United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Parofor Crypto 140 000 IU/ml Oral Solution for Pre-Ruminant Cattle

Date Created: July 2019

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0689/001/MR
Name, strength and pharmaceutical form	Parofor Crypto 140 000 IU/ml Oral Solution for Pre-Ruminant Cattle
Applicant	Huvepharma NV Uitbreidingstraat 80 2600 Antwerpen Belgium
Active substance(s)	Paromomycin
ATC Vetcode	QA 07 AA 06
Target species	Cattle
Indication for use	Reduction in the occurrence of diarrhoea due to diagnosed *Cryptosporidium parvum*. Calves should only receive the product upon confirmation of cryptosporidial oocysts in their faeces and before the onset of diarrhoea. Paromomycin reduces faecal oocyst shedding.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the mutual recognition procedure	13th March 2019
Date product first authorised in the Reference Member State (MRP only)	19th July 2018
Concerned Member States for MRP procedure	Austria, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovakia, Slovenia, Spain.

I. SCIENTIFIC OVERVIEW

This was a full application, submitted in accordance with Article 12 (3) of Directive 2001/82/EC, as amended.

The product is indicated for use in pre-ruminant calves, for reduction in the occurrence of diarrhoea due to diagnosed *Cryptosporidium parvum.*

The product is administered via the oral route at a dose rate of 35 000 IU of paromomycin/kg BW/day for 7 consecutive days, i.e. 2.5 ml of product / 10 kg BW/day for 7 consecutive days.

To ensure correct dosing, the use of either a syringe or an appropriate device for oral administration is necessary and the product should be administered directly in the mouth of the animal. To ensure the correct dosage, bodyweight should be determined as accurately as possible. The safety of the product has not been investigated in animals less than 3 days of age.

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, any reactions observed are indicated in the SPC.[1] The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used

[1] SPC – Summary of product Characteristics.

as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] 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. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains 140 mg paromomycin, equivalent to 200 mg paromomycin sulfate, (140 000 IU of paromomycin activity). The excipients are methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate, sodium metabisulphite and purified water.

The container/closure system consists of white HDPE bottle of 125 ml, 250 ml, 500 ml and 1 L with tamper-evident screw polypropylene closure. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and the presence of preservatives are justified.
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of loading a vessel with purified water, and the excipients added. After cooling, the active substance is added, mixed and quality tested, sterilised and placed in bottles

II.C. Control of Starting Materials

The active substance is paromomycin, an established active substance described in the Italian Pharmacopoeia under the monograph Aminosidina Solfato. 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. Acceptable Certificates of Suitability were provided.

Methyl parahydroxybenzoate, propyl parahydroxybenzoate and sodium metabisulfite are monographed in the European Pharmacopoeia (Ph. Eur)

[2] Efficacy – The production of a desired or intended result.

Copies of the specifications were provided plus certificates of analysis which indicate compliance to the monographs.

The packaging components meet the requirements of the relevant in-house specifications and Ph. Eur monographs.

II.C.4. Substances of Biological Origin

The applicant has provided a declaration stating compliance with the Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Veterinary Medicinal Products (EMEA/410/01 rev. 3).

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.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. Control tests on the finished product are those for: appearance, degree of colouration, clarity, identity and content of the active substance and excipients, pH, density, impurities, extractable volume, visible particles and microbial contamination.

II.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 VICH[3] approved conditions. Results of the analyses determined the stipulated shelf life of the product.

G. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after first opening the immediate packaging: 3 months.
Do not store above 25°C.

[3] VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Several references from the public literature together with proprietary study data were provided in order to characterise the pharmacology and toxicology of the active substance, paromomycin sulfate, and for the final formulation. The former includes the CVMP[4] MRL summary report for paromomycin. The latter includes three pharmacokinetic studies, two pharmacodynamic studies, a target species tolerance study and four safety studies (to evaluate the skin and eye irritation potential of the final formulation, and skin sensitisation potential of paromomycin).

