College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Pulmovet 250 mg/ml Solution for Use in Drinking Water or Milk Replacer for Cattle, Pigs, Chickens and Turkeys

Date Created: 27th July 2018

Updated: August 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0289/001/DC
Name, strength and pharmaceutical form	Pulmovet 250 mg/ml Solution for Use in Drinking Water or Milk Replacer for Cattle, Pigs, Chickens and Turkeys
Applicant	Dopharma Research B.V. Zalmweg 24 4941 VX Raamsdonksveer The Netherlands
Active substance(s)	Tilmicosin (as tilmicosin phosphate)
ATC Vetcode	QJ01FA91
Target species	Cattle (pre-ruminant), pigs, chickens (except hens producing eggs for human consumption) and turkeys.
Indication for use	Calves: For the treatment and metaphylaxis of bovine respiratory disease, associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma bovis* and *M. dispar* susceptible to tilmicosin. Pigs: For the treatment and metaphylaxis of respiratory disease associated with *Mycoplasma hyopneumoniae*, *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* susceptible to tilmicosin. Chickens: For the treatment and metaphylaxis of respiratory disease associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin. Turkeys: For the treatment and metaphylaxis of respiratory disease associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic application in accordance with Article 13(1) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	28th February 2018
Concerned Member States for original procedure	Austria, Belgium, Cyprus, Denmark, Estonia, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Romania, Spain

I. SCIENTIFIC OVERVIEW

This was an application for generic product in accordance with Article 13(1) of Directive 2001/82/EC, as amended. The reference product Pulmotil AC 250 mg/ml Concentrate for Oral Solution for Use in Drinking Water or Milk Replacer, authorised in the UK since 2000.

In calves, the product is indicated for the treatment and metaphylaxis of bovine respiratory disease, associated with *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma bovis* and *M. dispar* susceptible to tilmicosin, at a dose rate of 12.5 mg tilmicosin/kg bodyweight, twice daily for 3 to 5 days.

In pigs, the product is indicated for the treatment and metaphylaxis of respiratory disease associated with *Mycoplasma hyopneumoniae*, *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* susceptible to tilmicosin, at a dose rate of 15-20 mg/kg bodyweight for 5 consecutive days.

In chickens, the product is indicated for the treatment and metaphylaxis of respiratory disease associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin, at a dose rate of 15-20 mg/kg bodyweight for 3 consecutive days.

In turkeys the product is indicated For the treatment and metaphylaxis of respiratory disease associated with *Mycoplasma gallisepticum* and *M. synoviae* susceptible to tilmicosin, at a dose rate of 10-27 mg/kg bodyweight for 3 consecutive days.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] 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 [2] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains 250 mg tilmicosin (as tilmicosin phosphate) as the active substance, and the excipients propyl gallate (E310), disodium edetate, phosphoric acid (concentrated) and purified water.

The container/closure system consists of either a high-density polyethylene bottle with low-density polyethylene screw cap containing 960 ml or a high-density polyethylene can with high-density polyethylene screw cap containing 5040 ml of product. 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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of simple dissolution and pH adjustment. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is tilmicosin phosphate, an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice to the manufacturers own specifications and in

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

accordance with an Active Substance Master File (ASMF). 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 active substance is double packed in low density polyethylene (LDPE) bags. The inner bag is sealed with a rubber ring. These are then placed in a cardboard drum and sealed. A certificate of analysis has been provided which demonstrates compliance with the specification.

II.C.4. Substances of Biological Origin

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

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. 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. 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. Control tests on the finished product are those for: appearance, solubility, appearance of solution, pH, relative density, identification of the active, assay of the active, related substance, microbiological quality, and identification and assay of excipients.

II.F. 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.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The claim of a 24 hour stability after reconstitution in water is based on the demonstration of the stability for two batches of product stored for 24 hours at

25°C. Once batch of product was reconstituted in soft water (pH 6.5) and stored in stainless steel vessels and one batch was reconstituted in hard water (pH 8.1) and stored in PVC vessels.

The claim of a 6 hour stability after reconstitution in milk replacer is based on the demonstration of the stability of two batches stored at 42°C over a period of 6 hours under constant stirring.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening of the immediate packaging: 3 months.
Shelf life after reconstitution in drinking water: 24 hours.
Shelf life after reconstitution in milk replacer: 6 hours.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

This application is a generic application in accordance with Article 13(1) of Directive 2001/82/EC and bioequivalence has been accepted. Therefore, the pharmacological and toxicological data are not required.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the hazard profile, posology and tasks and situations that could lead to exposure and similar to that of the reference product.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- 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 or milk replacer, 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.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:
The product is administered to intensively reared calves, pigs, chickens and turkeys via dilution in drinking water (pigs, chickens, turkeys) or milk replacer (calves). Consequently, exposure of the environment may occur via spreading of slurry and/or sludge from treated animals onto soil after storage according to agricultural practice. In addition, the aquatic environment can be exposed via leaching, run-off and drainage from manure spread on land. The Phase I VICH exposure decision tree was followed to Question 17. All $PEC_{soil\ initial}$ values are above the trigger value for a Phase II assessment (100 µg/kg), except for broiler breeders, with a maximum calculated $PEC_{soil\ initial}$ seen in weaner pigs (868.9 µg/kg).

Phase II:
A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines. This included studies on physicochemical properties, environmental fate and effects. Studies were carried out using the active substance tilmicosin. The findings from the degradation study demonstrated that tilmicosin is persistent in some soils. In addition, the risk characterisation indicated that tilmicosin is toxic to aquatic organisms, including cyanobacteria, with potentially long lasting effects.

Due to the nature of the application as a generic, the risks for the environment are considered to be the same as to that of the reference product. Appropriate environmental information, warnings and precautions are included in the product literature, as outlined below.

- The active ingredient, tilmicosin, is persistent in soils.
- Tilmicosin is known to be toxic to aquatic organisms.

- Tilmicosin may be toxic to aquatic life, including cyanobacteria, with potentially long lasting effects.

III.B.2 Residues documentation

Residue Studies

This application is a generic application in accordance with Article 13(1) of Directive 2001/82/EC and bioequivalence has been accepted. Therefore, the results of residues studies are not required.

MRLs

Tilmicosin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues/milk. The marker substance is tilmicosin.

MRLs are listed below:

	All food producing species	Poultry
Muscle	50 µg/kg	75 µg/kg
Liver	1000 µg/kg	1000 µg/kg
Kidney	1000 µg/kg	250 µg/kg
Fat / skin	50 µg/kg	75 µg/kg
Milk	50 µg/kg	n/a

Withdrawal Periods

Calves: meat and offal: 42 days.
Pigs: meat and offal: 14 days.
Chickens: meat and offal: 12 days.
Turkeys: meat and offal: 19 days.

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

Not authorised for use in birds producing eggs for human consumption.

Do not use within 2 weeks of the start of the laying period.

IV CLINICAL DOCUMENTATION

This application is a generic application in accordance with Article 13(1) of Directive 2001/82/EC and bioequivalence has been accepted. Therefore, there is no requirement to provide pre-clinical or clinical data.

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 of the product is favourable.

MODULE 4

POST-AUTHORISATION

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 Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section 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.

•	30 August 2018	Change in RMS from UK to NL
•	13 August 2019	C.I.13 Other variation: This variation concerns Part 3.A.6 (Environmental risk assessment). A new KOC study, together with a revised ERA and revised product information.
•	8 May 2020	Type IA:B.I.b.1.b: Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance - Tightening of specification limits