IPAR

Publicly Available Assessment Report for a
Veterinary Medicinal Product

Parofor crypto 140 000 IU/ml oral solution for sheep and goats

PRODUCT SUMMARY

EU Procedure number	IE/V/0412/001/DC
Name, strength and pharmaceutical form	Parofor 140 000 IU/ml oral solution for sheep and goats
Active substances(s)	Paromomycin sulfate
Applicant	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium
Legal basis of application	New active substance (Article 12(3) of Directive No 2001/82/EC)
Date of completion of procedure	17/04/2019
Target species	Goats, sheep
Indication for use	Reduction of the severity and the duration of diarrhoea associated with *Cryptosporidium parvum* in individual animals confirmed to have cryptosporidial oocysts in their faeces. Paromomycin reduces faecal oocyst shedding.
ATCvet code	QA07AA06
Concerned Member States	AT, BG, CY, CZ, DK, EE, EL, ES, HR, HU, IT, LT, LU, LV, MT, PL, PT, RO, SI, SK, UK

PUBLIC ASSESSMENT REPORT

The public assessment report reflects the scientific conclusion reached by the HPRA at the end of the evaluation process and provides a summary of the grounds for approval of the marketing authorisation for the specific veterinary medicinal product. It is made available by the HPRA for information to the public, after the deletion of commercially confidential information. The legal basis for its creation and availability is contained in Article 25.4 of EC Directive 2001/82/EC as amended by Directive 2004/28/EC for veterinary medicinal products. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the product for marketing in Ireland.

The Summary of Product Characteristics (SPC) for this product is available on the HPRA's website.

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

II. QUALITY ASPECTS

A. Qualitative and Quantitative Particulars

The product contains 140,000 IU/ml paromomycin sulfate and the excipients methyl parahydroxybenzoate, propyl parahydroxybenzoate, sodium metabisulfite and purified water.
The container/closure system is 125 ml, 250 ml, 500 ml and 1 L white high density polyethylene (HDPE) bottles with polypropylene, tamper-evident screw closures.

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 for the manufacturing process has 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 has been provided.

Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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 has been provided.
Batch analytical data from the proposed production site has been provided demonstrating compliance with the specification.

F. 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 has been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

G. Other Information

Not applicable.

III SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

This application is for an oral solution containing paromomycin as an active substance, for use in lambs and goat kids. The application is submitted by Huvepharma NV. The legal basis for the application is in accordance with Article 12(3) of Directive 2001/82/EC, as amended. The active substance, paromomycin is a constituent of other veterinary medicinal products already authorised in the community.
The product is intended for administration to lambs and goat kids for the reduction of cryptosporidiosis-associated diarrhoea and faecal oocyst shedding after positive diagnosis. The product is formulated as an oral solution containing 200 mg paramomycin per ml and intended for administration at a dose rate of 50 mg paramomycin sulfate per kg bodyweight (bw) per day for 7 consecutive days.

III.A Safety Testing

Pharmacological Studies
The applicant conducted studies which demonstrate that paromomycin exhibits antiprotozoal activity. Although its mechanism of action is unclear, *in vitro* studies have demonstrated that the product has a cryptosporidiostatic effect on *C. parvum*.

The applicant also conducted studies in lambs and calves and provided bibliographical data demonstrating that paromomycin has low oral bioavailability and is largely eliminated unchanged in the faeces.

Toxicological Studies
The applicant has provided bibliographical data and made reference to the Committee for Medicinal Products for Veterinary Use (CVMP) Maximum Residue Limit (MRL) summary report for paromomycin to characterise the toxicological profile of paromomycin. The data provided illustrates the following:

Single Dose Toxicity:
Studies have demonstrated that paromomycin can be considered to have a low acute oral toxicity with a minimum lethal dose of 10,000 mg/kg bodyweight (bw) in the rat. When administered parenterally to the rat, the minimum lethal dose is 670 mg/kg bw for intramuscular injection and 620 mg/kg bw for intravenous injection.