Pharmacological Studies

Pharmacodynamics

Paromomycin inhibits bacterial protein synthesis by binding to 16S ribosomal RNA. Paromomycin binds to the 30S subunit, causing defective polypeptide chains to be produced. The continuous production of defective proteins leads to bacterial death.

Pharmacokinetics

According to a CVMP MRL[5] summary report (EMEA/MRL/718/99-Final):

- Following oral administration, and like other aminoglycosides, paromomycin sulfate is poorly absorbed from the GI tract and most of the dose is eliminated unchanged in faeces.
- Following parenteral administration accumulation occurs in the renal cortex and cochlea and excretion is almost exclusively in the urine as unchanged drug.
- PK studies, in compliance with OECD[6] and GLP[7] guidelines, performed in rabbits, poultry, cattle and pigs showed no substantial differences between species.
- In calves of different ages treated orally with 50 mg paromomycin sulfate/kg bw, analysis of blood over the 24 h post treatment revealed that absorption was better in new-born animals than older animals. Plasma peak concentrations were achieved at 2 – 6 h irrespective of age.
- In calves administered paromomycin parenterally (intravenously or intramuscularly) at a dose of 21 mg/kg bw. PK analysis demonstrated a

[4] CVMP - Committee for Medicinal Products for Veterinary Use.
[5] MRL - Maximum Residue Limit.
[6] OECD - Organization for Economic Cooperation and Development.
[7] GLP – Good Laboratory Practice.

- relatively long distribution half-life (about 1 h) and an elimination half-life of about 5 h (after IV injection) but a short absorption half-life (after IM injection). Quantitative analysis of the kidney showed persistence of residues up to 30 days.
- In rabbits orally administered 80 mg paromomycin sulfate/day for 7 days, 48 h following the final dose, levels were near the detection limit (0.16 µg/ml) in one rabbit only. Over 80% of the administered dose was excreted in faeces.

Toxicological Studies

The toxicological profile of paromomycin is based upon the CVMP summary report (EMEA/MRL/718/99-Final), unless stated otherwise.

- Single Dose Toxicity

Paromomycin sulfate exhibits low acute oral toxicity with a minimal lethal dose in the rat of 10 000 mg/kg bw, when compared to parenteral administration. Parenteral administration shows a minimal lethal dose of 670 mg/kg bw by the intramuscular route and 620 mg/kg bw by intravenous route.

The Merck Index reports LD_{50}[8] values in mice) of 15 000 mg/kg (oral), 700 mg/kg via the subcutaneous route and 110 mg/kg via the intravenous route.

- Repeated Dose Toxicity

A toxicological acceptable daily intake of 0.034 mg/kg was established based on the NOAEL[9] of 3.4 mg/kg bw/day derived from an oral chronic toxicity study in dogs following application of a safety factor of 100. Dose related increases in cataracts and renal tubular lesions were seen at doses above the NOAEL. The NOAEL was considered a suitable toxicological reference value to support the user risk assessment.

- Reproductive Toxicity, including Teratogenicity

Reproduction toxicity studies were reported, with paromomycin tested in mice, rats and rabbits revealing no evidence of adverse foetal effects or reproductive toxicity. Animals were dosed up to 400, 400 and 25 mg/kg bw/day, respectively, at various periods during gestation. These data are supported by the results of a review by CVMP of all publications related to the use of paromomycin in humans. No adverse effects on reproductive function were reported. Clinically, paromomycin is used extensively in pregnant women, children and infants and young adult men with a variety of pathological conditions. From the data presented, it can be concluded that paromomycin is neither a teratogenic, nor a reproductive toxin.

[8] LD_{50} - the amount of a toxic agent sufficient to kill 50 percent of a population of animals within a certain time.
[9] NOAEL – No observed adverse effect level.

- Mutagenicity

Genotoxicity tests were performed under GLP conditions, including an *in vitro* bacterial mutagenicity assay (Ames test), an *in vitro* assay for gene mutation in mammalian cells (Chinese hamster ovary), and an *in vivo* mouse micronucleus test. All tests gave negative results.

