacodynamic study and MIC data to support use in respiratory disease in rabbits at dose of 12.5 mg/kg bw/day for 7 days (submitted previously) were referenced in the answers to the CVMP list of questions and were found to be acceptable.

Inclusion rates

The marketing authorisation holders reported that the administration of feed to the food producing rabbits is via complete feedingstuff. The average size of a feed mixer can vary from 3 to 5 tons and complete medicated rabbit feedingstuff is produced in the same size mixers.

Regarding the target species feeding behaviour, it is known that rabbits feed frequently (up to 30 times per day of 2–8 g of feed over 4–6 minute periods[3]). Thus, one rabbit of 1.5 kg can consume in average 180 g of feed per day. Sick animals hereby consume less, being acceptable at 100 g per day.

The approved dose is 12.5 mg/kg bw/day for 7 days, which is achieved by incorporating tilmicosin at a rate of 200 g per ton of finished feed (equivalent to 200 ppm). Taking into account the information provided, the CVMP considered that the requirement for the dose being in at least half the daily ration was fulfilled, and that the target of 200 ppm of tilmicosin per ton of feed could be achieved with all the pack sizes of the different strengths (40 g, 100 g and 200 g).

Regarding meal feeds, concentrations are 10 – 13% higher than the expected nominal concentration of 200 mg/kg. These higher values require further consideration as they would lead to higher than target dose.

In a study provided on the homogeneity of a 200 g pre-mix two different batches of 200 g premix were used to prepare 4 pilot batches of medicated feedingstuff (2 batches of crumble feed and 2 batches of pelleted feed). Homogeneity was demonstrated as the coefficient of variation was less than 5 % in all the cases tested. Tilmicosin content was around 105% of the theoretical value of 200 ppm for crumble

[2] CVMP opinion following an Article 34 referral on Pulmotil 40 VET Premix, Pulmotil 100 VET Premix, Pulmotil 200 VET Premix and associated names (2009) - http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Pulmotil_Premix_34/WC500036654.pdf

[3] Cathy A. Johnson-Delaney, DVM, Dipl ABVP (Avian). Anatomy and Physiology of the Rabbit and Rodent Gastrointestinal System. In: Association of Exotic Mammal Veterinarians (AEMV) Sessions, Preceedings, 2006

feed and tilmicosin content recovery in pelleted feed was 100 – 103%. According to stability results, after 3 months no significant change was observed for appearance and loss on drying.

No data on incorporation were provided for Tilmicosin 40 g pre-mix. This was considered acceptable, as homogeneity of medicated feedingstuffs is reached with low concentrations of medicated pre-mixes. The incorporation rate of Tilmicosin 40 g pre-mix in the feed would be 5 kg per ton (the requirement of the European Pharmacopoeia monograph on pre-mixes for medicated feedingstuffs for veterinary use).

The results of a mixing uniformity study (with tilmicosin 100 g and 200 g pre-mixes) the homogeneity results obtained from ten analysed samples per batch, showed no samples out of the 85-115% range of the mean content. Mean content in pelleted feeds was in the range of 90-110% of the nominal content therefore, the homogeneity of those medicated feeds is considered demonstrated.

When comparing tilmicosin content in the meal feeds during the mixing uniformity test (i.e. prior to pelleting) versus tilmicosin content of the pelleted feeds, a significant decrease in tilmicosin content was observed, although that decrease was within the ± 15% preset acceptance range.

Regarding meal feeds, mean content was not in the range of 90-110% of the nominal content (180 – 220 ppm), since concentration values were higher than the expected nominal concentration of 200 ppm ± 10% (values rate between 198.1 – 243.6 ppm). Concentrations are 10 – 13% higher than the expected nominal concentration of 200 mg/kg. Whilst the demonstration of homogeneity was considered acceptable, the higher than expected values need explanation, taking into account that if those meal feeds were administered to animals, the concentration in those feeds would be higher than the target dose of 200 ppm.

