12 February 2025
EMA/171245/2025
Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use (CVMP)

# Withdrawal assessment report for Cunitraxx (Cuninox) (EMEA/V/C/006595/0000)

INN: fenbendazole

**Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.**

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# Introduction

The applicant Avimedical B.V. submitted on 1 October 2024 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Cunitraxx, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 22 May 2024 as no other marketing authorisation had been granted for the veterinary medicinal product within the Union.

At the time of submission, the applicant applied for the following indication: "Treatment and control of protozoan parasites in rabbits infected with *Encephalitozoon cuniculi."*

The active substance of Cunitraxx is fenbendazole, an antiparasitic belonging to the benzimidazole-carbamate group, which inhibits the polymerisation of tubulin to microtubules. This interferes with essential structural and functional properties of cells.

The intended target species was rabbits (non-food-producing). However, at the time of the application, rabbits were considered a food producing species, as Regulation (EU) 2019/6 was not considered to include a basis to treat them otherwise. Consequently, the restriction to non-food producing rabbits was not accepted and the applicant was requested to adjust the application to take this into account.

Cunitraxx oral suspension contained 25 mg/ml fenbendazole and was presented in Type III amber glass bottles of 10 ml, 30 ml and 50 ml with packs containing 1 or 10 bottles.

The applicant was registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

The dossier was submitted in line with the requirements for submissions under Article 23 of Regulation (EU) 2019/6 – an application for limited markets.

On 23 April 2025, Avimedical B.V. withdrew the application during the clock-stop at day 120 of the procedure. In its letter notifying the Agency of the withdrawal of the application, the applicant stated the reason for the withdrawal was the magnitude of the request for supplementary information.

## *Limited market status*

The applicant requested classification of this application as limited market by the CVMP.

The Committee confirmed on 7 September 2023 that limited market status would apply as rabbits are not listed in Article 4(29)(b) of Regulation (EU) 2019/6.

The CVMP also confirmed that the application would qualify to be submitted under Article 23 of Regulation (EU) 2019/6 (limited market), as the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation would not be provided. The data requirements in the relevant CVMP guideline(s) for applications for veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 were applicable when assessing the application.

# Part 1 - Administrative particulars

## *Summary of the Pharmacovigilance System Master File*

The applicant provided a summary of the pharmacovigilance system master file which fulfilled the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF), has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

## *Manufacturing authorisations and inspection status*

**Active substance**

Manufacturing of active substance and primary packaging of active substance and quality control takes place outside the EEA. A Qualified Person (QP) Declaration is provided from the QP of the EU batch release site confirming that the active substance is manufactured in compliance with EU GMPs. This was verified by an on-audit performed at the manufacturing site on 2-3 November 2023 by an auditing body.

**Finished product**

**Floris Veterinaire Producten B.V.**

Kempenlandstraat 33

5262 GK Vught

Noord-Brabant, The Netherlands.

Activities performed: batch release.

A GMP Certificate for this site is available in Eudra GMP. This certificate was issued on 25 October 2021, referencing an inspection on 6 April 2021 and covering the manufacturing operations of non-sterile products (including liquids for internal use), primary and secondary packaging and quality control testing (chemical and physical) and batch certification.

## *Overall conclusions on administrative particulars*

Prior to withdrawal of the application, additional information had been requested in regard to the GMP certification of the manufacturing sites.

# Part 2 - Quality

## *Composition*

The finished product was presented as oral suspension containing fenbendazole (25.0 mg/ml) as active substance and several excipients. The composition was described appropriately, and only minor corrections concerning the names of some excipients were outstanding at the time of withdrawal of the application.

The proposed commercial pack sizes were: 1 bottle of 10 ml, 1 bottle of 30 ml and 1 bottle of 50 ml. However, some discrepancies between the information in the dossier and section 5.4 of the SPC were noted and had been requested to be clarified.

The pack sizes were consistent with the dosage regimen and duration of use.

The product was supplied including dosing syringes:

- 1 ml dosing syringe with each 10 ml bottle,
- 1 ml and 5 ml dosing syringes with each 30 ml and 50 ml bottles.

## *Containers and closure system*

The primary packaging consisted of an amber glass bottle made of glass type III, according to Ph. Eur. The bottles were closed with a cap and a syringe insert.

Adequate specifications, certificates of analysis, technical drawing and confirmation of compliance with Ph. Eur. were provided for glass bottles. Regarding closures, appropriate specifications, certificates of analysis and a confirmation of compliance with Ph. Eur. were provided too. Appropriate data on the syringes inserts were also submitted, pending a clarification on the syringes provided with 30 and 50 ml bottles.

## *Product development*

The aim of the development was to make a product essentially similar to the product Meranox, which is authorised in the Netherlands and used in ornamental birds and small mammals' exotic species. The marketing authorization holder is the same company: Avimedical B.V.

Preservative efficacy testing studies were carried out to confirm that a preservative needed to be added to the formulation. Although studies were performed in accordance with Ph. Eur. 5.1.3, two questions related to the concentration of preservative and the results provided within the dossier were raised.

Appropriate dosing accuracy studies were performed to demonstrate the accuracy of dosing devices. The design of these studies was regarded adequate and the results obtained meet the Ph. Eur. limits.

Finally, the SPC of different fenbendazole-containing authorised products were evaluated to confirm that the formulation had no impact on the posology; particle size results obtained with batches of this product and batches of a similar product were also provided, and the results obtained were comparable.

Information included in this section of the dossier did not cover all the points highlighted in the "Guideline on the development pharmaceutics for veterinary medicinal products" (EMA/CVMP/QWP/684556/2022). Additional data related to compatibility of components, physicochemical parameters which can affect product quality, choice of primary packaging materials and manufacturing process were requested.

## *Description of the manufacturing method*

The finished product manufacturers and their responsibilities are described in Part 1. The manufacturing process is a standard process and consists of the weighing of all the components and preparation of three phases before mixing.

One batch size was described. However, the dossier also stated that other batch sizes could be processed. Therefore, prior to withdrawal of the application a clarification had been requested for specific batch size/range being stated in the dossier.

The batch formula and the description of the manufacturing process were included. The description needed be updated to include all the in-process controls (IPCs) established at each step, their analytical methods and acceptance criteria. A specific justification regarding one IPC was requested.

Additionally, the Applicant was requested to clarify what IPCs would be performed during the routine manufacturing process of this product, together with a request for an updated flow chart of the manufacturing process. Additionally, the equipment, working capacity and process parameters should also be stated.

The manufacturing process is a standard process. Although its validation was adequately performed on three production batches of the finished product, prior to withdrawal of the application the applicant was requested to confirm that the process parameters described in the validation report would be controlled during the routine manufacture of this product, and to provide the filling times of 2 of the validation batches used for validation purposes.

## *Control of starting materials*

## *Active substance*

The active substance fenbendazole has a monograph in the Ph. Eur. The finished product manufacturer sourced the active substance from a single manufacturer which was granted a Certificate of Suitability of the European Pharmacopoeia (CEP), a copy of which was provided within the application.

The control specifications for the active substance include the test of the Ph. Eur. monograph with additional tests included in the CEP and a control of particle size. The specifications proposed were considered adequate; however, there were several comments regarding limits, additional acceptance criteria and one test had been requested to be removed.

No descriptions and validations of the pharmacopoeial analytical methods were submitted.

An adequate description of the particle size test was provided. However, the entity responsible to performing this test as well as the micronisation of the active substance was not mentioned in the dossier, and no validation of this method was provided. The applicant had been requested to address these points. Additionally, adequate information regarding the micronisation process of this active substance needed be provided.

Appropriate description of the methods to determine the crystal morphology and identification and assay of fenbendazole were provided. Nevertheless, some validation parameters were not assessed in the method validation and still needed to be detailed at the time of withdrawal of the application.

Certificates of analysis of two batches of active substance tested by the finished product manufacturer and three batches tested by the active substance manufacturer were provided. All the results met the proposed limits.

The CEP included a retest period for this active substance.

## *Excipients*

The majority of the excipients were well known and controlled in accordance with their respective Ph. Eur. monographs. However, for some, there was either a request for deleting the test for heavy metals from the specifications outstanding, or a question about the functionality-related characteristics.

