AGENCE NATIONALE DU
MEDICAMENT VETERINAIRE

Agence nationale du médicament vétérinaire (ANMV) – French agency for veterinary medicinal products
AGENCE NATIONALE DE SÉCURITÉ SANITAIRE de l'alimentation, de l'environnement et du travail –
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Gabbrovet Multi 140 mg/ml solution for use in drinking water/ milk for pre-ruminant cattle and pigs [FR AT BE BG HR CY CZ EE DE EL HU IE IT LV LT LU NL PL PT RO SK SI ES IS UKNI]
Paromocrypto 140 mg/ml solution for use in drinking water/ milk for pre-ruminant cattle and pigs [DK]

DATE :
3 August 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0429/001/DC
Name, strength and pharmaceutical form	Gabbrovet Multi 140 mg/ml solution for use in drinking water/ milk for pre-ruminant cattle and pigs [FR AT BE BG HR CY CZ EE DE EL HU IE IT LV LT LU NL PL PT RO SK SI ES IS UKNI] Paromocrypto 140 mg/ml solution for use in drinking water/ milk for pre-ruminant cattle and pigs [DK]
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	**Cattle (pre ruminant cattle):** *Colibacillosis* Treatment of gastro-intestinal infections caused by *Escherichia coli* susceptible to paromomycin. **Cattle (newborn calves):** *Cryptosporidiosis* Treatment of infections caused by diagnosed *Cryptosporidium parvum*, by reduction of diarrhoea and reduction of faecal oocyst shedding. Administration has to start within 24 hours after the onset of diarrhoea. **Pigs:** *Colibacillosis* 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 https://www.anses.fr/en/thematique/veterinary-medicine-anmv

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Hybrid application in accordance with Article 13.3 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	25 May 2022
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(NI)

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 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 purified 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 sites 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) (*for pharmaceuticals only)*

III.A Safety Testing

Toxicological Studies

This is a hybrid application according to Article 13.3. Reference is made to the paromomycin MRL summary reports (1996 and 2000) for toxicity studies.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline. The new claimed indication is not considered to significantly increase the risk for the user. The current wordings are considered to be sufficient.

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

Environmental Risk Assessment

A Phase I and a Phase II environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

Phase I:

The PECsoil initial for all animal types treated with paromomycin sulfate exceeded the Phase I threshold of 100 µg/kg soil. Therefore, a more detailed evaluation of environmental risk arising from the use of paromomycin sulfate is provided according to the guidance for Phase II Tier A.

Phase II:

A Phase II data set was provided according to the requirements of the CVMP/VICH guideline GL38 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), The data were considered to be complete and acceptable.

Physical-chemical properties (Paromomycin sulfate)			
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 (Paromomycin sulfate)			
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*

Environmental fate (Paromomycin sulfate)			
Aerobic and Anaerobic Transformation in Soil		*DT50 = 1000*	*Cf above*

Effect studies (Paromomycin sulfate)					
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 192*	*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*	

Risk characterisation

The Predicted Environmental Concentration (PEC) for each compartment was 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)

Using the assessment factors (AF) in these VICH guidelines, predicted no effect concentrations (PNEC) were calculated and compared with the PEC values. This results in a risk quotient (RQ) for each compartment as follows:

Compartment	**PNEC**	**PEC**	**RQ**
surface water	63.4 µg/L	8 µg/L	0.12
groundwater		<0.1 µg/L	
soil microorganisms: Nitrogen transformation test	<25% difference in N transformation	NA	NA
Soil (Tier A)	10 mg/kg	19.2 mg/kg	1.9

Soil (Tier B)	100 mg/kg	19.2 mg/kg	0.19

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 very persistent in the environment."

PBT assessment

PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	BCF	logKow < 4	not B
Persistence	DT_{50}	1000	(v)P
Toxicity	EC_{50}	6.34 mg/L	not T
PBT-statement:	The compound is not considered as PBT nor vPvB		

The outcome of the environmental risk assessment indicates that the use of the product is not expected to pose a significant concern to the environment.

III.B Residues documentation

Residue Studies

For the Colibacillosis indication in pre-ruminant cattle and pigs:
No depletion study was provided with the new product. It is acceptable according to the legal basis of the application, Article 13(3) hybrid and the fact that the products are administered orally at the same dose as the reference product and that bioequivalence between the tested and the reference product is accepted.

