Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL)
Federal Office of Consumer Protection and Food Safety
Mauerstraße 39-42
10117 Berlin
(Germany)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Tulieve 100 mg/ml
Solution for injection for cattle, pigs and sheep

Date: 05 February 2020

MODULE 1

PRODUCT SUMMARY

EU Procedure number	DE/V/0322/001/DC
Name, strength and pharmaceutical form	Tulieve 100 mg/ml Solution for Injection for Cattle, Pigs and Sheep
Applicant	Norbrook Laboratories (Ireland) Limited Rossmore Industrial Estate Monaghan Ireland
Active substance(s)	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* susceptible to tulathromycin. The presence of the disease in the group must be established before the product is used. 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. The product should only be used if pigs are

	expected to develop the disease within 2–3 days. <u>Sheep</u> 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 Heads of Veterinary Medicinal Agencies website (www.hma.eu).

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	05 February 2020
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	BE, DK, EE, FR, HU, IE, IT, LV, LT, NL, PL, PT, ES and UK

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.
Tulieve 100 mg/ml solution for injection is a generic application according Article 13 (1) of Directive 2001/82/EC (as amended) via the decentralised procedure (DCP).
The reference product is Draxxin 100 mg/ml Solution for Injection of the company Zoetis, Belgium (EU/2/03/041/001-005), which has been authorised via centralized pocedure on 11.11.2003 on the basis of a complete dossier.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains tulathromycin (100 mg/ml) as the active substance and the excipients citric acid, monothioglycerol, propylene glycol, hydrochloric acid, sodium hydroxide, and water for injections

The container/closure system are Type I clear glass vials containing 50ml, 100ml, 250 ml or 500 ml or high density polyethylene (HDPE) plastic septum crimp vials containing 50ml, 100ml, 250 ml or 500 ml and 1000ml closed with Type I bromobutyl rubber stoppers and sealed with aluminum seals.

The choice of the formulation and the presence 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 at 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.

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

D. Control on intermediate products

Not applicable.

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.

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 28-day stability after broaching is based on the demonstration of stability results.

G. Other Information

None.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

As this is a generic application according to Article 13(1) of Directive 2001/82/EC (as amended) via the decentralised procedure and bioequivalence with the reference product has been demonstrated, safety studies are not required.

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

No data presented. Given the legal basis of the application (Article 13.1 – a generic application), the omission of toxicological studies is accepted.

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.

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

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.

Wash hands after use.

Accidental self-injection may cause pain reactions and local swellings which can persist for several days. Take care to avoid self-injection.

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

Environmental Risk Assessment

The ERA has been prepared in accordance with 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 ($PEC_{soil\_initial}$ = 14.28 µg/kg for pigs and cattle and 4.0 µg/kg for sheep) is less than 100 µg/kg.

III.B Residues documentation

Residue Studies

As this is a generic application according to Article 13(1) of Directive 2001/82/EC (as amended) via the decentralised procedure and bioequivalence with the 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
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(1) of Directive 2001/82/EC (as amended) via the decentralised procedure and bioequivalence with the 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/016/00-Rev. 2) 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

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

Since the application is made on the basis of essential similarity to a reference product in accordance with Article 13 (1) of Directive 2001/82/EC as amended, 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 Heads of Veterinary Medicinal 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>