One of the excipients, despite being well-known, was not described in a pharmacopoeia. Therefore, prior to withdrawal of the application the applicant had been required to detail its qualitative and quantitative composition together with a confirmation of compliance with colouring matters and food additives in accordance with the relevant European legislation.

## *Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies*

Valid TSE declarations from the manufacturers of the active substance and excipients were provided. However, compliance of the finished product with the last version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3) still needed to be confirmed.

## *Control tests on the finished product*

The finished product specification at release included tests for appearance of container, appearance, homogeneity, extractable volume, relative density, pH, viscosity, particle size, identification and assay of fenbendazole, identification and assay of the preservative, and microbiological quality.

These specifications are adequate for the dosage form, however several changes had been requested to be introduced in the specifications table.

Regarding the specifications proposed at release, it was agreed that this could be accepted provided that the Applicant responded to the questions raised.

Regarding shelf-life specifications, these are broadly the same as at release except for extractable volume, degradation products and assay of the preservative acceptance criteria.

The descriptions of the analytical methods provided were considered adequate with only minor comments yet to be resolved.

A validation study on an analytical method was requested.

The microbiological quality method was described and validated and some questions were raised.

Certificates of analysis of two production batches of finished product issued by the manufacturer were provided. All the results met the acceptance criteria.

An elemental impurities risk assessment in compliance with ICH Q3D requirements was performed. This was acceptable.

## *Stability*

The finished product specification at the end of shelf-life included tests for appearance of container, appearance, homogeneity, relative density, pH, viscosity, particle size, identification and assay of fenbendazole, identification and assay of the preservative, fenbendazole related substances, and microbiological quality. All these specifications were controlled in stability studies.

Stability studies were performed in batches of finished product stored in 10 ml and 50 ml pack sizes (stability of 30 ml bottles was considered proven as both the 10 and 50 ml were shown to be stable) at the following conditions:

- At 25ºC/60% RH for 36 months. Results up to 25 months were provided.
- At 40ºC/75% RH. Results up to 6 months were provided.

The frequency of the tests was as established in the relevant stability guidelines except for the viscosity, particle size and microbiological quality tests, that were not tested at the 3, 9 and 18 month time-points. However, this was accepted by the CVMP.

All the results met the acceptance criteria at both real time and accelerated conditions. A shelf life of 3 years without special storage conditions was claimed.

No photostability studies were performed. However, since section 5.3 of the SPC includes the warning "Keep the bottle in the outer carton in order to protect from light", this could be accepted.

An in-use stability study was performed in batches of the finished product in order to justify an in-use shelf life of 28 days.

## *Other information*

This section included information on residual solvents compliance for each component of the veterinary medicinal product. A table summarizing the requirements and specifications was provided, as well as individual residual solvents statements. However, a mistake was noted in the summary table provided that still needed to be corrected at the time of withdrawal of the application.

## *Overall conclusions on quality*

The finished product was presented as an oral suspension containing fenbendazole (25.0 mg/ml) as active substance. Its composition was appropriately described. Only minor corrections had been requested at the time of withdrawal of the application.

The primary packaging consisted of amber type III glass bottles of 10, 30 and 50 ml closed with a cap and a syringe insert. Additional information on the pack sizes intended to be marketed was requested.

The aim of the development was to make a product essentially similar to the product Meranox, authorised in the Netherlands and used in ornamental birds and small mammals' exotic species. The marketing authorization holder is the same company: Avimedical B.V.

The development pharmaceutics section included preservative efficacy testing studies performed in accordance with Ph. Eur. 5.1.3. There were questions outstanding.

Additionally, dosing accuracy studies were also provided, the SPC of different fenbendazole-containing authorised products evaluated and compared, and particle size results obtained on batches of this product and of a similar product – these results were also provided.

The information included in this section of the dossier did not cover all the points highlighted in the development pharmaceutics guideline. Therefore, additional data was required.

The manufacturing process consisted of the weighing of all the components and the preparation of different phases which were mixed to obtain a homogeneous suspension and filled in bottles. A typical batch size was described. However, the dossier also stated that other batch sizes could be processed. This point needed to be clarified.

The batch formula and the description of the manufacturing process were included. The description needed to be updated to include all the in-process controls (IPCs), analytical methods and acceptance criteria.

Regarding the IPCs, at the time of withdrawal of the application additional information about one of them was outstanding, the controls to be performed during the routine manufacturing process remained to be detailed and an updated flow chart remained to be provided including the appropriate IPCs.

The manufacturing process was a standard process and its validation was adequately performed on production batches of the finished product. However, several questions were outstanding.

Information on the control of starting materials was provided. The active substance fenbendazole has a monograph in the Ph. Eur. and its manufacturer was granted a Certificate of Suitability of the European Pharmacopoeia (CEP).

The specifications proposed were considered adequate however there were some outstanding points to be addressed.

Certificates of analysis of the active substance tested by the finished product manufacturer and batches tested by the active substance manufacturer were provided. All the results met the proposed limits.

The CEP included a retest period for this active substance.

The majority of excipients were well known and controlled in accordance with their respective Ph. Eur. monographs. Prior to withdrawal of the application, however, two questions about the specifications were raised.

One of the excipients, despite being well-known, was not described in a pharmacopoeia. Therefore, the applicant was required to detail its qualitative and quantitative composition together with a confirmation of compliance with colouring matters and food additives in accordance with the relevant European legislation.

The primary packaging consisted of an amber glass bottle made of glass type III, according to Ph. Eur. The bottles were closed with a cap and a syringe insert.

Regarding primary packaging, adequate specifications, certificates of analysis and compliance with Ph. Eur. were provided for the glass bottles and caps. Satisfactory data on the syringes inserts was also submitted.

Valid TSE declarations from the manufacturers of all the components were provided. However, compliance of the finished product with the last version of the Note for guidance on minimising the

risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3) needed to be confirmed.

Finished product specifications for release and shelf life were provided. The finished product specifications at time of release controlled the appropriate parameters for the dosage form. However, there were some outstanding questions at the time of withdrawal.

The descriptions of the analytical methods provided were considered adequate with one point for clarification outstanding at time of withdrawal.

There were some questions outstanding regarding validation at the time of withdrawal.

Microbiological quality method was described and validated.

Certificates of analysis of two production batches of finished product issued by the finished product manufacturer were provided. All the results met the acceptance criteria.

An elemental impurities risk assessment in compliance with ICH Q3D requirements was performed.

Stability studies were performed in batches of finished product (packaged in 10 ml and 50 ml bottles) which were stored at long term (25ºC/60% RH) and at accelerated conditions (40ºC/75% RH). Obtained results up to 25 months and 6 months respectively were provided. All of them met the acceptance criteria and no deviations were observed. Therefore, a shelf life of 3 years without special storage conditions was claimed by the applicant.

Photostability studies were not performed. However, an appropriate sentence in section 5.3 of the SPC was included.

An in-use stability study was carried out in three batches of finished product in order to justify an in-use shelf life of 28 days. Results were satisfactory.

Information on residual solvents compliance for each component of the medicinal product were provided in section 2G of the dossier.

Overall, data provided in part 2 of the dossier was considered not satisfactory, as a number of other concerns were raised prior to withdrawal of the application.

# Part 3 – Safety documentation (Safety and residues tests)

Fenbendazole is an antiparasitic belonging to the benzimidazole-carbamate group.

The candidate formulation was an oral suspension intended for use in pet rabbits with fenbendazole as active ingredient for treatment and control of protozoan parasites in rabbits infected with *Encephalitozoon cuniculi*.

A summary of different toxicity studies from the literature was provided, which were also summarised in the previous MRL assessment by the CVMP (EPMARs for Fenbendazole). No product-specific safety or toxicology studies were undertaken by the applicant. Rather, reference was made to publicly available data from the EMA (CVMP) EPMARs and the JECFA Monograph for fenbendazole. The pharmacological and toxicological data on the active substance were reviewed previously by the CVMP in the context of an application to establish MRLs (Fenbendazole Summary Report, EMEA/MRL/193/97-FINAL and EMEA/MRL/866/03-FINAL). Therefore, in this report, reference is made to the CVMP conclusions on those data. According to section II.3(2) of Annex II to Regulation (EU) 2019/6 "when the substance has been previously evaluated for the establishment of maximum residues limit ("MRL") to address certain safety requirements reference may be made to the European public MRL assessment reports ("EPMARs").