For the Cryptosporidiosis indication in pre-ruminant cattle:
Three original pivotal residue depletion studies were provided.

- A first GLP tissue residue study in 22 new-borns healthy calves after administration of the product at the maximal recommended dose of 150 mg/kg bw/day for 5 consecutive days.
- A second GLP complementary residue study in 25 new-borns healthy calves after administration of the product at the maximal recommended dose of 150 mg/kg bw/day for 5 consecutive days.
- A third GLP confirmatory residue study in 37 new-borns healthy calves after administration of the product at the maximal recommended dose of 150 mg/kg bw/day for 5 consecutive days.

The LC-MS/MS method for the determination of paromomycin in cattle tissues was fully validated.

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

For the Colibacillosis indication in pre-ruminant cattle and pigs:
The two products being bioequivalent, withdrawal periods agreed for the reference product can be applied to the generic product.
Meat and offal:

- Pre-ruminant cattle: 20 days.
- Pig: 3 days.

For the Cryptosporidiosis indication in pre-ruminant cattle:
The withdrawal period in meat and offal was established based upon the alternative method in kidney with the addition of a safety span of 10% i.e. 110 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.

For the Colibacillosis indication in pre-ruminant cattle and pigs:
The exemption of the need of *in vivo* bioequivalence study 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).

For the cryptosporidiosis indication, which is not indicated for the reference product, the applicant provided a literature overview of the pharmacodynamics of paromomycin in relation with the treatment of gastrointestinal infections caused by *C.parvum*.

Regarding pharmacokinetics, the applicant submitted two studies to evaluate the absorption of paromomycin after administration in the target species at the recommended dose.

The first study evaluates the bioavailability of paromomycin after oral and intravenous administration. The results indicate that paromomycin has a low bioavailability of 3.23%.
The second study investigated the effect of food on the rate and extent of paromomycin absorption. These latter were decreased when paromomycin was administered to 5-days old calves in fed conditions (in milk replacer) compared to fasted conditions.

Tolerance in the Target Species of Animals

In a non-GLP pilot target animal safety study conducted in 5 day old calves with 3x and 5x the recommended dose, inappetence was observed after both dosages with severity positively correlating with increasing dose levels.

5x the recommended dose seemed to be toxic for 5 day old calves from the second administration, 3 animals showing clinical signs of illness had to be euthanized prematurely due to welfare reasons.

Histopathological findings revealed necrotising inflammation of the urinary bladder in one calf, and severe inflammation of the gastrointestinal tract in the other two.

A pivotal tolerance study performed accordingly to VICH GL43 has been provided. The final formulation has been administered in young calves (5-13 days old) at 0, 1x, 2 and 3x the recommended dose during three times the recommended duration (15 days).

No mortality has been observed in this study.

A possible dose effect inappetence has been observed but without statistical impact on bodyweight gain.

Upon necropsy, the only serious lesions were observed in kidney. The lesions observed were compatible with fibroblastic nephritis. Nephrotoxicity is already included in section 4.6 of the SPC and a contra-indication to use in animals with impaired function of the kidneys is included in section 4.2.

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

Resistance

The bibliographical information and proprietary data provided were conform with the requirements of applicable guidelines at the time of application. The information suggests that the prevalence of resistance of *E. coli* to paromomycin was relatively stable between 2002 to 2015 and around 40% for bovine pathogens and 10% for porcine pathogens.
However, resistance of cryptosporidia to paromomycin has not yet been described. Nevertheless, the use of aminoglycosides is associated with the occurrence of bacterial resistance. Paromomycin may select for cross-resistance to other aminoglycosides.

Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory trials

No results of clinical studies for the Colibacillosis indication are required as bioequivalence of this product to the reference product is demonstrated. The results of a palatability study were provided showing a similar intake of the candidate and the reference product.

In addition, to support the efficacy of the product for another claim (treatment of cryptosporidiosis in pre-ruminant cattle), the results of one dose determination study and two dose confirmation studies were provided.

Field Trials

The results of two field trials were provided to confirm the efficacy of the product for the treatment of infections caused by diagnosed *Cryptosporidium parvum*, by reduction of diarrhoea and reduction of faecal oocyst shedding in pre-ruminant cattle.

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.