The conditioning and pelleting were described. Only medicated rabbit feed prepared with tilmicosin 100 g pre-mix was used. The testing of only one strength was considered valid because the concentration of tilmicosin in the final medicated feeding stuffs would be 200 ppm in all cases, as the homogenicity of the other medicated premixes was sufficiently justified.

Pellet storage stability was evaluated by examining the difference in the level of tilmicosin assay over a 12 week period at 25 °C/60% relative humidity (RH) and 40 °C/70% RH. Taking into account that stability results on medicated pelleted rabbit feeds were similar to those obtained for medicated pelleted pig feeds, a shelf life period of 3 months after incorporation into feeding stuffs was considered acceptable.

Decrease on tilmicosin content for swine medicated pelleted feeds containing more than 30% wheat was noted. Taking into account the characteristics of a rabbit feed used to prepare pelleted medicated feedingstuffs, it was concluded that the maximum limit of cereal meals that can be used in commercial feedingstuffs for fattening rabbits should be less than 30% (the inclusion of 30% of wheat meal is not appropriate due to the risk of triggering severe enteric problems).

Consequently, since the inclusion of 30% of wheat meal in medicated pelleted feed in rabbits would not be appropriate, it was considered that there would be no problem with the restriction on the shelf life after incorporation into meal adopted through a worksharing procedure because that case was not expected to be presented in rabbit. As the product information is common for pigs and rabbits, the one month shelf life after incorporation into pelleted feed containing more than 30% wheat was considered acceptable.

3. Benefit-risk assessment

Benefit Assessment

Direct benefits

The effective dosage in feed is 12.5 mg/kg bw/day for 7 days in the prevention and treatment of respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica* in the minor species rabbits.

Taking into account the information provided, it is considered that the target of 200 g of tilmicosin per ton of rabbit pelleted feed (200 ppm) could be achieved with the appropriate inclusion rate of the tilmicosin 40 g pre-mix, tilmicosin 100 g pre-mix and tilmicosin 200 g pre-mix, and with all of the pack sizes mentioned.

Risk Assessment

A risk has been identified on the assessment due to the high values of tilmicosin content in the meal feed prior to the conditioning/pelleting process and no explanation has been provided

Evaluation of the benefit-risk balance

It is agreed that the effective dosage in feed is 12.5 mg/kg bw/day for 7 days in the prevention and treatment of respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica* in the minor species rabbits.

High values of tilmicosin content in the rabbit feed meal have been observed prior to the conditioning/pelleting process. Even though it was confirmed that no overage was used in the formulation, no justification was found for those results and it was considered that the results do not fall into the normal range observed in other feed studies.

Conclusion on the benefit-risk balance

With regard to the recommended dose it is agreed that the effective dosage in feed is 12.5 mg per kg BW per day for 7 days in the prevention and treatment of respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica* in the minor species rabbits.

With regard to the inclusion rates it is considered that the requirement for the dose being in at least half the daily ration was fulfilled, and that the target of 200 ppm of tilmicosin per ton of feed could be achieved with all the pack sizes of the different strengths (40 g, 100 g and 200 g).

Regardless of the unexplained high meal assay results, it has been considered that if rabbit feed meal was correctly formulated with a concentration of 200 ppm (instead of the high values reported) it would be expected that the tilmicosin content in the pelleted feed would still be within the specification range of ±15 % of nominal value. This was further supported considering further data provided in which no such problems were presented thus far with pilot scale batches.

The high values of tilmicosin in the medicated feed prior to the pelleting process need further explanation. The CVMP therefore requests that conditioning/pelleting stability studies with three batches of medicated rabbit feeds are carried out in order to confirm whether or not the high tilmiscosin valuies are typical results (see Annex IV).