## *Safety tests*

## Pharmacology

See part 4.

## Toxicology

Fenbendazole is a well-known active substance, and reference was made to published data concerning its toxicity from a JECFA Monograph (Keller, 1991) which is also summarized in the CVMP EPMARs for Fenbendazole and therefore assessed by CVMP in the above-referenced MRL procedures.

### *Single-dose toxicity*

Fenbendazole was shown to be of low acute toxicity when administered for different routes. Oral $LD_{50}$ values in laboratory rats and mice were greater than 10000 mg/kg bw.

### *Repeat-dose toxicity*

Repeated dose toxicity was studied in rats. From an oral repeated-dose toxicity study in rats (30 days; 10 animals per sex), fenbendazole was administered at dose levels of 0, 25, 250 or 2500 mg/kg bw per day, and no treatment related effects were observed.

In a 90-day study, groups of Wistar rats (15 per sex) were given daily oral fenbendazole doses of 0, 25, 200 or 1600 mg/kg bw per day. For 5 animals per sex the top dose was increased to 2500 mg/kg bw per day from day 61 onwards. Two rats from the 1600 mg/kg bw group and 5 rats from the 2500 mg/kg bw group had tremors; there were no other treatment-related effects.

In a series of studies in dogs, fenbendazole was administered in gelatine capsules for periods of 6 days to 6 months. The main toxic effect was lymphoid hyperplasia in the gastric mucosa and mesenteric lymph nodes. The overall NOEL was 4 mg/kg bw per day.

An ADI of 7 µg/kg bw per day for oxfendazole (*in vivo*, fenbendazole mainly exists in its oxidised oxfendazole form) had been previously established by the CVMP by applying a safety factor of 100 to the NOEL of 0.65 mg/kg bw per day for hepatic vacuolation seen in a carcinogenicity study in rats treated with oxfendazole. See carcinogenicity section below.

***Tolerance in the target species***

See Part 4.

***Reproductive toxicity, including developmental toxicity***

**Study of the effect on reproduction**

In a 3-generation study Charles River CD rats were given fenbendazole in the diet at doses equivalent to 0, 5, 15, 45 or 135 mg/kg bw per day. At doses of 45 mg/kg bw and above, parental animals had diarrhoea, reduced bodyweight gain and pathological changes in the liver. At these doses there were also reductions in fertility, survival and growth of the neonates during lactation. The NOEL was set at 15 mg/kg bw per day.

**Study of developmental toxicity**

In a teratogenicity study in Wistar rats, groups of 20 mated females were given daily oral fenbendazole doses of 0, 25, 250 or 2500 mg/kg bw per day from days 7 to 16 of gestation. There was no evidence of maternal toxicity, foetotoxicity or teratogenicity at any dose level.

Groups of 10 mated yellow silver rabbits were given daily oral doses of 0, 10, 25 or 63 mg/kg bw per day from days 7-19 of gestation. An increase in delayed ossification was observed in the 63 mg/kg bw group. The NOEL was therefore 25 mg/kg bw per day.

There were no treatment-related effects in the offspring of dogs, pigs, sheep and cattle, administered fenbendazole at various times during gestation.

It was further noted that oxfendazole, the common sulfoxide metabolite of fenbendazole, caused embryolethality and an increase in external malformations already at a dose of 2 mg/kg bw/day in Sprague-Dawley rats. In another study in rats, teratogenic effects and embryolethality were also observed for oxfendazole, resulting in a NOEL of 10 mg/kg bw/day. Also, in rabbits doses of 100 mg oxfendazole/kg of body weight per day and higher produced fetal malformations; no embryotoxicity was observed at doses of 0, 10, 30 or 45 mg/kg of body weight per day. A LOAEL of 2 mg/kg bw, which corresponds to 1.9 mg/kg bw/day for fenbendazole should therefore also be considered in the risk characterisation.

***Genotoxicity***

Fenbendazole gave negative results in the Ames test with *Salmonella typhimurium*, and in an in vitro assay for DNA repair in primary rat hepatocytes. Negative results were also obtained in an in vivo cytogenetic assay in Chinese hamster bone marrow and in an in vivo mouse bone marrow micronucleus test. Fenbendazole and the 2-amino metabolite were positive, in the presence of

metabolic activation only, in mouse lymphoma forward mutation assay. Many benzimidazole compounds are known to be mitotic spindle poisons. The microtubules of exposed cells are affected in such a way as to impair normal cell division and cause mis-segregation of chromosomes into the daughter cells resulting in aneuploidy.

The mutagenicity data available for fenbendazole showed no clear evidence of genotoxicity and although no specific tests for aneugenicity had been conducted, the clastogenicity studies conducted were generally reassuring.

***Carcinogenicity***

There was no evidence of carcinogenicity in a study in which groups of 60 per sex per dose Charles River CD-1 mice were given fenbendazole in the diet at concentrations designed to produce 0, 45, 135 or 405 mg/kg bw per day for up to 2 years. Survival was reduced in treated groups compared to controls.

In Charles River CD rats, the animals were exposed to dietary doses of fenbendazole of 0, 5, 15, 45 or 135 mg/kg, including an initial in utero phase where the dams received the same dosages. Effects on survival were seen at the high dose and bodyweight gain was affected at 45 and 135 mg/kg. Alkaline phosphatase was consistently elevated at 15 to 135 mg/kg and serum glutamic-oxaloacetic transaminase (SGOT) at 135 mg/kg only. Histological changes were seen primarily in the liver including hepatocellular hypertrophy, hyperplasia and vacuolation, bile duct proliferation and biliary cyst formation. The overall NOEL was 5 mg/kg.

In the conclusion by JECFA (50$^{th}$ meeting, 1999), another carcinogenicity study using oxfendazole is described, which determined the ADI (for oxfendazole as well as fenbendazole). In the rat dietary carcinogenicity study, rats (strain & number/dose unspecified) were fed oxfendazole in the diet at concentrations of 0, 10, 30 or 100 mg/kg for 2 years. The only treatment-related effect noted was dose-related hepatocellular lipid vacuolation at 30 and 100 mg/kg in the diet. The NOEL was 10 mg/kg in the diet (0.7 mg/kg bw/d (males) and 0.9 mg/kg bw/d (females)). The Committee established a group ADI of 0-7 µg/kg bw for febantel, fenbendazole, and oxfendazole on the basis of a NOEL of 0.7 mg/kg bw/d in a two-year study on oxfendazole in rats (evaluated at the 38th and 45th meetings) and a safety factor of 100. It is assumed this value was based on the same NOEL of 0.65 mg/kg bw/day mentioned in the EPMAR report which allowed for the establishment of an ADI of 7 µg/kg bw, though rounded up.

## Other requirements

***Special studies***

No special studies were submitted. It was noticed, however, that for veterinary medicinal products containing fenbendazole a user safety warning with respect to hypersensitivity reactions is included. Also for the structurally related substance mebendazole allergic reactions had been reported (Martindale the complete drug reference).

***Observations in humans***

Fenbendazole is not authorised for use in humans. However, human toxicity data for fenbendazole were extracted from the JECFA Monograph for fenbendazole where no relevant changes in blood pressure, pulse rate, symptom list and self-rating scale and clinical chemistry values were established in the subjects given oral doses of 300 mg fenbendazole with breakfast (five healthy

males) and 600 mg fenbendazole 12 hours after their last meals (six healthy males)(Rupp & Hajdu, 1974).

## Excipients

Information on the safety profile of the excipients was not provided. Excipients of the product are currently used in veterinary and human medicines and do not raise any toxicological systemic concern. However, local adverse effects due to some excipients should not be ruled out. That is, some may cause allergic reactions when administered topically and the preservative may cause mild local irritation.

## User safety

The applicant submitted a user safety risk assessment which was largely carried out in accordance with the CVMP Guideline EMEA/CVMP/543/03-Rev.1, though did not exactly fit with the outlined structure and was very limited.