Repeated Dose Toxicity:
Parenteral repeated dose toxicity studies were performed for a duration of 2 months in rats and mice and 1 month in rabbits and cats. Tubular nephrotic lesions were noted in the rabbit following intramuscular administration of paromomycin at a dose of 60 mg/kg bw. Vestibular and neurological abnormalities were noted in the cat following subcutaneous administration of paromomycin at a dose of 50 mg/kg bw. A two year study in dogs illustrated increases in the development of cataracts and renal tubular lesions when orally administered paromomycin at a dose of 68 mg/kg bw. The No Observed Effect Level (NOEL) in rats was 2,000 mg/kg feed or 3.4 mg/kg bw whilst the NOEL in dogs was 100 mg/kg feed or 3.4 mg/kg bw.

Reproductive Toxicity, including Teratogenicity:
Data provided in the CVMP MRL summary report demonstrated that following administration of up to 400 mg/kg bw of paromomycin to mice, 300 mg/kg bw in rats and 25 mg/kg bw in rabbits, no foetotoxic, teratogenic or maternotoxic effects were observed. No studies on reproductive effects in the target species were provided, however this product is only intended for use in pre-ruminant lambs and pre-ruminant kid goats.

Carcinogenicity:
Studies in rats administered paromomycin orally at up to 1950 mg/kg bw and dogs administered paromomycin orally at up to 1700 mg/kg bw for 2 years failed to illustrate an increase in neoplastic or non-neoplastic alterations. The NOEL was 100 mg/kg feed or 3.4 mg/kg bw in dogs.

Other Studies
The applicant provided bibliographical data which shows that paromomycin does not appear to have genotoxic potential.

Observations in Humans
Paromomycin is used in human medicine to treat both intestinal parasites and bacterial diseases; a large volume of information regarding its safety is available due to its extensive clinical use in humans. A toxicological ADI of 0.034 mg/kg was established based on a NOEL of 3.4 mg/kg bodyweight/day. Adverse effects reported in humans are analogous to those induced by other aminoglycosides such as hypersensitivity reactions and tubular nephrotoxicity.

User Safety

The applicant provided a user safety assessment in compliance with the relevant guideline and this took both the active substance paromomycin and the product excipients into account. Paromomycin is currently used in both human and veterinary medicine. The applicant provided details of studies performed investigating the local effects of both the active substance and the final formulation for marketing. The studies demonstrated that whilst the active substance, paromomycin sulfate is a skin sensitiser, the final formulation is not considered to be a skin irritant nor an ocular irritant. The applicant provided information on the excipients included in the product and it was concluded there would be no concerns for user safety arising from use of the excipients. The user warnings in the SPC were considered adequate to warn against handling by people with known hypersensitivity to aminoglycosides:

'This product contains paromomycin, which can cause allergic reactions in some people.
People with known hypersensitivity (allergy) to paromomycin or any other aminoglycosides should avoid contact with the veterinary medicinal product.
Avoid contact with the skin and eyes.
In the event of accidental contact with the skin or eyes, rinse with plenty of water.
If you develop symptoms following exposure, such as skin rash, you should seek medical advice and show the physician this warning. Swelling of the face, lips and eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.
Personal protective equipment consisting of protective clothing and impervious gloves should be worn when handling the veterinary medicinal product. Do not eat, drink and smoke when handling the product.
Do not ingest. In case of accidental ingestion, seek medical advice immediately and show the label to the physician.
Wash hands after use.'
Warnings and precautions as listed on the product literature are considered adequate to ensure safety to users of the product and the product is unlikely to present an unacceptable risk for the user when handled, used, stored and disposed of in accordance with the recommendations included in the SPC.

Environmental Risk Assessment

The environmental risk assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I

A Phase II ERA was required as the Phase I assessment showed that the product is an endoparasiticide for use in animals at pasture.

Phase II Tier A

A Phase II Tier A assessment was conducted, the results of which are summarised below:

Physico-chemical properties	
Study type	**Result**
Water solubility	689 mg/l
Dissociation constants in water pKa	pKa = 7.594
UV-visible absorption spectrum	203 nm 200 nm 220 nm
Melting point/range	> 400 °C
Vapour pressure	<1.5 x 10-3 Pa
n-octanol/water partition coefficient	< -2.0

Environmental fate	
Soil Adsorption/Desorption	Koc = 25,916.9
Aerobic and Anaerobic Transformation in Soil	DT90 of >1000 days (20°C)

