I. INTRODUCTION

Apotil 300 mg/ml Solution for Injection is authorised for use in cattle and sheep. In both sheep and cattle, the product is used to treat respiratory disease associated with *Mannheimia haemolytica* and *Pasteurella multocida.* The product can also be used for the treatment of ovine mastitis associated with *Staphylococcus aureus* and *Mycoplasma agalactiae*. The product may also be used for the treatment of interdigital necrobacillosis in cattle (bovine pododermatitis, foul in the foot) and ovine footrot caused by *Dichelobacter nodosus* and *Fusobacterium necrophorum*.

The application for a national MA for a generic product was submitted in accordance with Article 13 (1) of Directive 2001/82/EC, as amended by 2004/28/EC. The applicant claimed exemption from bioequivalence studies in accordance with exemption 4.b) of the Guidelines for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products. The reference product is Micotil 300 mg/ml Solution for Injection, a product marketed by Eli Lilli & Co Ltd. Micotil 300 mg/ml Solution for Injection was first authorised in Ireland in October 1990 and in the UK in August 1991.

The product is supplied in Type-II amber vials with bromobutyl rubber stoppers and aluminium overseals, in 50 ml, 100 ml and 250 ml pack sizes. For all sheep indications and for pneumonia in cattle, the dosage rate is 10 mg tilmicosin per kg (1 ml/30 kg) subcutaneously. For the treatment of footrot in sheep, the dosage rate is 5 mg tilmicosin per kg (0.5 ml/30 kg) and for the treatment of interdigital necrobacillosis in cattle, the dosage rate is 5-10 mg tilmicosin per kg (0.5-1 ml/30 kg).

It has been shown that the product can be safely used in the target species. The slight reactions observed are indicated in the SPC[1].

II. QUALITY ASPECTS

Product Development and Composition

The active substance in Apotil 300 mg/ml Solution for Injection is tilmicosin 300 mg/ml, and the excipients are propylene glycol, phosphoric acid concentrated (for pH adjustment) and water for injection.

The product is an established pharmaceutical form and its development has been adequately described in accordance with the relevant European guidelines.

Active Substance

There is no Ph. Eur[2] monograph for tilmicosin, but it is described in the USP[3]. The supporting data have been provided in the form of a certificate of suitability. It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

[1] Summary of Product Characteristics
[2] European Pharmacopoeia
[3] United States Pharmacopoeia

Other Substances
All excipients, propylene glycol, phosphoric acid concentrated and water for injection, have monographs in the European Pharmacopoeia and each complies with the current edition of the Ph. Eur.

Packaging Materials
The packaging materials used in the manufacture of the product comply with the requirements of the applicant's specification and meet the requirements of the European Pharmacopoeia. This is considered acceptable.

Manufacture of the Finished Product
The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The manufacturing formula, method of manufacture and in-process controls were considered appropriately described. There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

Finished Product Quality Control
The finished product specification controls the relevant parameters for the pharmaceutical form. The tests performed during production are considered appropriate for a product of this type. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

Stability of the Product
Active substance
Data have been provided which indicate that the active substance is stable when stored in the appropriate container under appropriate conditions. The retest period of 3 years is justified.

Finished Product
Data have been provided which indicate that the finished product is stable for 3 years when stored at a temperature below 30°C and away from light.

In-Use
An in-use shelf life of 28 days is justified.

Other information
Special precautions for storage:
- Do not store above 30°C.
- Protect from light.

CONCLUSIONS ON QUALITY
The application was supported in regard to quality.

III. SAFETY ASPECTS

Introduction
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the results of pharmacological and toxicological tests are not required. Bioequivalence was claimed the reference product, Micotil 300 mg/ml Solution for Injection.

Pharmacology
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the results of pharmacological tests are not required. Bioequivalence was claimed the reference product, Micotil 300 mg/ml Solution for Injection.

Toxicology
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the results of toxicological tests are not required. Bioequivalence was claimed the reference product, Micotil 300 mg/ml Solution for Injection.

Residues
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the applicant has not provided any data on this section. This is considered acceptable.

Withdrawal Periods:
Cattle (meat & offal): 70 days
Cattle (milk): 36 days
Sheep (meat & offal): 42 days
Sheep (milk): 18 days

Environmental Safety
The applicant provided a Phase I environmental risk assessment in compliance with the relevant guidelines. The PEC_{soil}[4] values derived from several studies were acceptable and in accordance with VICH[5] guidelines.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed. The product literature highlights the fact that the product is extremely dangerous to aquatic vertebrates, and that care must be taken not to contaminate ponds, waterways or ditches with the product or used container.

[4] Figure provided after calculation of the predicted concentration of active substance in the upper 5 cm of soil.
[5] International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

CONCLUSIONS ON SAFETY AND RESIDUES

Conclusions on User Safety

The following warnings and precautions as listed on the product literature and SPC are adequate to ensure safety to users of the product:

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 APOTIL 300 MG/ML SOLUTION FOR INJECTION 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 APOTIL 300 MG/ML SOLUTION FOR INJECTION.
- 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 eyes.
- 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:0844 892 0111.

Conclusions on Consumer Safety
The withdrawal periods for meat and offal for cattle and sheep are sixty days and forty two days respectively and the withdrawal periods for milk for cattle and sheep are thirty six days (864 hours) and fifteen days (360 hours) respectively.

Conclusions on Environmental Safety
Apotil 300 mg/ml Solution for Injection is appropriate for use with regard to environmental safety.

IV. CLINICAL ASPECTS

Introduction
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the applicant has not provided any further preclinical or clinical data. Bioequivalence was claimed the reference product, Micotil 300 mg/ml Solution for Injection.

Clinical Pharmacology
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the applicant has not submitted any data on this section. This is considered acceptable.

Tolerance in the Target Species
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the applicant has not submitted any data on this section. This is considered acceptable.

Resistance
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the applicant has not submitted any data on this section. This is considered acceptable.

Clinical Efficacy
This application was made in accordance with Article 13.1 of Directive 2001/82/EC, as amended by 2004/28/EC and therefore the applicant has not provided any data on this section. Bioequivalence was claimed the reference product, Micotil 300 mg/ml Solution for Injection.

PART V. OVERALL CONCLUSION ON THE PRODUCT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(WWW.GOV.UK/CHECK-ANIMAL-MEDICINE-LICENSED)