The main potential routes of exposure were considered to be dermal contact by adult users (pets-owners) during administration of the product to pet rabbits and accidental oral ingestion by children as the product may be kept in the household. The worst-case scenario for user safety was ingestion of 5 ml by a child (i.e. a full 5 ml dosing syringe which corresponds to a realistic swallow volume), with an estimated margin of exposure (MOE) of 0.4 when compared to the NOEL of 4 mg/kg bw as derived from the repeated dose toxicity studies in dogs were fenbendazole was administered up to 6 months. Although acute exposure by the child was compared to a (sub)chronic TRV, this risk could not be dismissed, and appropriate warnings and safety measures to prevent exposure to the filled syringe had been requested to be included in the product. Moreover, the applicant was requested to confirm that the "resistant cap" was child-resistant, otherwise this mitigation measure needed be implemented. In addition, if the veterinary medicinal product was to be administered via food, children may have access to the bowl with medicated feed. The applicant was requested to reflect on this and implement appropriate risk mitigation measures if necessary.

Hypersensitivity reactions, as well as mild local irritation, both due to the active substance and some excipients needed also to be taken into account in the product information.

The risk for systemic adverse effects after dermal exposure including hand-to-mouth contact was considered acceptable. However, with respect to the risk for women of childbearing age a question was raised, as embryolethality was observed for oxfendazole (in vivo, fenbendazole mainly exists in its oxidised oxfendazole form).

Finally, the user safety warnings to include in the product information as proposed by the applicant were not fully in line with the risks identified in the URA submitted for this VMP. Therefore, the applicant was requested to review the proposed risk mitigation measures. Moreover, the applicant was requested to adapt the risk management measures for the user to the ABCD format and QRD template v9.

## Environmental risk assessment

The applicant provided a phase I environmental risk assessment (ERA) 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- Corr.1) that stops in Q3, as the product was intended to be used in non-food producing animals. A risk for the environment was not envisaged.

## *Overall conclusions on the safety documentation: safety tests*

Fenbendazole is an antiparasitic belonging to the benzimidazole-carbamate group.

The candidate formulation is an oral suspension intended for use in pet rabbits with fenbendazole as active ingredient for treatment and control of protozoan parasites in rabbits infected with *Encephalitozoon cuniculi.*

A summary of different toxicity studies from the literature was provided, which are also summarised in the previous MRL assessment by the CVMP (EPMARs for Fenbendazole). No product-specific safety or toxicology studies were undertaken by the Applicant. Rather, reference was made to publicly available data from the EMA (CVMP) EPMARs and the JECFA Monograph for fenbendazole. The pharmacological and toxicological data on the active substance were reviewed previously by the CVMP in the context of an application to establish MRLs (Fenbendazole Summary Report, EMEA/MRL/193/97-FINAL and EMEA/MRL/866/03-FINAL). Therefore, in this report, reference was made to the CVMP conclusions on those data. According to section II.3(2) of the Annex II to Regulation (EU) 2019/6 "when the substance has been previously evaluated for the establishment of maximum residues limit ("MRL") to address certain safety requirements reference may be made to the European public MRL assessment reports ("EPMARs").

Pharmacology is addressed in Part 4.

Toxicology:

- Oral LD50 values in laboratory rats and mice were greater than 10000 mg/kg.
- From an oral (gelatine capsules) repeated dose toxicity study in dogs up to 6 months, a NOEL of 4 mg/kg bw per day was retained, based on lymphoid hyperplasia in the gastric mucosa and mesenteric lymph nodes
- The ADI for fenbendazole was based on the NOEL of 0.65 mg/kg bw per day for hepatic vacuolation seen in a 2-year carcinogenicity study in rats treated with oxfendazole (in vivo, fenbendazole mainly exists in its oxidised oxfendazole form). Based on MW (299.35 for fenbendazole versus 313.35 for oxfendazole), this would correspond to 0.62 mg/kg bw fenbendazole.
- Reproductive study in rats indicated a NOEL of 15 mg/kg bw per day orally; based on diarrhoea, reduced bodyweight gain and pathological changes in liver of the parental animals and reductions in fertility, survival and growth of the neonates during lactation.
- Embryotoxicity/Teratogenicity study in rabbits indicated a NOEL of 25 mg/kg bw per day orally; based on an increase in delayed ossification. It is further noted that oxfendazole, the common sulfoxide metabolite of fenbendazole, caused embryolethality and an increase in external malformations already at a dose of 2 mg/kg bw/day in Sprague-Dawley rats. In another study in rats, also teratogenic effects and embryolethality was observed for oxfendazole, resulting in a NOEL of 10 mg/kg bw/day. This indicates a LOAEL of 2 mg/kg bw, which corresponds to 1.9 mg/kg bw/day for fenbendazole.
- The data available show no clear evidence of genotoxicity nor of carcinogenicity.

- No information was provided on local effects due to fenbendazole. However, based on the information of other veterinary medicinal products, hypersensitivity reactions could not be excluded.

The toxicity of this product will be determined by its active substance. Most of the excipients of the candidate product, were not expected to cause any systemic effects and were not of toxicological concern. However, some may produce hypersensitivity reactions, and local irritation due to the presence of the preservative could not be excluded. Therefore, local adverse effects due to these excipients in the VMP needed to be taken into account.

User Safety:

The applicant submitted a brief user safety risk assessment which was largely carried out in accordance with CVMP Guideline EMEA/CVMP/543/03-Rev.1, though did not exactly fit with the outlined structure and was very limited.

The main potential routes of exposure were considered to be dermal contact by adult users (pets-owners) during administration of the product to pet rabbits and accidental oral ingestion by children as the product may be kept in the household. The worst-case scenario for user safety was ingestion of 5 ml by a child (i.e. a full 5 ml dosing syringe, which corresponds to a realistic swallow volume), with an estimated margin of exposure (MOE) of 0.4 when compared to the NOEL of 4 mg/kg bw as derived from the repeated dose toxicity studies in dogs were fenbendazole was administered up to 6 months. Although acute exposure by the child was compared to a (sub)chronic TRV, this risk could not be dismissed, and appropriate warnings and safety measures to prevent exposure to the filled syringe had been requested to be included in the product information. Moreover, the applicant was required to confirm that the "resistant cap" was child-resistant, otherwise this mitigation measure needed to be implemented. In addition, if the veterinary medicinal product was to be administered via food, children may have access to the bowl with medicated feed. The applicant was requested to reflect on this potential new risk and implement appropriate risk mitigation measures if necessary.

The risk for systemic adverse effect after dermal exposure including hand-to-mouth contact was considered acceptable. However, with respect to the risk for women of childbearing age a question was raised, as embryolethality has been observed for oxfendazole (in vivo, fenbendazole mainly exists in its oxidised oxfendazole form).

Hypersensitivity reactions, as well mild local irritation, both due to the active substance and some excipients needed to be taken into account in the product information.

Finally, the user safety warnings to include in the product information as proposed by the applicant were not fully in line with the risks identified in the URA submitted for this VMP. Therefore, the applicant was requested to review the proposed risk mitigation measures. Moreover, the applicant was requested to adapt the risk management measures for the user to the ABCD format and QRD template v9.

Environmental risk assessment:

In relation with the environmental risks, the use of the product in accordance with the SPC was not expected to pose a risk for the environment. In line with QRD, warnings were included to ensure a safe disposal of the unused medicines. In this sense, slight amendments needed to be performed in the product information.

# Part 4 – Efficacy

This was an application for a marketing authorisation for Cunitraxx, submitted through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6. In addition, this was an application submitted in accordance with Article 23 of Regulation (EC) 2019/6 (an application for limited markets).

The product was intended to be used in pet rabbits (non-food producing). At the time of submission, the applicant applied for the following indication: "Treatment and control of protozoan parasites in rabbits infected with Encephalitozoon cuniculi."

Regarding this point, it should be noted that according to the NCBI taxonomy browser, E. cuniculi was classified as a microsporidia belonging to fungi kingdom. Nevertheless, regardless of the taxonomy classification, the use of the active substance (fenbendazole) in this application seemed to be as an antimicrobial, which may have implications regarding the proposed indication, warnings or ATCvet classification.

The CVMP confirmed that the application would qualify to be submitted under Art. 23 of Regulation (EU) 2019/6 (limited market), as the benefit of the availability on the market of the veterinary medicinal product (VMP) to the animal or public health outweighs the risk inherent in the fact that certain documentation was not provided. As such, with regards to target animal safety and efficacy, the data requirements as outlined in the CVMP Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 (EMA/CVMP/52665/2020) apply.