Effect studies			
Study type	**Endpoint**	**Result**	**Unit**
Algae growth inhibition test/ *Pseudokirchneriella subcapita*	EC_{50}	147.2	µg/l
Cyanobacteria *Anabaena flos-aquae growth*	ErC50	19.3	mg/l
Daphnia sp. immobilisation	EC_{50}	62.17	mg/l
Effect of compound on soil microflora compared to control	25%	21	%
Terrestrial plants: fresh weight biomass	NOEC	120	mg/kg
Fish, acute toxicity/ *Oncorhynchus mykiss*	LC_{50}	≥ 100 mg	mg/l

Earthworm/*Eisenia fetida* reproduction	NOEC	23.9	mg/kg soil dry weight

Risk characterisation:
The Predicted Environmental Concentration (PEC) for each compartment was calculated in accordance with environmental requirements.
Using the relevant assessment factors, predicted no effect concentrations (PNECs) were calculated and compared with the PEC values to determine a risk quotient (RQ) for each compartment.
The risk characterisation resulted in risk quotients below 1 which show that the product does not pose a concern for earthworms, algae, *Daphnia* or fish when used as recommended. However, a potential risk to terrestrial plants due to a lack of acute ecotoxicological data was identified.
Based upon the data provided, an unacceptable risk for the environment could not be excluded and a Tier B assessment was performed.

Phase II Tier B
A Phase II Tier B assessment was conducted which was to highlight potential risks for terrestrial plants. This assessment concluded that the compound would pose an acceptable risk to terrestrial plants and that the release of the product to the environment resulting from use will pose an acceptable risk to terrestrial organisms, aquatic organisms and groundwater.

PBT Assessment
An assessment of the compound in terms of its potential for Persistence, Bioaccumulation and Toxicity (PBT) for the environment or whether it may be considered as being very Persistent or very Bioaccumulative (vPvB) was performed.
The compound was determined to fulfil the Persistence (P) criterion as the maximum DT50 was >120 days.
The log K_{ow} of the compound was demonstrated to be < -2.0 and therefore the Bioaccumulation (B) criterion was not fulfilled and the compound is not considered a B compound.
Based on freshwater acute toxicity, carcinogenic, mutagenic, reproductive and chronic mammalian toxicity, the Toxicity (T) criterion was not fulfilled and the compound is not considered a T compound.
Paromomycin was determined to fulfil the very Persistent (vP) criterion with a maximum DT50 >180 days and thus it is considered a vP compound.
Based on log Kow values of < -2.0, there was no requirement to generate further evidence of a bioaccumulative potential and the compound is not considered a vB compound.

Conclusion
The product is not expected to pose an unacceptable risk for the environment when used according to the SPC.

III.B Residues Documentation

Residue Studies
Residue depletion studies using the final formulation have been conducted in lambs and kid goats. Samples of tissues were taken from animals at several time points. Results show that residues depleted to below the MRL in all tissues before the end of the withdrawal period. Statistical analysis of the results were used to establish the withdrawal period for the product.
The analytical method was performed with liquid chromatography-tandem mass spectrometry in compliance with the principles of GLP. The method was fully validated.

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

Animal Species	Target tissues	MRL
All food-producing species	Muscle	500 µg/kg
	Liver	1500 µg/kg
	Kidney	1500 µg/kg
	Milk	Not for use in animals from which milk is produced for human consumption

Withdrawal Periods
Based on the data provided, a withdrawal period of 24 days for meat and offal in lambs and kid goats is justified.

IV. CLINICAL ASSESSMENT

IV.A Pre-Clinical Studies

Pharmacology

The active substance, paromomycin is an aminoglycoside antibiotic with antiprotozoal properties. The cryptosporidiostatic effect on *C. parvum* has been demonstrated under *in-vitro* conditions; studies conducted to determine the Minimum Inhibitory Concentration (MIC) of paromomycin against *C. parvum,* identified the optimum concentration required to inhibit 60-70% of *C. parvum* as 400 µg/ml.