- Carcinogenicity

Paromomycin was not found to be mutagenic in a series of mutagenicity test systems. No neoplastic lesions or changes indicative of neoplasia were observed in two GLP-compliant 2-year studies in rats (a combined chronic toxicity/carcinogenicity study) and dogs, (a chronic toxicity study). The data provided indicate that paromomycin is not carcinogenic.

Studies of Other Effects

No specific studies were presented on immune function. Information was provided showing that the product does not have any effect on the response to fowl cholera vaccine in chickens given 1000 mg paromomycin/kg feed for 2 months. No effects indicative of immunotoxicity were observed in any of the standard toxicity studies.

Observations in Humans

Published literature on paromomycin was submitted, indicating that, as an aminoglycoside, it has the potential to elicit hypersensitivity type reactions in sensitised individuals. Aminoglycosides are known to be potentially ototoxic in both animals and humans. According to the CVMP MRL[10] summary report, following parenteral administration paromomycin accumulation occurs in the renal cortex and cochlea, and vestibular effects (i.e. disequilibrium) are reported in cats. However, although paromomycin is used in human therapy, the published literature does not suggest that paromomycin-induced ototoxicity is a clinical concern. It is also noted that paromomycin is poorly absorbed from the GI tract following oral administration.

Microbiological Studies

Current guidelines were considered. The applicant assessed the potential for use of the product to select for antimicrobial-resistant bacteria of human health concern in the UK, in both the GI tract of the treated animal and the environment following excretion of the active substance. Although the proposed new indication could lead to an increase in the volume of use of paromomycin, it is accepted that the risk of selecting resistant strains of commensal species is sufficiently low in treated calves and in the environment, such that any increase in the risk to public health is not likely to be of significance.

[10] MRL – Maximum residue limit.

Studies on Metabolites, Impurities, Other Substances and Formulation

Four GLP-compliant user safety studies (to evaluate the skin and eye irritation potential of the final formulation, and skin sensitisation potential of paromomycin) conducted in accordance with appropriate OECD guidelines, have been provided. All the tests met the validity criteria. Under the experimental conditions of the studies, the final formulation is considered to be neither a skin irritant nor an eye irritant.

Concerning hypersensitivity, a positive result was recorded (at all concentrations of the test item investigated) and, hence, the active substance, paromomycin sulfate, is considered to be a potential skin sensitiser.

The excipients are commonly used in veterinary medicinal products, are well tolerated and, therefore, it can be concluded that they do not raise a toxicological concern.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. A satisfactory hazard identification of the active substance and final formulation has been presented. The routes of exposure for a product of this nature have been correctly identified as oral, ocular and dermal and the exposure and risk associated with each route of exposure have been satisfactorily characterised.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore the following applicant's user recommendations are appropriate:

- 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 product.
- Avoid contact with the skin and eyes.
- Personal protective equipment consisting of protective clothing and impervious gloves should be worn when handling the veterinary medicinal product.
- In the event of accidental contact with the skin or eyes, rinse with plenty of clean 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.

- 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.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:

The initial predicted environmental concentration (PEC) in soil was greater than 100 µg/kg (1999 µg/kg), and a Phase II ERA was required.

Phase II Tier A:

A Phase II tier A data set was provided according to the requirements of the VICH GL 38 and the CVMP guideline in support of the VICH guidelines including studies on physico-chemical properties, environmental fate and effects.