The applicant based the dossier submitted in a bibliographical revision of the available information related to the intended use. Though there appear to be no officially authorised formulations for rabbits, it was acknowledged that the active fenbendazole is a well-known active substance. Use of the active for the treatment of rabbits infected with Encephalitozoon cuniculi, had previously been described in scientific literature. At the time of withdrawal of the application it could be agreed that fenbendazole had been used off-label commonly and globally during a considerable time in the proposed target species. Scientific interest in the use of this active substance was also clear, noting that there were multiple scientific publications available in the dossier. While this approximation was therefore acceptable, the final acceptance of such an application ultimately depended on the justification of the preclinical and/or clinical parts. Therefore, if suitable data were provided in the clinical part to characterise the efficacy and tolerance of the test product in terms of the proposed indication, posology and route(s) of administration, product-specific pharmacokinetic and pharmacodynamic data could be omitted.

## *Pre-clinical studies*

*Encephalitozoon cuniculi* is an obligate intracellular protozoan parasite which can cause a range of clinical signs including hind limb paresis, head tilt, collapse, urinary incontinence, cataract formation and lens induced uveitis and death. Neurological involvement is the most common manifestation and is most frequently associated with vestibular disease with infected rabbits presenting with varying degrees of head tilt, nystagmus, ataxia, circling and rolling. Distribution of the pathogen is worldwide, and pet rabbits are commonly found to be infected. Transmission is primarily via ingestion of spores which have been shed in the urine and contaminated food and/or water.

Cunitraxx was an oral suspension containing 25 mg/ml of Fenbendazole intended for use in pet

rabbits for the treatment and control of *Encephalitozoon cuniculi*. The proposed dose was 20 mg fenbendazole per kg body weight per day to be administered on 28 consecutive days.

The active substance of Cunitraxx was fenbendazole, an antiparasitic belonging to the benzimidazole-carbamate group, which inhibits the polymerisation of tubulin to microtubules. This interferes with essential structural and functional properties of cells. Fenbendazole is one of the most common off-label used active ingredients for treating *E. cuniculi* infections in pet rabbits.

## Pharmacology

### *Pharmacodynamics*

Three published papers by Li et al. (1996)[1], Wei et al. (2022)[2], and Didier (1997)[3], and a Bachelor's thesis in chemistry by Usland (2022)[4] were provided to describe the mode of action of the active substance. Of these, one had more relevance for the dossier (Usland, 2022).

Based on the data provided, fenbendazole has shown a mechanism of action based on the polymerisation of tubulin to microtubule which interferes with essential structural and functional properties of cells although the exact mechanism of action of these drugs is unknown and a better understanding of it may help finding novel benzimidazole drugs with better affinity and efficacy (Suter et al., 2001[5], Aguayo-Ortiz et al., 2013[6]).

The mode of action was captured in section 4.1 of the SPC, 'pharmacodynamics'. Nevertheless, at the time of withdrawal of the application, section 4.1 of the SPC needed to be updated to reflect the wording according to the reference provided (Usland, 2022).

### *Pharmacokinetics*

The applicant provided some bibliographical references to characterise the pharmacokinetic profile of fenbendazole in the target species rabbits.

The reference Keller (1991)[7] was a bibliographical review of the available data at the time of publication of that document and was included in the 'WHO Food Additives Series 29'. This document presents various studies that were performed to obtain basic information on the pharmacokinetics of 14C-fenbendazole after single oral administration as an aqueous suspension in 2% starch mucilage at a dose of 10 mg/kg bw. Nevertheless, the blood concentration data obtained in the reported studies were not directly relevant given that the doses used were different from those stated for the proposed product information.

Within the review by Keller (1991), other references provided relevant data about its metabolism: Klopffer (1973), Kellner and Christ (1973), Villner et al. (1974), and Düwel and Uihlein (1980),

[1] Li, J., Katiyar, S. K., Edlind, T. D. (1996). Site-directed mutagenesis of saccharomyces cerevisiae b-tubulin: interaction between residue 167 and benzimidazole compounds. FEBS Letters, 385(1-2), 7–10.
[2] Wei, J., Fei, Z., Pan, G., Weiss, L. M., & Zhou, Z. (2022). Current Therapy and Therapeutic Targets for Microsporidiosis. Frontiers in microbiology, 13, 835390. https://doi.org/10.3389/fmicb.2022.835390
[3] Didier, E. S. (1997). Effects of albendazole, fumagillin, and TNP-470 on microsporidial replication in vitro. Antimicrob. Agents Chemother. 41, 1541– 1546. doi: 10.1128/AAC.41.7.1541
[4] Usland, A. O., (2022). Four different benzimidazoles as treatment against Encephalitozoon cuniculi infection in rabbits and how they may bind to β-tubulin. Bachelor's thesis in Chemistry. Supervisor: Huiling Liu. Norwegian University of Science and Technology, Faculty of Natural Sciences, Department of Chemistry.
[5] Suter, C., Müller-Doblies, U. U., Hatt, J. M., & Deplazes, P. (2001). Prevention and treatment of Encephalitozoon cuniculi infection in rabbits with fenbendazole. The Veterinary record, 148(15), 478–480. https://doi.org/10.1136/vr.148.15.478
[6] Aguayo-Ortiz, R. O. (2013). Towards the identification of the binding site of benzimidazoles to β-tubulin of trichinella spiralis: Insights from computational and experimental data. Journal of Molecular Graphics and Modelling, 41, 12–19.
[7] Fenbendazole (WHO Food Additives Series 29) 29-06. Dr. William C. Keller, Food and Drug Administration, Rockville, Maryland USA.

determined the serum levels of fenbendazole and its metabolites in rabbits after oral administration of fenbendazole. The main blood metabolites were oxfendazole and fenbendazole sulfone and the main elimination metabolite was p-OH fenbendazole.

In the work by Zhu et al. (2011)[8] it was reported the optimisation and validation of a quantitative HPLC/MS/MS method for the determination of flubendazole, albendazole, fenbendazole, mebendazole, thiabendazole and their metabolites in plasma of rabbits which were given an aqueous suspension of fenbendazole (1.25 mg/ml) in a single dose of 4 mg/kg bw with gastric perfusion administration.

Although these references characterised the pharmacokinetic profile of fenbendazole in rabbits, no information about the proposed formulation was provided nor the proposed dosage regimen, so they had a limited value.

In addition, no information was provided at repeated doses. Short et al. (1988)[9] discussed about the role of the caecum as a reservoir from which these compounds either re-entered the intestine or were absorbed and underwent renal elimination over a prolonged period. Since this possible accumulation could impact on the tolerance of the target species, at the time of withdrawal of the application this point still needed to be addressed by the applicant.

In addition, it was noted that in Suter et al. (2001) the administration of fenbendazole was made as medicated pellets. However, no data regarding the comparability of the PK profile when administered as oral suspension vs. administration with food was provided. A question was raised prior to withdrawal of the application.

Ultimately, the applicant was required to ensure that all relevant information on pharmacokinetics (absorption, distribution and elimination) presented in the dossier, was included in section 4.3 of the SPC. A question to that effect was also raised.

## Development of resistance and related risks in animals

It was noted that there are almost no reports on fenbendazole resistance in protozoal and nematodal parasites of exotic species, including in the target species. Benzimidazole/fenbendazole resistance is known to occur in specific nematodal parasites of sheep, cattle and horses.

The mechanism of resistance appears to be characterised by a loss of high affinity BZ-parasite tubulin interactions and an increase in lower affinity interactions, as reported by Lacey and Gill (1994)[10].

Currently, four genotypes of *E. cuniculi* have been determined according to the number of 5'-GTTT-3' repeats in the ribosomal internal transcribed spacer (ITS) region of the rDNA gene; "rabbit" genotype I with three repeats, "mouse" genotype II with two repeats, "dog" genotype III with four repeats and "human" genotype IV with five repeats (Didier et al., (1995), Talabani et al., (2010) and Xiao et al., (2001) in Kotkova et al., (2017)[11]).

