FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
AGENCE NATIONALE DU MEDICAMENT VETERINAIRE
Agence nationale du médicament vétérinaire
14 rue Claude Bourgelat – PA de la Grande Marche – Javené - CS 70611 – 35306 FOUGERES Cedex - FRANCE

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Macrosyn 100 mg/ml solution for injection for cattle, pigs and sheep

DATE: 28/07/2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0418/001/DC
Name, strength and pharmaceutical form	Macrosyn 100 mg/ml solution for injection for cattle, pigs and sheep
Applicant	Bimeda Animal Health Limited Unit 2/3/4 Airton Close Tallaght Dublin 24 IRELAND
Active substance(s)	Tulathromycin
ATC Vetcode	QJ01FA94
Target species	Cattle, pigs and sheep
Indication for use	Cattle Treatment and metaphylaxis of bovine respiratory disease (BRD) associated with Mannheimia haemolytica, Pasteurella multocida, Histophilus somni and Mycoplasma bovis susceptible to tulathromycin. The presence of the disease in the group must be established before the product is used for metaphylactic treatment. Treatment of infectious bovine keratoconjunctivitis (IBK) associated with Moraxella bovis susceptible to tulathromycin. Pigs Treatment and metaphylaxis of swine respiratory disease (SRD) associated with Actinobacillus pleuropneumoniae, Pasteurella multocida, Mycoplasma hyopneumoniae, Haemophilus parasuis and Bordetella

	bronchiseptica susceptible to tulathromycin. The presence of the disease in the group must be established before the product is used for 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 website http://www.anmv.anses.fr/

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Application in accordance with Article 13 (1) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	29/07/2020
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	AT, BE, DE, DK, EE, ES, IE, IT, LT, LV, NL, PL

I. SCIENTIFIC OVERVIEW

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 risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 100 mg/ml tulathromycin and excipients monothioglycerol, propylene glycol, water for injections, citric acid, hydrochloric acid and sodium hydroxide.
The packaging of the finished product is as described on the SPC. The particulars of the containers and controls performed are provided and conform to the regulation.
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 from a licensed manufacturing site.
Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is tulathromycin, an established active substance. The active substance 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.

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.
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 has 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.
An in-use shelf-life as detailed on the SPC has been supported by appropriate data.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Not applicable.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This application was submitted in accordance with Article 13(1) of Directive 2001/82/EC (a “generic” veterinary medicinal product). The reference veterinary medicinal product is Draxxin 100 mg/ml solution for injection for cattle, pigs and sheep containing tulathromycin as active substance.

III.A Safety Testing

Pharmacological Studies

This is a generic application according to Article 13(1) of Directive 2001/82/EC, as amended. The reference and the generic product are comparable in terms of the qualitative and quantitative composition of the active substance and the excipients. Data on pharmacodynamics, pharmacokinetics are not required. The pharmacodynamic as well as the pharmacokinetic properties of the product are properly reflected in the SPC and are in line with the reference product.

Toxicological Studies

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

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.
Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

The product is irritating to the eyes. In case of accidental eye exposure, flush the eyes immediately with clean water.

The product may cause sensitisation by skin contact. In case of accidental spillage onto skin, wash the skin immediately with soap and water.

Wash hands after use.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or

the label to the physician.

People with known hypersensitivity to macrolide antibiotics should avoid contact with the veterinary medicinal product.

Environmental Risk Assessment

A Phase I environmental risk assessment (ERA) was provided according to the the Guideline on Environmental Impact Assessment (EIA) for Veterinary Medicinal Products- Phase I (VICH GL6) and the Revised Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38.

Phase I

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the initial predicted environmental concentration in soil is less than 100 µg/kg.

III.B Residues documentation

Residue Studies

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, residue depletion studies are not required.