Grounds for amendment of the Summary of Product Characteristics and labelling

Whereas:

- the CVMP considered the recommended dose and inclusion rates in feed for pre-mixes for medicated feedingstuffs containing 40, 100 or 200 g tilmicosin per kg pre-mix and administered to rabbits.
- the CVMP considered that the recommended dose in feed is 12.5 mg/kg bw/day for 7 days for rabbits in the prevention and treatment of respiratory disease caused by *Pasteurella multocida* and *Bordetella bronchiseptica.*
- the CVMP considered the data provided regarding the inclusion rates and agreed that the requirement for the dose being in at least half the daily ration was fulfilled, and that the target of 200 ppm of tilmicosin per ton of feed could be achieved with all the pack sizes of the different strengths (40 g, 100 g and 200 g).
- the CVMP considered that high values of tilmicosin content in the meal rabbit feed have been observed prior to the conditioning/pelleting process.

The CVMP has recommended variations of the Marketing Authorisation for all the pre-mixes for medicated feedingstuff containing 40, 100 or 200 g tilmicosin per kg pre-mix and administered to rabbits (see Annex I) in order to amend the Summary of Product Characteristics and labelling in line with recommended changes in the product information as set out in Annex III.

The condition of the Marketing Authorisations is described in Annex IV.

Annex III

Amendments in the relevant sections of the Summary of Product Characteristics and labelling

Amendments in the relevant sections of the Summary of Product Characteristics

Note: The text in grey shading below is not applicable for MICLOZAN 200 premix (**see Annex I of the opinion)**

Summary of Product Characteristics

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:

$$\text{kg pre-mix/ton feed} = \frac{\text{Dose rate (mg/kg bodyweight) x bodyweight (kg)}}{\text{Daily feed intake (kg) x pre-mix strength (g/kg)}}$$

Rabbits

Administer in the feed at 12.5 mg/kg bodyweight/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	12.5 mg/kg bodyweight/day	7 days	1 kg tilmicosin 200 g pre-mix /ton 2 kg tilmicosin 100 g pre-mix/ton 5 kg tilmicosin 40 g pre-mix /ton

"To ensure through dispersion of the product, it should first be mixed with a suitable quantity of feed ingredients (20 – 50 kg) before incorporation into the finished feed.

……

6.3 Shelf life

Shelf life after incorporation into meal or pelleted feed: 3 months

Shelf life after incorporation into pelleted feed containing more than 30% wheat: 1 month

……

Amendments in the relevant sections of the labelling

Note: The text in grey shading below is not applicable for MICLOZAN 200 pre-mix (see Annex I):

6. INDICATIONS

……

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:

$$\text{kg pre-mix/ton feed} = \frac{\text{Dose rate (mg/kg bodyweight) x bodyweight (kg)}}{\text{Daily feed intake (kg) x pre-mix strength (g/kg)}}$$

Rabbits

Administer in the feed at 12.5 mg/kg bodyweight/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	12.5 mg/kg bodyweight/day	7 days	1 kg tilmicosin 200 g pre-mix /ton 2 kg tilmicosin 100 g pre-mix/ton 5 kg tilmicosin 40 g pre-mix /ton

"To ensure through dispersion of the product, it should first be mixed with a suitable quantity of feed ingredients (20 – 50 kg) before incorporation into the finished feed.

……

10. EXPIRY DATE

…

Shelf life after incorporation into meal or pelleted feed: 3 months

Shelf life after incorporation into pelleted feed containing more than 30% wheat: 1 month

……

Annex IV

Conditions of the marketing authorisation

National Competent Authorities, coordinated by the Reference Member State as applicable, should ensure that following conditions are fulfilled by the marketing authorisation holders:

The marketing authorisation holders should conduct conditioning/pelleting stability studies with three batches of medicated rabbit feeds (manufactured using tilmicosin 200 g per kg pre-mix) in order to confirm that if meal rabbit feed was correctly formulated with a concentration of 200 ppm, tilmicosin content in the pelleted feed would still be within the specification range of ±15 % of nominal value over a period of 3 months. The results of those studies should be provided to the relevant authorities for assessment not later than 12 months after the Commission Decision on this referral procedure.