Kotkova et al. (2017) studied the course of infection caused by *Encephalitozoon cuniculi* genotype

[8] Xinle, Z., Shuhuai, W., Liu, Q., Qian, X., Congmin, Z., Shixin, X., Xia, W., Dan, L., Haiyan, H. (2011). Simultaneous Determination of Benzimidazoles and Their Metabolites in Plasma Using High-Performance Liquid Chromatography/Tandem Mass Spectrometry: Application to Pharmacokinetic Studies in Rabbit. Journal of AOAC INTERNATIONAL, 94(3), 839–846. https://doi.org/10.1093/jaoac/94.3.839

[9] Short, C. R., Barker, S. A., Hsieh, L. C., Su-Pin, O. U., McDowel, T. (1988). Disposition of fenbendazole in the rabbit. Research in Veterinary Science, 44(2), 215-219. https://doi.org/10.1016/S0034-5288(18)30842-7.

[10] Lacey, E., & Gill, J. H. (1994). Biochemistry of benzimidazole resistance. Acta tropica, 56(2-3), 245–262. https://doi.org/10.1016/0001-706x(94)90066-3

[11] Kotková, M., Sak, B., Hlásková, L., & Kváč, M. (2017). The course of infection caused by Encephalitozoon cuniculi genotype III in immunocompetent and immunodeficient mice. Experimental parasitology, 182, 16–21. https://doi.org/10.1016/j.exppara.2017.09.022

III in immunocompetent and immunodeficient mice. They demonstrated that there are also some albendazole resistance variations in different genotypes of Encephalitozoon and that response to treatment depends not only on the immunological status of the host, but also on the genotype of microsporidia.

The results of this study demonstrated that although the infection caused by *E. cuniculi* III had a much more progressive course than infection caused by *E. cuniculi* II, these mice survived significantly longer, implying that the survival of mice does not correspond to spore burden but more likely depends on the strain of microsporidia, although it was noted that rabbits were treated with albendazole.

Sak et al. (2020)[12] determined the effect of a 100X recommended daily dose of albendazole on an *Encephalitozoon cuniculi* genotype III course of infection in immunocompetent and immunodeficient mice and compared the results with those from experiments performed with a lower dose of albendazole and *E. cuniculi* genotype II. The administration of the regular dose of albendazole during the acute phase of infection reduced the number of affected organs in all strains of mice and absolute counts of spores in screened organs. However, the effect on genotype III was minor. Noteworthy, no substantial effect was recorded after the use of a 100X dose of albendazole, with larger reductions seen only in the number of affected organs and absolute counts of spores in all strains of mice, implying variations in albendazole resistance between these *Encephalitozoon cuniculi* genotypes. Although the active substance is different, these results could impact on the proposed regimen of dose and the applicant was questioned about this prior to its withdrawal of the application.

Based on the data available, the applicant proposed risk mitigation measures in sections 3.4 and 3.5 of the SPC. At the time of withdrawal of the application, the CVMP generally agreed with the proposed warnings. However, it was noted that some of the wording could promote the prophylactic use of the product and should therefore be deleted. In addition, further warnings were proposed by the CVMP in accordance with the Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/383441/2005-Rev.1 Corr.1).

## Dose determination and confirmation

### *Dose justification*

No specific dose determination studies were performed.

The proposed dose of 20 mg/kg bw for 28 days for Cunitraxx was established based on studies described in the target species in published literature. The dose selected was like the dose tested by Suter et al. (2001), which was studied for prevention of infection and treatment of infected rabbits. (Please also refer to the clinical trial(s) section).

The applicant provided some bibliographical references to support the selection of this dosage. It was noted that three of these papers (Kunzel and Fisher, (2018)[13]; Keeble (2021)[14]; Dobosi et al.,

[12] Sak, Bohumil & Brdickova, Klara & Holubová, Nikola & Květoňová, Dana & Hlásková, Lenka & Kváč, Martin. (2020). Encephalitozoon cuniculi Genotype III Evinces a Resistance to Albendazole Treatment in both Immunodeficient and Immunocompetent Mice. Antimicrobial agents and chemotherapy. 64. 10.1128/AAC.00058-20.
[13] Künzel, F., & Fisher, P. G. (2018). Clinical Signs, Diagnosis, and Treatment of Encephalitozoon cuniculi Infection in Rabbits. The veterinary clinics of North America. Exotic animal practice, 21(1), 69–82. https://doi.org/10.1016/j.cvex.2017.08.002
[14] Keeble, E. (2011). Encephalitozoonosis in rabbits - What we do and don't know. In Practice. 33. 426-435. 10.1136/inp.d6077.

(2022)[15]) were revisions, while another (Graham et al., (2022)[16]) was a master class. In addition, Sieg et al. (2012)[17] provided an overview of the outcome after treatment of 95 rabbits with suspected encephalitozoonosis in a veterinary hospital. Similarly, Harcourt-Brown and Holloway (2003)[18] reviewed the results of a serological test for *Encephalitozoon cuniculi* in 125 pet rabbits, together with follow-up studies of clinical cases.

The proposed dose regimen is also recommended in the ESCCAP guidelines (2017)[19] although it is stated that fenbendazole (FBZ) can assist in reducing the severity of the clinical signs, but elimination of the infection is not possible.

Regarding this point, in the reference Kunzel and Fisher (2018) it is stated that, despite the elimination of spores from the CNS in the study reported by Suter et al. (2001), clinical signs are not always reversible in a certain number of rabbits with neurologic encephalitozoonosis. An explanation for the poor therapeutic clinical response seen in some rabbits with neurologic disorders might be because microsporum associated with the granulomatous inflammatory tissue alterations within the brain remain, despite a successful reduction in the number of infectious spores. To add to the confusion of what determines successful treatment is the fact that *E. cuniculi* infections typically follow a chronic course whereby the manifestation of clinical signs vary and the time from infection until clinical encephalitozoonosis may be months to years and almost always occurs long after initial infection and when only a low number of organisms are present within affected tissues.

On the other hand, other references like Keeble (2021) state that fenbendazole (Lapizole, Genitrix; Panacur, Intervet) 20 mg/kg orally every 24 hours for 28 days, reduces clinical signs in less advanced cases and prevents infection in exposed rabbits. This review confirmed that no clinically trialled treatment protocols have been reported in pet rabbits, and that the publication by Suter et al. (2001) forms the basis for the treatment regimens that are recommended by the author herself.

Other papers, like the publication by Dobosi et al. (2022), also state that most authors use the off-label treatment with fenbendazole orally dosed at 20 mg/kg body weight daily for 28 days, with the success rate in acute or chronic cases of encephalitozoonosis being lower than in prophylactic administration. This review primarily refers to publications in which animals received fenbendazole concomitantly with other treatments, such as antimicrobials.

In summary, although the dose of 20 mg/kg of FBZ is used in most of the public papers submitted, no other justification than the reference Suter et al. (2001) is found to justify this dose. It is noted that this reference has some limitations (see comments on clinical trials(s) section). No other data related to minimum effective dose (in vitro or in vivo) were found.

The same issue was noted with regards to the treatment duration. Regarding this point, in one of the references provided (Hocevar et al., 2014[20]) it is stated: The appropriate duration of therapy required to eradicate infection with *E. cuniculi* not only in immunodeficient host is unknown. The relapse of

[15] Dobosi, A. A., Bel, L. V., Pastiu, A., Pusta, D. (2022). A Review of Encephalitozoon cuniculi in Domestic Rabbits (Oryctolagus cuniculus)—Biology, Clinical Signs, Diagnostic Techniques, Treatment, and Prevention. Pathogens. 11. 1486. 10.3390/pathogens11121486.
[16] Graham, J., Griffin, C., Kanfer, S., Keeble, E., Lennox, A., Ritzman, T., Biswell, E. (2022). Encephalitozoon cuniculi – Biology, Diagnostics, and Treatment – Q&A: Master Class and panel discussion', Association of Exotic Mammal Veterinarians, United States, 28/08/22 - 2/09/22.
[17] Sieg, J., Hein, J., Jass, A., Sauter-Louis, C., Hartmann, K., & Fischer, A. (2012). Clinical evaluation of therapeutic success in rabbits with suspected encephalitozoonosis. Veterinary parasitology, 187(1-2), 328–332. https://doi.org/10.1016/j.vetpar.2011.12.014
[18] Harcourt-Brown, F. M., & Holloway, H. K. (2003). Encephalitozoon cuniculi in pet rabbits. The Veterinary record, 152(14), 427–431. https://doi.org/10.1136/vr.152.14.427
[19] ESCCAP Guideline 07. Control of Parasites and Fungal Infections in Small Pet Mammals. First Edition. July 2017.
[20] Hocevar, S.N., Paddock, C.D., Spak, C.W., Rosenblatt, R., Diaz-Luna, H., Castillo, I., Luna, S., Friedman, G.C., Antony, S., Stoddard, R.A., Tiller, R.V., Peterson, T., Blau, D.M., Sriram, R.R., da Silva, A., de Almeida, M., Benedict, T., Goldsmith, C.S., Zaki, S.R., Visvesvara, G.S., Kuehnert, M.J., Microsporidia Transplant Transmission Investigation Team. (2014). Microsporidiosis acquired through solid organ transplantation: a public health investigation. Ann. Intern Med. 160, 213e220.

infection can be as long as 1 year after termination of albendazole therapy and positive urine samples after more than 5 months of therapy have been described.