MRLs

The active substance Tulathromycin and the excipients are allowed substances as described in Table 1 of the Annex to Commission Regulation (EU) No 37/2010:

Active substance	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification

Active substance	Animal species	MRL	Target tissues	Other provisions	Therapeutic classification
Tulathromycin	Ovine Caprine	450 µg/kg 250 µg/kg 5400 µg/kg 1800 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption	Anti-infectious agents/ Antibiotics
	Bovine	300 µg/kg 200 µg/kg 4500 µg/kg 3000 µg/kg	Muscle Fat Liver Kidney		
	Porcine	800 µg/kg 300 µg/kg 4000 µg/kg 8000 µg/kg	Muscle Fat Liver Kidney		
Monothioglycerol	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY
Propylene glycol	All food producing species	No MRL required	NOT APPLICABLE	NO ENTRY	NO ENTRY
Hydrochloric acid	All food producing species	No MRL required	NOT APPLICABLE	For use as an excipient	NO ENTRY
Food additives* (substances with a valid E number approved as additives in foodstuffs for human consumption)	All food producing species	No MRL required	NOT APPLICABLE	Only substances approved as additives in foodstuffs for human consumption, with the exception of preservatives listed in part C of Annex III to European Parliament and Council Directive 95/2/EC.	NO ENTRY

*The excipients Citric acid and Sodium hydroxide are used as food additives.

Withdrawal Periods

The same withdrawal periods as for the reference product are applicable.

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

Not authorized 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 ASSESSMENT (EFFICACY)

As this is a generic application according to Article 13, and bioequivalence with a reference product has been demonstrated, efficacy studies are not required. The efficacy claims for this product are equivalent to those of the reference product.

IV.A Pre-Clinical Studies

Pharmacology

This is a generic application according to Article 13(1) of Directive 2001/82/EC, as amended. The reference and the generic product are comparable in terms of the qualitative and quantitative composition of the active substance and the excipients. Therefore, exemption from the need to demonstrate bioequivalence *in vivo* according to section 7.1 b of the Guideline for the Conduct of Bioequivalence Studies for Veterinary Medicinal Products (EMEA/CVMP/016/2000-Rev.3) is justified and data on pharmacodynamics, pharmacokinetics or target animal tolerance are not required. The pharmacodynamic as well as the pharmacokinetic properties of the product are properly reflected in the SPC and are in line with the reference product.

Tolerance in the Target Species of Animals

No tolerance study has been provided.
As this is a generic application according to Article 13 (1) of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been demonstrated, results of tolerance study is not required.

The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

In line with the requirements of the Revised guideline on the SPC for Antimicrobial products (EMEA/CVMP/SAGAM/383441/2005), additional standard warnings in relation to the development of resistance to antibiotics were included.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

The application is made in accordance with Article 13 (1) of Directive 2001/82/EC as amended. Since bioequivalence with a reference product has been demonstrated, data from clinical studies are not required.

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 risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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 veterinary Heads of 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.

<None>

or

Complete this section for extensions to the same VPA range or defined, significant variations, using the table shown below.

Some examples of significant changes in safety or efficacy data are:

- *Changes to pharmacokinetic data leading to a change in the SPC*
- *Changes to toxicological data leading to a change in the SPC*
- *Changes to user safety warnings*
- *Changes to ecotoxicological information as given in the SPC or changes to disposal warnings*
- *New residue studies in new target species or tissues*
- *Reassessment of residue data or new studies resulting from changes to MRL*
- *Changes to withdrawal period*
- *Changes to target species*
- *Changes to target species tolerance data leading to change in warnings/precautions for target species*
- *New or changed indications*

Significant changes in administrative or quality data include any Type II change, which affects the initial report. The following Type IA or IB changes may also apply:

- *Name of product [Type IA: 2]*
- *Name of active substance [Type IA: 3}*
- *MAH [Type IA: 1]*
- *Composition of the medicinal product [Type IB: 18, Type IA/B: 25, 34, 35, 39]*
- *Container/closure system [Type 1/B: 26, 28, 29, 36, 41, 43]*
- *Method of preparation [Type 1B: 33]*
- *Active substance specification [Type IB: 25]*
- *CEP [Type IA/B: 15]*

- *Re-test period or storage conditions of active substance [Type IB: 17]*
- *Excipient specifications [Type 1A/B: 25]*
- *Packaging materials[Type 1A/B: 28, 29, 36, 41, 43]*
- *TSE [Type 1A: 16, 22]*
- *Shelf-life or storage conditions of the finished product [Type 1B: 42]*

Quality changes

Summary of change **(Application number)**	**Section updated in Module 3**	**Approval date**
<Example: Change to active substance specification> (MS/V/XXX/X/IB/XX)	N/A	

Safety/efficacy changes

Summary of change **(Type; application number)**	**Section updated in Module 3**	**Approval date**
<Example: Addition of target species - pigs> (MS/V/XXX/X/II/XX)	<IIIA> <IIIB> <IV>	