Physico-chemical properties

Study type	Guideline	Result
Water solubility	OECD 105	0.69 kg/l (20°C)
Dissociation constants in water pKa	OECD 112	pKa: 7.594 (20°C)
UV-Visible Absorption Spectrum	OECD 101	Neutral: 200 nm Acidic: 203 nm Basic: 220 nm
Melting Point	OECD 102	>400°C
Vapour Pressure	OECD 104	<1.5 x 10^{-3} Pa (20°C)
n-Octanol/Water Partition Coefficient $logP_{ow}$	OECD 107	<-2.0

Environmental fate

Study type	Guideline	Result
Soil Desorption	OECD 106	DT50 = >1000 days
Sorption behaviour	OECD 307	K_{oc}: >19723.3 - 50404.0 ml/g

Environmental effects

Study type	Guideline	Endpoint	Result
Algae: *Pseudokirchneriella Subcapitata* growth inhibition test:	OECD 201	EC_{50}	95.5 µg/ml
Fresh-water crustacean: *Daphnia magna* immobilisation test	OECD 202	EC_{50}	48 hr immobilisation 62.7/mg/l
Fish, acute toxicity: *Oncorhynchus mykiss*	OECD 203	LC_{50}	LC50 >100mg/l
Soil micro-organisms: nitrogen transformation test (28 days)	OECD 216	% effect	<25% of control at 28 days
Terrestrial plants: *Brassica napus* *Glycine max* *Cucumis sativus* *Lycopersicon esculentum* *Allium cepa* *Lolium perenne* growth Test	OECD 208	NOEC	120 mg/kg
Earthworm*: Eisenia foetida andrei* subacute/reproduction	OECD 220/222	NOEC	≥23.9 mg/kg
Cyanobacteria: *Anabaena flos-aquae* growth inhibition	OECD 224	EC_{50}	19.3 mg/l

Exposure assessment (Predicted exposure concentration)

PEC value for soil, groundwater and surface water were calculated using the equations provided in the CVMP guidelines. The dose and duration of treatment were taken from the proposed SPC of the product. The following PEC values were calculated.

Parameter	**Value**
Production group	Calves
Dose (mg/kg)	50 mg/kg
No. treatments	7
Fraction of herd treated	1
Bodyweight (kg)	140
Vapour pressure (mPa)	0.5
Molecular weight (g/mol)	615.63 (base)
Water solubility (mg/l)	690000
DT_{50}	>1000 days
K_{oc} (ml/g)	19723

Parameter	**Value**
Production group	Calves
PEC_{soil-} initial (µg/kg)	1999
$Pec_{soil-plateau}$ (µg/kg)	8945
$PEC_{groundwater}$ (µg/l)	1.44
$PEC_{surface\ water}$ run-off (µg/l)	2.14

PNEC calculations
The applicant has calculated PNECs at Tier A according to VICH Phase II guidance as follows:

Species	**Endpoint**	**Assessment factor**	**PNEC**
Soil microorganisms	<25% difference in N transformation (28 d)	NA	NA
Plant	NOEC 120 mg/kg	10	12000 µg/kg
Earthworm	NOEC ≥215.2 mg/kg	10	21520 µg/kg
Algae	EC_{50} = 95.5 µg/l	100	0.955 µg/kg
Aquatic invertebrate	EC_{50} = 62.7 mg/l	1000	62.7 µg/l
Fish	LC_{50} = >84.7 mg/l	1000	100 µg/l

Risk Characterisation (Risk Quotient)

In accordance with the VICH and CVMP guidelines, the applicant has carried out a risk characterisation for terrestrial and aquatic organisms.

PEC (µg/kg or l)	**Species**	**PNEC (µg/kg or l)**	**RQ (PEC/PNEC)**
	Soil microorganisms	NA – no risk at 6 x PEC	
Soil = 8945	Plant	12000	0.75
	Earthworm	21520	0.42
Surface water = 2.14	Algae	0.955	0.50
	Daphnia	62.7	0.03
	Fish	100	0.02

As all RQ values were <1 the ERA ended at tier A. The product is not expected to pose a risk for the environment when used as recommended.

III.B.2 Residues documentation

Residue Studies

The applicant submitted two GLP-compliant tissue residue depletion studies in order to ascertain withdrawal periods.

The first study, in pre-ruminant calves was conducted to appropriate standards, and analysed the depletion of the proposed product at the assigned dose in young calves, following oral administration.