Furthermore, Sak et al. (2020) (see also resistance section) questioned the effect of albendazole in controlling encephalitozoonosis based on the introduction of modern diagnostic methods used in combination with experimental infections, indicating reactivation of the infection after treatment termination and spreading within the host body to an extent like that seen before treatment.

Although it is noted that this study was conducted in mice and with another active substance (albendazole), these issues could question the proposed dose regimen.

In summary, the information submitted was not considered sufficient to justify the proposed dose and the applicant was requested about the overall justification provided in support of the proposed dose.

***Dose determination studies***

No dose determination studies were reported.

***Dose confirmation studies***

No dose confirmation studies were reported.

## Tolerance in the target animal species

No specific target animal safety studies were performed with the candidate formulation.

Taking into consideration the Limited Markets (LM) character of this application, and the well-established off-label use of several fenbendazole formulations (also for the proposed indication) in rabbits, the applicant did not consider it feasible nor necessary to conduct a standard 1x, 3x and 5x dose tolerance study for a prolonged period in healthy target animals. Instead, the applicant refers to the well-established use of the drug substance and provided a literature overview of safety and toxicity studies, both recent and old, performed with fenbendazole in the field and in the laboratory setting.

The reference Keller (1991) made reference to the publication of Scholz and Baeder (1973), that provided information about the potential embryotoxicity of fenbendazole in rabbits. This publication was, however, not included in the dossier, and only a short summary of the outcome was available. Therefore, prior to withdrawal of the application, the applicant was requested to provide this publication. From the available data, fenbendazole was administered as a suspension in 2% starch mucilage. According to the results, embryotoxicity was not seen. Fetotoxicity were only observed at the higher dose (63 mg/kg b.w.) although the period of administration was shorter (12 days from day 7 to 19 of gestation) than that proposed for the candidate product. Unless justified, the applicant was requested to include this information in the SPC. Also, it was considered appropriate to strengthen the warning in SPC section 3.7, stating that use of the product was not recommended in such cases.

Additional literature data

Graham et al. (2014)[21] studied benzimidazole toxicosis in rabbits (13 cases over the period 2003 to 2011). Histopathologic records were reviewed from rabbit cases that were diagnosed with suspected

[21] Graham, J. E., Garner, M. M., Reavill, D. R. (2014). Benzimidazole toxicosis in rabbits: 13 cases (2003 to 2011). J Exotic Pet Med, 23(2), 188-195.

benzimidazole toxicosis at 2 specialty pathology services. In all, 13 cases were included in this retrospective study.

Histologically, presumed radiomimetic lesions of benzimidazole toxicosis were noted in 3 cases. An additional 10 cases exhibited lesions suggestive of benzimidazole toxicosis. Common clinical signs observed in the study of rabbits included inappetence, lethargy, haemorrhage, and death. One rabbit with suspected benzimidazole toxicosis survived. Though the publication of Graham et al. (2014) was not provided by the applicant, and a question raised on this matter, it appears that adverse events were already observed when applying the proposed posology, and therefore not merely after 'prolonged use'. As such, it was not understood why these observations were not included as Adverse Events. Therefore, the applicant was requested to confirm that all adverse events observed in literature were included in the PI.

Adverse reactions in terms of crypt necrosis of small intestine or bone marrow hypoplasia/ aplasia have been reported with the use of benzimidazoles in rabbits, and as a result, practitioners should strictly adhere to recommended dosages and treatment intervals when using benzimidazole derivatives and consider monitoring complete blood counts during treatment of *E. cuniculi* (Suter et al., (2001); Graham et al., (2014); Kunzel and Fisher, (2018)]. This information still needed to be translated into the PI at the time of withdrawal of the application.

Cray and Altman (2022)[22] had published an update on the biologic effects of fenbendazole in bone marrow and the immune system.

*Bone marrow*: Myelosuppression is considered to be a side effect of fenbendazole treatment in many species, including birds, reptiles, porcupines, and many other mammals (Villar et al., 2007). Albendazole and fenbendazole are commonly used to treat *Encephalitzoon cuniculi* infection in rabbits. Toxicosis, including lethargy, haemorrhage, and death were reported in 13 cases involving pet rabbits, especially in association with high doses or prolonged administration (Graham et al., 2014). A CBC count conducted early after the start of treatment has been recommended as being helpful in the detection of changes consistent with toxicosis, including anaemia, leukopenia, and thrombocytopenia.

*Immune system*: Several studies report effects on the immune system, including the development of lymphoma in athymic mice, the induction of Th2-mediated autoimmunity, increased antibody production, and alteration of an adjuvant-induced arthritis model (Beattie et al., 1980, Pearson and Taylor, 1975, and Sato et al., 1995, as reviewed by Cray and Altman, 2022).

Nevertheless, limited information could be found regarding rabbits and no information about the doses at which these effects were observed is provided, so it is considered that the applicability of this information to the current application is limited.

In summary, the applicant provided some references related to the toxicology and possible adverse effects of fenbendazole. Overall, considering also references assessed in the clinical section (see below) and that present some limitations, it was difficult to draw firm conclusions. The information provided was considered limited since most of the references don´t provide information about posology or provide information in different target species. The applicant had been required to address these deficiencies.

In addition, based on the bibliographic data provided the applicant has proposed several warnings to be included in the product information in sections 3.5 'Special precautions for use', '3.6 Adverse reactions (frequency and seriousness)', 3.7 'Use during pregnancy, lactation or lay', 3.8 'Interaction

[22] Cray, C., Altman, N. H. (2022). An Update on the Biologic Effects of Fenbendazole. Comparative medicine, 72(4), 215–219. https://doi.org/10.30802/AALAS-CM-22-000006

with other medicinal products and other forms of interaction' and 3.10 'Overdose (symptoms, emergency procedures, antidotes)'. At the time of withdrawal of the application it was acknowledged that these warnings were consistent with the references provided but were considered of limited value in veterinary practice. Therefore, additional warnings were considered necessary in several sections of the product information.

## *Clinical trial(s)*

No proprietary clinical trials were conducted by the applicant with the candidate product. The applicant provided an argumentation and justification based on published scientific literature. The most relevant publications provided by the applicant were the following:

**Suter et al. (2001)**

The efficacy of fenbendazole for preventing an experimental infection of *Encephalitoozon cuniculi* and for eliminating the spores from the central nervous system of naturally infected rabbits was investigated. This peer-reviewed paper is considered pivotal in support of the proposed indication and posology.

a) Prophylactic study:

Eight mixed-breed rabbits obtained from an *Encephalitozoon*-free colony were used in two experiments. Prophylactic doses of fenbendazole were administered daily to 4 rabbits beginning 7 days before they were infected orally with 1 million spores of *E. cuniculi*. The remaining 4 rabbits were left untreated as controls. In the first experiment, 2 rabbits received 10 mg fenbendazole/kg twice daily of an oral suspension of fenbendazole (Panacur 10% suspension; Hoechst Roussel) until 21 days after infection. In the second experiment, the rabbits (n=2) were fed with the medicated pellets (dose of 20 mg fenbendazole/kg/day) until 2 days after infection. All the rabbits were euthanized after 6 months.

The 4 rabbits treated with fenbendazole (either suspension or medicated pellets) remained seronegative until 120 days after infection, and *E. cuniculi* could not be isolated from their brain tissue. In contrast, the 4 untreated rabbits seroconverted between day 23 and 40 and developed high antibody titres. *E. cuniculi* spores were isolated from brain tissue of each of them.

