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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Gabbrovet 140 mg/ml solution for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs

DATE: 2018.05.17.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0317/001/DC
Name, strength and pharmaceutical form	Gabbrovet 140 mg/ml solution for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs
Applicant	CEVA SANTE ANIMALE 10 AVENUE DE LA BALLASTIERE 33500 LIBOURNE
Active substance(s)	Paromomycin (as sulfate)
ATC Vetcode	QA07AA06
Target species	Cattle (pre-ruminant cattle), pigs
Indication for use	Treatment of gastro-intestinal infections caused by *Escherichia coli* susceptible to paromomycin.

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	Generic application in accordance with Article 13.1 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	2018.01.31.
Date product first authorised in the Reference Member State (MRP only)	-
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, HR, HU, IE, IS, IT, LT, LU, LV, NL, PL, PT, RO, SI, SK, UK

I. SCIENTIFIC OVERVIEW

For public assessment reports for the first authorisation in a range:

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 140 000 IU/ml of paromomycin (as sulfate) (equivalent to 140 mg/ml of paromomycin) as active substance and the following excipients: benzyl alcohol, sodium metabisulfite, disodium edetate and purifier water.

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 paromomycin sulfate, 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 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.
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)

III.A Safety Testing

Pharmacological Studies

See IV.A

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.

The toxicological aspects of the active are identical to the reference product.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline.
The formulation is qualitatively and quantitatively the same as the reference product in regard to the active substance. The excipients are different from the reference product (oral powder). These excipients, benzyl alcohol, sodium metabisulfite and disodium edetate are common excipients for an oral formulation. Toxicity studies have been performed with the final formulation to document the skin and ocular irritation potentials, and hypersensitivity reactions due to aminoglycosides are acknowledged.

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

Environmental Risk Assessment

The applicant has provided a comprehensive data package on the environmental fate and toxicity of paromomycin sulfate. All pivotal studies were conducted in accordance with Good Laboratory Practices and the relevant OECD guidelines. Analytical issues were encountered when conducting both soil adsorption/desorption study and soil degradation study, therefore experimentally derived Koc values and soil DT_{50} values could not be determined. The potential effect of a lower K_{OC} value to groundwater and surface water was investigated by conducting modelling using a K_{OC} of 10,000 L/kg and 100,000 L/kg. A worst case soil DT_{50} of 1000 days was assumed, in line with guidance from other regulatory areas when soil DT_{50} values are not known.

Physical-chemical properties			
Study type	*Test protocol*	*Result*	*Remarks*
Water solubility	*OECD 105*	*613 000 mg/l at 20°C*	
Dissociation constants in water pKa	*OECD 112*	*pKa = 6.9 at 20°C*	
n-Octanol/Water Partition Coefficient logP_{ow}	*OECD 107*	*logK_{ow} = -2.1 at 20 to 25°C*	

Environmental fate			
Soil Adsorption/Desorption		*Koc = 10 000 (arbitrary value)*	*Analytical issues were encountered when conducting both the soil adsorption/desorption study and the soil degradation study and experimentally derived Koc values and soil DT_{50} values could not be determined*
Aerobic and Anaerobic Transformation in Soil		*DT50 = 1000*	*Cf above*

Effect studies					
Study type	*Test protocol*	*Endpoint*	*Result*	*Unit*	*Remarks**
Algae and or cyanobacteria, growth inhibition test/ Anabaena flos-aquae	*OECD 201*	*EC50*	*6.34*	*mg/l*	
Daphnia sp. immobilisation	*OECD 202*	*EC50*	*193*	*mg/l*	
Fish, acute toxicity/ Oncorhyncus mykiss	*OECD 203*	*LC50*	*>1000*	*mg/l*	
Soil microorganisms: Nitrogen transformation test (28 days)	*OECD 216*	*% effect*	*<15% at 18*	*mg/kg*	*Trigger value: 25% deviation from the control*
Terrestrial Plants, growth test	*OECD 208*	*NOEC*	*>1000*	*mg/kg*	*Raphanus sativus, Glycine max, Helianthus annuus, Cucumis sativus, Avena sativa, Allium cepa*
Earthworm reproduction	*OECD 222*	*NOEC*	*500*	*mg/kg*	