The test animals were of mixed sex. In line with the VICH[11] GL48, there were four calves per time point and at least four time points. Calves were allocated to test groups in a randomised manner based on sex and bodyweight. The test animals were acclimatised for an adequate period.

The test product was identical to the proposed product, Parofor 140 mg/ml Oral Solution for Non-Ruminant Calves.

The second residue depletion study was a confirmatory study in neonatal calves. This was performed because it was noted form pharmacokinetic data that the active substance displayed age-related pharmacokinetics. The test animals were of mixed sex and appropriate age. They were acclimatised for an acceptable period. As a confirmatory study, one group of four calves was used to investigate a single time point reflecting the longest time point investigated as part of the main study in pre-ruminant calves.

[11] VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

MRLs

The active substance is listed in Table 1 of Regulation 37/2010, and MRLs have been established for the following tissues:

Pharmacologically active substance(s)	Marker residue	Animal species	MRLs (µg/kg)	Target tissues	Other provisions
Paromomycin	Paromomycin	All food producing species	500 µg/kg 1500 µg/kg 1500 µg/kg	Muscle Liver Kidney	Not for use in animals from which milk is produced for human consumption. Not for use in animals from which eggs are produced for human consumption.

The excipients are all covered within Table 1 of Commission Regulation (EU) 37/2010 as no MRL being required other than purified water which is included on the latest Out of Scope List for requiring MRLs.

Withdrawal Periods

Due to accumulation of paromomycin in the liver and kidneys, any repeated course of treatment during the withdrawal period must be avoided.

Meat and offal: 62 days.

IV. CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The applicant provided an overview of the pharmacodynamics of paromomycin and provided *in vitro* studies to support the application. The following is included in the SPC:

Paromomycin has antiprotozoal activity, although its mechanism of action is unclear. In *in vitro* studies using HCT-8 and Caco-2 cell lines inhibitory activity against *C. parvum* was observed. Resistance of cryptosporidia to paromomycin has not been described to date. Nevertheless, the use of aminoglycosides is associated with the occurrence of bacterial resistance. Paromomycin may select for cross-resistance to other aminoglycosides.

Pharmacokinetics
The applicant cited appropriate studies. The SPC cites suitable information:

The bioavailability of paromomycin when administered as a single oral dose of 35 000 IU paromomycin/kg bodyweight to 2 - 6-week-old calves was 2.75%.
Regarding the absorbed fraction, the mean peak plasma concentration (C_{max}) was 1.48 mg/l, the mean time to attain the peak plasma concentration (T_{max}) was 4.5 hours and the mean terminal half-life ($t_{1/2,\ el}$) was 11.2 hours. The main part of the dose is eliminated unchanged in the faeces while the absorbed fraction is excreted almost exclusively in urine as unchanged paromomycin.
Paromomycin displays age-related pharmacokinetics, with the greatest systemic exposure occurring in newborn animals.

Tolerance in the Target Species

Two target animal safety studies were performed in young animals.

Study 1
This was a randomised, blinded, GLP-compliant study investigating the safety of the proposed product in calves, in order to establish any adverse reactions and establish the margin of safety of use of the product under increased duration of treatment. Twenty-six calves (2 to 5 weeks old) were acclimatised and assessed for 7 days prior to first treatment. Each animal was randomly allocated to one of 4 treatment groups, consisting of either a negative control group, or one of 3 product administration groups, at x 1.4, (72 mg/kg paromycin sulphate), x 4.4 and x 7.2 the recommended dose, for 21 days. This was deemed acceptable, as although all the doses exceeded that recommended, the likelihood of detecting any adverse reactions increased. Suitable blood samples were taken at appropriate time points, and tissues analysed at necropsy. Statistical analyses of between-group comparisons consisted of a one-way ANOVA test for non-repeated measures followed by an *ad hoc* comparison test, or a two-way ANOVA test for repeated measures, followed by an *ad hoc* comparison test. Statistical significance was set at 0.05. Towards the end of the study there were some differences noted in feed intake, but no statistical differences for bodyweight and rectal temperature, or any blood and urine analysis parameters. Upon analysis at necropsy, it was noted that adverse reactions occurred in the gastro-intestinal tract, likely to be associated with prolonged use of the product. Some mortality occurred, with gastrointestinal lesions as the likely cause. A warning appears on the SPC:

