Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Macrosyn 100 mg/ml Solution for Injection for Cattle, Pigs and Sheep

Date Created: October 2020

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Macrosyn 100 mg/ml Solution for Injection for Cattle, Pigs and Sheep
Applicant	Bimeda Animal Health Limited 2, 3, 4 Airton Close Tallaght Dublin 24 IE-D24 E032 Ireland
Active substance	Tulathromycin
ATC Vetcode	QJ01FA94
Target species	Cattle Pigs Sheep
Indication for use	Cattle: Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* sensitive to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment. Treatment of infectious bovine keratoconjunctivitis (IBK) associated with Moraxella bovis sensitive to tulathromycin. Pigs: Treatment and metaphylaxis of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida, Mycoplasma hyopneumoniae*, *Haemophilus parasuis* and *Bordetella bronchiseptica* sensitive to tulathromycin. The presence of the disease in the herd should be established before metaphylactic treatment. The product should only be used if pigs are expected to develop the disease within 2–3 days.

	Sheep: Treatment of the early stages of infectious pododermatitis (foot rot) associated with virulent *Dichelobacter nodosus* requiring systemic treatment.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

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 procedure	24/08/2020

I. SCIENTIFIC OVERVIEW

This was a generic application, submitted in accordance with Article 13(1) of Directive 2001/82/EC as amended. The product is indicated for the treatment of a variety of bacterial infections in cattle, pigs and sheep. The reference product was Draxxin 100 mg/ml Solution for Injection for Cattle, Pigs and Sheep, authorised via a centralised procedure in November 2003. The reference product was also authorised in the UK within this centralised procedure.

The proposed 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, 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 CONSTITUENTS

II.A. Composition

The product is a sterile aqueous solution for injection containing the active substance tulathromycin and the excipients propylene glycol, monothioglycerol, citric acid and water for injections. The pH is adjusted, if necessary, by the addition of either sodium hydroxide and/or hydrochloric acid.

The container/closure system consists of Type I clear glass vials with chlorobutyl rubber stoppers and aluminium overseals with flip-off caps.

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

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 compounding, sterile filtration and filling.

Limited process validation data on the product have been presented in accordance with the relevant European guidelines and the applicant commits to conduct full process validation on the first three consecutive commercial batches manufactured at a scale of 1500 litres and inform the relevant Competent Authorities in the event of obtaining any out-of-specification (OOS) result.

II.C. Control of Starting Materials

The active substance is tulathromycin an established active substance which is manufactured in accordance with the principles of good manufacturing practice.

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 excipients are citric acid, anhydrous, propylene glycol, monothioglycerol, hydrochloric acid, sodium hydroxide, water for injections and nitrogen.

The active tulathromycin is packaged in transparent double low-density polyethylene bags followed by an aluminium foil bag. The desiccant is added to the aluminium foil bag. The bags are placed in HDPE drums and sealed.
The finished product will be marketed in Type I clear glass vials, filled to 50, 100, 250 and 500 ml. The vials are closed with a grey chlorobutyl rubber stopper and sealed with an aluminium crimped seal with a flip-off cap. Vials are labelled and packed, with the leaflet, into individual printed cardboard cartons.

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 container closure, appearance, PH, tulathromycin assay & identification, impurities, monothioglycerol and sterility.

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.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 28 days.
This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological & Toxicological Studies

This is an application for a generic product submitted in accordance with article 13(1) of Directive 2001/82/EC, as amended. The product has the same pharmaceutical form as the reference product, the same qualitative and quantitative composition of the active substance and the same qualitative composition in terms of excipients. Since details on pharmacodynamics, pharmacokinetics and toxicology, have been sufficiently described in the dossier of the reference product, no such data are required in these sections.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the applicant has considered all the relevant routes of exposure, provided a brief hazard characterisation of the active substance, tulathromycin, and the excipients in the formulation, and characterised the risks qualitatively and quantitatively, using reasonable worst-case assumptions.

Since this generic product is quantitatively the same as the reference product with regard to the active substance, qualitatively the same in terms of the excipients, bioequivalence with the reference product can be accepted. The generic product is to be administered to the same target species, for the same indications, at the same dose, and using the same route of administration as the reference product, it was agreed that the hazards, exposure and, therefore, risks to the user, are comparable to those 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:

- Tulathromycin may cause sensitisation by skin contact. In case of accidental spillage onto skin, wash the skin immediately with soap and water.
- This product may cause hypersensitivity (allergy) reactions. People with known hypersensitivity to tulathromycin should avoid contact with the product.

Environmental Safety

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

Phase I:

A Phase I environmental risk assessment was provided comprising a description of the product, its pattern of use and a working through of the VICH Phase I decision tree. The ERA concluded in Phase I at Question 17 of the decision tree on the basis that the PEC_{soil} value calculated for each category of target animal species is below the threshold value (100 µg/kg) for progressing to a Phase II assessment. The disposal advice is in accordance with current guidance and the product is not expected to pose a risk for the environment when used in accordance with the recommendations included in the proposed SPC.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted because that the generic product is bioequivalent to the reference product.

MRLs

Tulathromycin is listed in Table 1 of Regulation 37/2010 and MRLs have been established for edible tissues and milk.
MRLs are listed below:

Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
(2R,3S,4R,5R,8R, 10R,11R,12S, 13S,14R)-2-ethyl-3,4,10,13-tetra-hydroxy-3,5,8,10,12,14-hexamethyl-11-[[3,4,6-trideoxy-3-(dimethy-lamino)-ß-D-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopent-decan-15-one expressed as tulathromycin equivalents	Porcine	800 µg/kg 300 µg/kg 4000 µg/kg 8000 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney	Not for use in animals from which milk is produced for human consumption
	Bovine	300 µg/kg 200 µg/kg 4500 µg/kg 3000 µg/kg	Muscle Fat Liver Kidney	
	Ovine Caprine	450 µg/kg 250 µg/kg 5400 µg/kg 1800 µg/kg	Muscle Fat Liver Kidney	

Withdrawal Periods

Based on the data provided, the following withdrawal periods are justified:

Cattle (meat and offal): 22 days
Pigs (meat and offal): 13 days
Sheep (meat and offal): 16 days

Not authorised for use in animals producing milk for human consumption.
Do not use in pregnant animals, which are intended to produce milk for human consumption, within 2 months of expected parturition.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC, therefore data were not submitted

IV.II. Clinical Documentation

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended by 2004/28/EC, therefore data were not submitted

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 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.

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