** all the tests were performed with paromycin sulfate*

Risk characterisation

The Predicted Environmental Concentrations (PEC) for each compartment were calculated in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1)

Predicted no effect concentrations (PNEC) were calculated using the assessment factors (AF) in these VICH guidelines, and compared with the PEC values. The risk quotients (RQ) obtained for each compartment are as follows:

Compartment	*PNEC*	*PEC*	*RQ*
Surface water	*63.4 µg/l*	*3.67 µg/l*	*0.06*
Soil microorganisms: Nitrogen transformation test	*<25% difference in N transformation*	*NA*	*NA*

Soil	*10 mg/kg*	*7.774 mg/kg (PEC plateau)*	*0.77*

The risk characterisation resulted in risk quotients below 1 for the surface water and soil compartments, indicating that the product will not pose a risk to those compartments when used as recommended.

As a soil DT_{50} of 1000 days was assumed, the following information on environmental properties has been included in the product literature:

"The active ingredient paromomycin sulfate is persistent in the environment."

PBT assessment

The log Kow of paromycin sulphate is below 4. Therefore, it is not necessary to consider the potential for bioaccumulation of the substance. The active is not considered as a PBT substance.

III.B Residues documentation

Residue Studies

No depletion study has been provided with the candidate product, which is acceptable according to the legal basis of the application (Article 13(1) of the Directive 2001/82/EC, as amended – generic application) and the fact that both candidate and reference products are administered orally.

MRLs

The active substance paromomycin is included in table 1 of the MRL regulation 37/2010, as follows:

Marker residue	Animal Species	MRL	Target Tissues	Other Provisions	Therapeutic Classification	Regulation
Paromomycin	All food producing species	500 µg/kg 1500 µg/kg 1500 µg/kg	Muscle Liver Kidney	For fin fish the muscle MRL relates to « muscle and skin in natural proportions ». MRLs for liver and kidney do not apply for fish. Not for use in animals from which milk or eggs are produced for human consumption	Anti-infectious agents/ Antibiotics	37/2010 of 22.12.2009

The composition of the product Gabbrovet 140 mg/ml solution for use in drinking water, milk or milk replacer for pre-ruminant cattle and pigs is acceptable according to the European Regulation (EC) 470/2009.

Withdrawal Periods

The withdrawal periods agreed for the reference product can be applied to the generic product except for meat and offal in pigs, for which the withdrawal period for pigs has been updated to 3 days:

Cattle
Meat and offal: 20 days
Milk: not relevant

Pigs
Meat and offal: 3 days

IV. CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Given the legal basis of the application, the provided documentation on pharmacodynamics, pharmacokinetics and resistance are satisfactory.

The exemption of demonstration of bioequivalence between the two products is acceptable according to the European “Guideline on the conduct of bioequivalence studies for veterinary medicinal products” (EMA/CVMP/016/00-Rev.2 - waiver from bioequivalence study requirements 7.1.C).

Tolerance in the Target Species of Animals

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

Warnings and precautions as listed on the product literature are the same as those of the reference product and are adequate to ensure safety of the product to the target species of animals.

Resistance

An overview of the level of resistance to paromomycin in target pathogens and commensal bacteria has been submitted, based on paromomycin MIC studies conducted on *Escherichia coli* strains recently isolated in target animal species and recent bibliographical data.
Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Given the legal basis of this application (generic product - Article 13.1 (a)(iii) of Directive 2001/82/EC, as amended) and the satisfactory justification for a waiver from the requirement to demonstrate *in vivo* bioequivalence with the reference product in accordance with EMA/CVMP/016/00-Rev.2, section 7.1, c), clinical data are not required.
The efficacy claims for this product are equivalent to those of the reference product.

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.HEVRA.org).

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.