IPAR

Publicly Available Assessment Report for a Veterinary Medicinal Product

TILMODIL 300 mg/ml Solution for Injection for cattle and sheep

PRODUCT SUMMARY

EU Procedure number	IE/V/0564/001 (formerly UK/V/0348/001)
Name, strength and pharmaceutical form	Tilmodil 300 mg/ml Solution for Injection for cattle and sheep
Active substances(s)	Tilmicosin
Applicant	Emdoka bvba John Lijsenstraat 16 B-2321 Hoogstraten Belgium
Legal basis of application	Generic application (Article 13(1) of Directive No 2001/82/EC)
Target species	Cattle,Sheep
Indication for use	The product is indicated for the treatment of pneumonia in cattle and sheep, associated with *Mannheimia haemolytica, Pasteurella multocida* and other microorganisms sensitive to tilmicosin, and for the treatment of ovine mastitis associated with *Staphylococcus aureus* and *Mycoplasma agalactiae*. For the treatment of interdigital necrobacillosis in cattle (bovine pododermatitis, foul in the foot) and ovine footrot.
ATCvet code	QJ01FA91
Date of completion of the original decentralised procedure	26 January 2011 (UK) 21 April 2011 (IE)
Date product first authorised in the Reference Member State (MRP only)	Not applicable.
Concerned Member States	Belgium, Denmark, Germany, Ireland (now RMS), Luxembourg, The Netherlands. UK added via RMS change

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of

commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.
The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

I. SCIENTIFIC OVERVIEW

This was an application for a Marketing Authorisation for a generic product, Tilmodil 300 mg/ml Solution for Injection for Cattle and Sheep. The application was made in accordance with Article 13 (1) of Directive 2001/82/EC, as amended. Bioequivalence was claimed with the reference product, Micotil 300 mg/ml Solution for Injection, marketed in the UK since August 1991.

The product is a solution for injection containing 300 mg/ml tilmicosin, indicated for the treatment of pneumonia in cattle and sheep. Causative organisms treated are *Mannheimia haemolytica, Pasteurella multicoda* and other organisms sensitive to tilmicosin. The product may also be used to treat ovine mastitis associated with *Staphylococcus aureus* and *Mycoplasma agalactiae*, and for the treatment of interdigital necrobacillosis in cattle and sheep. The dose rate in cattle for treating pneumonia is 10 mg/kg bodyweight, for interdigital necrobacillosis, 5 mg/kg bodyweight. For sheep the dose rate for pneumonia and mastitis is 10 mg/kg bodyweight, and 5 mg/kg bodyweight for footrot. The product should not be used in sheep weighing less than 30 kg, and must not be administered to pigs, horses or goats.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, the slight reactions observed are indicated in the SPC. The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 300 mg/ml tilmicosin and excipients propylene glycol, phosphoric acid and water for injections.

The container/closure system consists of a cardboard box with 1 or 12 multi-dose amber coloured Type II glass vials of 50 ml or 100 ml. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the absence of preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice (GMP) from a licensed manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines.

Ingredients are weighed followed by addition of tilmicosin and subsequent measurement of pH. Phosphoric acid is added to dissolve the tilmicosin, followed by the addition of propylene glycol. The product is brought up to volume with water for injections, and the solution filtered into a suitable vessel after aseptic filtration. The product is then filled into Type II glass bottles and immediately sealed with rubber closures and aluminium caps.

C. Control of Starting Materials

The active substance is tilmicosin, an established substance described in the United States Pharmacopoeia. The active substance is manufactured in accordance with the principles of GMP.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

The specifications for propylene glycol, phosphoric acid concentrated and water for injections comply with the European Pharmacopoeia.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The product is analysed for appearance, pH, relative density, identification of tilmicosin, tilmicosin-related substances, sterility and bacterial endotoxins.

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.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Three pilot batches of Tilmodil 300 mg/ml Solution for Injection for Cattle and Sheep were used for stability testing, and the product was sampled under VICH conditions at 25°C/60% RH for 36 months and 40°C/75% RH for 6 months. Any observed effects were consistent with those expected. Tests were also performed on three batches of the finished product, in accordance with EMEAguidelines. A further test on product stored for 5.5 years, testing the rubber seals for sealing capacity. Results were satisfactory, indicating that the piercing of vials should not exceed 25 times.

Due to the nature of this product the following storage conditions should be applied:-

- Do not store above 25°C.
- Protect from light.
- Keep vial in outer carton.
- Once opened use contents within 28 days. Discard unused material.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf-life after first opening the immediate packaging: 28 days.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been appropriately demonstrated, results of pharmacological and toxicological tests are not required.

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to users, the environment and consumers.

III.A Safety Testing

User Safety

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. The user safety data is the same as that provided for the reference product, Micotil 300 mg/ml Solution for Injection.
The following user safety warnings are stated on the SPC and packaging:

INJECTION OF THIS DRUG 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 Tilmodil 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 Tilmodil 300 mg/ml Solution For Injection.
- In case of human 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 THIS DRUG 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 ofdobutamine 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 0870 600 6266.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.
Tilmicosin and its metabolites may reach the environment via the spreading of contaminated manure. A suitable PEC_{soil}[1]calculation for all appropriate parameters, concluding that the PEC_{soil} values were below the trigger value of 100 µg/kg.
Therefore, the risk assessment stops at Phase I. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

III.B Residues documentation

Residue Studies

No residue depletion studies were conducted exemption was claimed due the bioequivalence of the product with the reference product.

Withdrawal Periods

Cattle tissues 60 days.
Sheep tissues 42 days.
Sheep milk: 15 days (360 hours)
Do not use in cattle producing milk for human consumption.
Do not use in pregnant dairy heifers or dry cows within 60 days of calving.
[1] PEC_{soil} – Prediction of concentration of elements in the uppermost 5 cm of topsoil in prevailing cold climatic conditions over a period of 20 years.

IV. CLINICAL ASSESSMENT

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated via appropriate reference data, efficacy

studies are not required. The efficacy claims for this product are equivalent to those of the reference product. The SPC for Tilmodil 300 mg/ml Solution for Injection for Cattle and Sheep is the same as the reference product. There was no requirement for further data in this section.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

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.