Parofor 140 mg/ml solution for use in drinking water, milk or milk replacer	BE/V/0027/002/DX/001
Huvepharma S.A.- N.V.	DCP
	Publicly available assessment report

FEDERAL AGENCY FOR MEDICINES AND HEALTH PRODUCTS

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(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Parofor 140 mg/ml solution for use in drinking water, milk or milk replacer

Date created: July 2017

MODULE 1

PRODUCT SUMMARY

EU Procedure number	BE/V/0027/002/DX/001
Name, strength and pharmaceutical form	Parofor 140 mg/ml solution for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs
Applicant	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium
Active substance(s)	paromomycin sulfate
ATC Vetcode	QA07AA06
Target species	Cattle (pre-ruminant calves), pigs
Indication for use	Treatment of gastro-intestinal infections caused by *Escherichia coli* susceptible to paromomycin.

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MODULE 2

The Summary of Product Characteristics (SPC) for this product is available in the VMRI Product Index on the Heads of Veterinary Medicines Agencies website (http://mri.medagencies.org/veterinary/).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Line extension application: addition of a new strength/potency addition of a new pharmaceutical form under Art 13 of Directive 2001/82/EC as amended (generic application)
Date of completion of the original decentralised procedure	24/05/2017
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, France, Hungary, Ireland, Italy, Lithuania, Luxembourg, Latvia, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, United Kingdom

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I. SCIENTIFIC OVERVIEW

This application was for a line extension under Article 13 of Directive 2001/82/EC as amended, to add Parofor 140 mg/ml solution for use in drinking water, milk or milk replacer to the existing marketing authorisation of Parofor 70 mg/g powder for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs (authorised via decentralised procedure BE/V/0027/001/DC, EoP 23/07/2014, generic application), in accordance with Annex I of Variation Regulation 1234/2008 as amended.

The extension related to §2 - Changes to strength, pharmaceutical form and route of administration:
(c) Addition of a new strength: Paromomycin sulfate 200 mg/ml, equivalent to paromomycin base 140 mg or 140.000 IU of paromomycin activity per ml
(d) Addition of a new pharmaceutical form: solution for use in drinking water, milk or milk replacer.

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; the rare 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 according to the claims made in the SPC is supported by the reference product.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The product contains 200 mg/ml paromomycin sulfate (equivalent to 140 mg/ml paromomycin base or 140.000 IU/ml of paromomycin activity) as active substance and the excipients methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium metabisulphite and purified water.

The container/closure system is a white high density polyethylene (HDPE) bottle, with tamper-evident screw polypropylene closure.

Pack sizes: 125 ml, 250 ml, 500 ml and 1 L.

The choice of the presence/absence of preservatives is 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 paromomycin sulfate, an established substance described in the Italian Pharmacopoeia. 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. Control tests on the finished product include physico-chemical controls, identification and assay of the active substance and preservatives, determination of anti oxydant content, control of impurities and microbial contamination.

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 the following approved shelf lives when stored under the following approved conditions:

- veterinary medicinal product as packaged for sale: 2 years, when not stored above 25°C

- after first opening the immediate packaging: 3 months, when not stored above 25°C

- after reconstitution in drinking water: 24 hours

- after reconstitution in milk/milk replacer: 6 hours

Following reconstitution: there are no special restrictions on storage conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

As this is a generic application according to Article 13 of Directive 2001/82/EC as amended, and Parofor 140 mg/ml solution may be considered bioequivalent with a reference product, the results of pharmacological tests are not required.

In accordance with point 7.1.C of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) the principle of exemption from bioequivalence studies for Parofor 140 mg/ml solution and its reference product was applied.

Toxicological Studies

As this is a generic application according to Article 13 of Directive 2001/82/EC as amended, and Parofor 140 mg/ml solution may be considered bioequivalent with a reference product, the results of toxicological studies are not required.

User Safety

As this is a generic application according to Article 13 of Directive 2001/82/EC as amended, and bioequivalence with a reference product may be considered, full user safety data are not required.

The applicant has provided a revised user risk assessment which addresses quantitative risk characterization of dermal exposure route and the fact that the test product is two-fold more concentrated than its reference product.
Moreover the risk characterization related to the presence of methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium metabisulfite as excipients in the candidate product was also evaluated.

Warnings and precautions as listed on the product literature are adequate to ensure the safety to the users of the product.

Environmental Risk Assessment

An Environmental Risk Assessment (ERA) consisting of both a Phase I and Phase II assessment has been provided. The assessment was performed in accordance with VICH, CVMP and EFSA guidelines.

Phase I

The product will be used to treat groups of pigs and pre-ruminant calves. The main route of exposure to the environment will be the spreading of manure from treated animals onto agricultural land.

Phase I assessment showed that the concentration for paromomycin sulphate in soil for the treatment of calves and pigs exceeds the soil trigger value of 100 µg/kg. Therefore a Phase II ERA is required.

Phase II Tier A

In phase II, data on toxicity, persistence and mobility of paromomycin were used to characterise the risks to organisms in the environment.

The phase II assessment considered the following:

1. Risk to soil-dwelling organisms
2. Risks to aquatic organisms
3. Risks to ground waters
4. Assessment to the potential for paromomycin to be absorbed by and accumulate in soils.

The strong affinity of paromomycin to soil matrices was demonstrated by harsh extraction techniques.

In accordance with EFSA "Guidance document on estimating persistence and degradation kinetics from environment fate studies on pesticides in EU registration "(Sanco/10058/2005, June 2006), a DT_{50} of 1000 days for degradation in different soils was chosen and was considered as a worst-case scenario, indicating the persistence of the compound in soils.

Using estimates of environmental concentrations and available ecotoxicity data (experimental and publicly available), risks to fish, aquatic and terrestrial invertebrates, microbes and plants are deemed acceptable.

Predicted concentrations of paromomycin in groundwater were lower than 0.1 µg/l, indicating an acceptable risk of groundwater contamination.

Conclusion

Based on the data provided the product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues documentation

No residue depletion studies were conducted because this is a line extension generic application according to Article 13 of Directive 2001/82/EC as amended and Parofor 140 mg/ml may be considered bioequivalent with a reference product.

MRLs

Paromomycin is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs	Target tissues	Other provisions
Paromomycin	Paromomycin	All food producing species	500 µg/kg 1500 µg/kg 1500 µg/kg	Muscle Liver Kidney	For fin fish themuscle MRL relatesto 'muscle and skinin natural proportions'. MRLs for liver andkidney do not applyto fin fish. Not for use in animals from whichmilk or eggs are produced for humanconsumption

Withdrawal Periods

Based on a review of the data available from the reference product, a withdrawal period of 20 days for meat and offal in calves and a withdrawal period of 3 days for meat and offal in pigs has been determined and is applicable to Parofor 140mg/ml.

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

As this is a line extension application submitted under Article 13 of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, the results of pharmacological studies are not required.

Tolerance in the Target Species of Animals

As this is a line extension application submitted under Article 13 of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, the results of tolerance studies are not required.

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Resistance

As this is a line extension application submitted under Article 13 of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established, resistance data are not required.

IV.B Clinical Studies

As this is a line extension application submitted under Article 13 of of Directive 2001/82/EC as amended, and bioequivalence with a reference product has been established the results of clinical studies are not required.

Other Studies

The applicant has provided a study in pigs demonstrating that consumption of the product is not inferior to its comparator. The applicant committed to demonstrate adequate consumption of the product in a group of calves.

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 overall risk / benefit 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 in the VMRI (http://mri.medagencies.org/veterinary/).

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