- Do not administer for more than 7 days since clinical signs associated with gastrointestinal lesions were observed after prolonged treatment duration. In 2 to 5 week old calves, overdoses in excess of 35 000 IU paromomycin/kg bodyweight may induce gastrointestinal lesions (ulceration, pustules, chronic hyperplastic inflammation) mostly in the rumen and reticulum. Bruxism and poor appetite have been reported. Repeated overdose may be associated with death.

Study 2
This was a blinded, GLP-compliant study investigating the safety of the proposed product in pre-ruminant calves (approximately 4 days old), in order to establish any adverse reactions and establish the margin of safety of use of the product under increased duration of treatment. Twenty-six calves were acclimatised and assessed for 1 to 4 days prior to first treatment. Each animal was randomly allocated to one of 4 treatment groups, consisting of either a negative control group, or one of 3 product administration groups, at x 1, x 3 and x 5 the recommended dose, for 21 days. Suitable blood samples were taken at appropriate time points, and tissues analysed at necropsy. Statistical analyses of between-group comparisons consisted of a one-way ANOVA test for non-repeated measures followed by an *ad hoc* comparison test, or a two-way ANOVA test for repeated measures, followed by an *ad hoc* comparison test. Statistical significance was set at 0.05. No statistically significant treatment effects were noted. No mortality occurred, but there were sporadic occurrences of diarrhoea with associated dehydration. As this occurred also in the control group, this was not thought to be related to treatment with the proposed product. Some occurrence of minor gastro-intestinal lesions was noted. It was not clear if this was product-related.

Differences in results between Study 1 and Study 2 were attributed tentatively to the rumination status of the animals. Therefore, the following instruction was added to the SPC:

- Do not use in ruminating animals.

Resistance

A literature review was conducted, which did not yield any information with regard to paromomycin resistance in *Cryptosporidium parvum*. However, as is noted in the SPC:

Aminoglycosides are considered as critically important in human medicine. Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to paromomycin and may decrease the effectiveness of treatment with aminoglycosides due to the potential for cross-resistance.

The applicant conducted a calf faecal flora study, in which twenty calves were either treated with paromomycin according to the proposed dosage regimen or left untreated. Faecal samples were collected prior to treatment and at various time points after initiation of treatment. Isolates of *Escherichia coli* and enterococci were obtained from these samples and minimum inhibitory concentrations for a range of antibiotics determined. A rightward shift in the MIC distribution for paromomycin against *Escherichia coli* and *Enterococcus* spp. was observed; however, this effect was transient.

IV.II. Clinical Documentation

Laboratory Trials

Dose Determination Studies

The applicant conducted two dose determination studies. The first evaluated different dose levels (25, 50 and 100 mg/kg), the second, different durations of treatment (3 days or 7 days). In the first study, due to the presence of other pathogens (*Escherichia coli* and *Clostridium perfringens*), measurement of faecal score could not be used as the primary end point. Instead, faecal oocyst count was used and a dose level of 50 mg/kg was considered to be acceptable. From the second study, it was considered that a treatment duration of 7 days could be justified.

Field Trials

Three field studies (blinded, randomised, negatively controlled) were conducted, considering different housing conditions and geographical locations. Calves received the product upon confirmation of cryptosporidial oocysts in their faeces but before the onset of diarrhoea. In these studies, 23% to 32% of calves in treated groups presented with diarrhoea, in comparison to 53% to 73% of calves in untreated groups, during the 7-day treatment period.

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 benefit/risk 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 on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)