Tolerance in the Target Species of Animals

The applicant conducted a target animal safety study, during which one of the target species, pre-ruminating lambs, was administered the product at up to 5 times the recommended daily dose. All doses were administered orally on 21 occasions which equated to 3 times the proposed duration of treatment. Tolerance was evaluated by clinical inspections, blood testing for biochemical, haematological and coagulation parameters and also urinalysis. Adverse effects observed during the study period were deemed to be sporadic in nature and unlikely to be treatment related. The study demonstrated that paromomycin was well tolerated in lambs from 3-6 days of age when administered at up to 5 times the proposed dose and for up to 3 times the proposed duration of treatment. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

Bibliographical data provided suggests that there have been no reports of resistance in cryptosporidium to paromomycin. However, the compound may select for resistance and also cross-resistance to other aminoglycosides in intestinal bacteria, which could represent a risk that resistance is spread to bacteria which are pathogenic to humans. The applicant provided information on a study carried out, which indicated that the use of paromomycin could select for isolates for which a higher concentration of aminoglycoside would be required to treat, however, these effects were transient and as this product is indicated for new-born animals only, it was deemed that it was unlikely to have any significant impact on meat products which would be obtained several months after treatment. The SPC for the product clearly indicates that the product is to be used in individual animals (pre-ruminant kids and goats) confirmed to have cryptosporidial oocysts in their faeces and warnings have been included relating to the development of resistance to antimicrobials.
It was concluded that the product is unlikely to present an unacceptable risk for the user in relation to the development of resistance provided the product is used in accordance with the recommendations included in the SPC.

IV.B Clinical Studies (pharmaceuticals and immunologicals)

Laboratory Trials

The applicant conducted both dose determination and dose confirmation studies in young lambs.
For the dose determination study, following experimental infection with *C. parvum,* animals were administered the product orally at a range of doses (0 mg/kg bw, 25 mg/kg bw, 50 mg/kg bw or 100 mg/kg bw) over a period of either 3 days or 7 days. Throughout the study period, animals were observed twice daily and parameters monitored included demeanour, body condition, faecal consistency, rectal temperature and dehydration. Faecal samples were also collected at regular intervals to analyse faecal *C. parvum* oocysts shedding. Based on faecal consistency and the shedding of oocysts, a dose of 50 mg paromomycin/kg bodyweight daily for 7 days was considered to be the most appropriate posology for the product.
For the dose confirmation study, following experimental infection with *C. parvum*, animals were either administered the product orally at 50 mg/kg bw daily for 7 days or received no treatment for the duration of the study. Throughout the study period, animals were observed twice daily and parameters monitored included demeanour, body condition, faecal consistency, rectal temperature and dehydration. Faecal samples were also collected at regular intervals to analyse faecal *C. parvum* oocysts shedding. Based on faecal consistency and the shedding of oocysts, a dose of 50 mg paromomycin/kg bodyweight daily for 7 days was confirmed as an appropriate posology to be investigated under field conditions.

Field Trials

The applicant conducted field studies which show that the product is both safe and effective for use in pre-ruminant lambs and kid goats.
One field study which was conducted across four sites, evaluated the efficacy of the product as indicated in goat kids naturally infected with *C. parvum*. 173 animals were confirmed to be infected with *C. parvum* and then assigned to either a treatment group (treated with the product at a dose of 50 mg/kg bw daily for 7 days) or a control group (which received no treatment). The study was blinded, and randomised. Clinical observations were performed daily throughout the study and involved assessment of behaviour, dehydration and faecal scoring. Faecal samples were collected at regular intervals to analyse faecal *C. parvum* oocyst shedding. The results of the study indicated that treatment with the product resulted in a significant improvement in the severity and duration of the clinical signs associated with confirmed cryptosporidium infection and also resulted in a reduction in faecal oocyst shedding.

A multicentre field study was conducted to evaluate the efficacy of the product in lambs naturally infected with *C. parvum*. The study was blinded, negative controlled and randomised. 161 animals were confirmed to be infected with *C. parvum* and then assigned to either a treatment group (treated with the product at a dose 50 mg/kg bw daily for 7 days) or a control group (which received no treatment). Clinical observations were performed daily throughout the study and involved assessment of behaviour, dehydration and faecal scoring. Faecal samples were collected at regular intervals to analyse faecal *C. parvum* oocyst shedding. The results of the study indicated that treatment with the product resulted in a significant improvement in the severity and duration of the clinical signs associated with confirmed cryptosporidium infection and also resulted in a reduction in faecal oocyst shedding.

V. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data submitted in the dossier demonstrates that when the product is used in accordance with the Summary of Product Characteristics, the benefit/risk profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

VI. POST-AUTHORISATION ASSESSMENTS

None