No justification on the dosing scheme administered to the animals was provided in this reference. In addition, no data were provided on the clinical signs of the animals and its evolution during the study. Prior to withdrawal of the application, the applicant had been asked to further discuss the relevance of these data for the justification of the efficacy of the product for the claimed indications, considering that only 2 animals received the oral suspension of fenbendazole and that the dosage schemes described in this publication did not correspond exactly with the one proposed for the candidate product.

b) Therapeutic study:

The effect of fenbendazole on established infection was assessed by comparing the success of attempts to isolate the parasites from the brains of 8 rabbits treated with 5 g medicated pellets daily for 4 weeks and from the brains of 9 untreated rabbits. The rabbits were selected from a clinical study of rabbits with *E. cuniculi*-specific antibody titres above 1:640. It is unclear whether the animals included demonstrated any clinical signs related to the infection upon entry in the study.

Six of the eight treated rabbits died of causes that were considered unrelated to encephalitozoonosis and 2 were euthanized after 4 weeks of treatment because they showed

persistent neurological signs consistent with *E. cuniculi* infection. Four of the nine untreated rabbits showed neurological signs which were attributed to encephalitozoonosis while unrelated clinical pathology was observed in 5 cases.

Attempts to isolate *E. cuniculi* from the brain tissue of the 17 naturally infected rabbits were successful in 7 of the 9 untreated animals but in none of the 8 rabbits treated with fenbendazole.

It is noted that fenbendazole was administered as medicated pellet while the proposed VMP is an oral suspension. No pharmacokinetic data have been provided allowing to compare the PK profile of the drug after administration as an oral suspension or as medicated pellet and the applicant had been asked to further discuss this issue. In addition, there was a lack of information on the initial condition of the study animals and whether the parasite was already present in the rabbits before the treatment. Also, it was not possible to know whether fenbendazole could eliminate the pathogen from other affected tissues different from the brain. Thus, the applicant was asked to justify the relevance of these data to support the efficacy of the candidate product.

In summary, a certain degree of protective effect was demonstrated (although based on a very low number of animals) by measuring antibody levels and the absence of the microorganism in the brain tissue. As a therapeutic treatment, no relevant conclusion could be drawn from this study in support of the efficacy of the candidate product, since fenbendazole was administered in a different pharmaceutical form and with a different administration method. Although the parasite's spores were not detected in the brains of treated animals, the lack of information on the condition of the rabbits prior to the drug administration and the death of several animals due to different diseases (including worsening of neurological signs of encephalitozoonosis) made it difficult to assess the efficacy of the treatment.

**Kunzel et al. (2008)[23]**

The authors tested 184 pet rabbits with suspected encephalitozoonosis in an animal hospital. Rabbits were serologically examined for antibodies against *E. cuniculi*. After examination, 144 clinically affected rabbits were positive compared with 14 positives out of 40 clinically healthy rabbits tested as part of standard health check. Additionally, further diagnostic procedures were performed to rule out differential diagnosis. Neurological symptoms were the most common signs among the positive animals.

All seropositive rabbits with supposed encephalitozoonosis received fenbendazole (Panacur, Intervet) orally in a single daily dose of 20 mg/kg for 4 weeks, corresponding with the proposed dosing scheme. In addition, all animals received concomitant treatments (e.g. antibiotics, corticosteroids, fluid therapy) or surgery, depending on the organs affected.

The course of the disease varied according to the clinical signs: rabbits with ocular signs did not show other symptoms during further clinical examination and all of them survived. Among the animals exhibiting neurological symptoms, 54% recovered, usually within a few days. However, 7 out of 8 rabbits suffering from kidney failure (including rabbits with combined symptoms) died or had to be euthanised.

The study failed to detect *E. cuniculi* DNA by PCR in the cerebrospinal fluid (CSF) or urine, indicating that further investigations were necessary to evaluate elimination rate of spores in naturally infected rabbits for an extended period of time.

Although a clinical recovery of about half of the rabbits with neurological signs was reported, there

[23] Künzel, F., Gruber, A., Tichy, A., Edelhofer, R., Nell, B., Hassan, J., Leschnik, M., Thalhammer, J. G., & Joachim, A. (2008). Clinical symptoms and diagnosis of encephalitozoonosis in pet rabbits. Veterinary parasitology, 151(2-4), 115–124. https://doi.org/10.1016/j.vetpar.2007.11.005

was a lack of information from this published reference, since no efficacy endpoints were defined to perform an appropriate evaluation and only "survival" was reported for the rabbits with ocular affection. It was unknown whether an appropriate follow-up period was established in order to assess the improvement of the animals at a long-term. The effect of the drug on the microorganism was not evaluated. The applicant was asked to further discuss on these issues.

**Sieg et al. (2012)**

A total of 95 pet rabbits with suspected encephalitozoonosis showing neurological signs were treated at a veterinary center. Diagnostic was based on clinical signs, exclusion of other diseases associated with the ear, haematological and biochemical evaluation, CSF puncture and bulla radiographs in some cases, and positive *E. cuniculi* serum antibody titres. Encephalitozoonosis was confirmed if spores were detected in urine by PCR or if characteristic microscopic lesions were detected in postmortem histopathological examination of the brain.

The treatment protocols consisted of oxytetracycline (n=50) or the combination of fenbendazole and oxytetracycline (n=45). In each of these groups, the rabbits were randomly assigned to receive or not additional treatment with dexamethasone. Fenbendazole was administered at a dose of 20 mg/kg orally once a day for 10 days.

Signs of vestibular disease or severity of paresis were graded using a neurological score. Therapeutic success was evaluated using the survival rate (%) on day 10 in all rabbits and the neurological score on day 10 in the surviving rabbits. Individual treatment groups did not significantly differ regarding age, weight, gender and neurological score at day 0.

Among all animals treated with fenbendazole (*i.e.* fenbendazole+oxytetracycline and FDZ+OTC+dexamethasone), a statistically significant improvement of the neurological score was observed at day 10 (p=0.008). The median neurological score of animals treated with fenbendazole decreased from 8.5 at day 0 to 3 at day 10 (reduction of 5.5); in comparison, the score of animals not receiving fenbendazole (*i.e.* oxytetracycline and OTC+dexamethasone) decreased from 8.5 (day 0) to 5 at day 10 (reduction of 3.5). Rabbits treated with fenbendazole were 1.6 times more likely to survive until at least day 10 compared with rabbits without fenbendazole. In addition, a significant effect of fenbendazole was demonstrated on long-term survival.

However, this study had some limitations. Mainly, the use of a novel and not yet validated score for neurological signs and the fact that an untreated control group was not included for comparison (thus, some rabbits may have also improved with supportive care only). In addition, only part of the sample selection was conducted in a prospective and blinded manner. It was also noted that the treatment duration was 10 days instead of the 28 days as proposed for the candidate product. The short duration of the study may be insufficient to appropriately assess the long-term effects of the treatment. Thus, despite the apparent positive effect of fenbendazole on the reduction of neurological signs after 10 days, the relevance of these data to support the efficacy claims of the proposed product were questioned.

**Abu-Akkada and Oda (2016)[24]**

This study was conducted to evaluate the efficacy of oral administration of fenbendazole at a dose of 20 mg/kg bw prior to and after experimental infection of immunosuppressed rabbits with *Encephalitozoon cuniculi*. The animals were immunosuppressed by intramuscular injection of dexamethasone.

[24] Abu-Akkada, S. S., & Oda, S. S. (2016). Prevention and treatment of Encephalitozoon cuniculi infection in immunosuppressed rabbits with fenbendazole. Iranian journal of veterinary research, 17(2), 98–105.

Thirty rabbits were included in the study, and divided into the following groups:

- NN group (non-immunosuppressed, non-infected).
- IN group (immunosuppressed, non-infected)
- IPI group (immunosuppressed, protected-infected)
- ITI group (immunosuppressed, treated-infected)
- II group (immunosuppressed, infected)

Fenbendazole was administered as a prophylactic agent to the IPI group for 7 days before challenge with *E. cuniculi* spores. In the ITI group, fenbendazole was administered as a therapeutic treatment daily for 4 weeks beginning on day 28 post-challenge (PC), when infection was confirmed by serology and detection of *E. cuniculi* spores in urine of infected rabbits. The study ended 8 weeks PC and then all rabbits were slaughtered. The parameters evaluated were body weight, detection of *E. cuniculi* spores in the urine, serum antibody assay, and haematological, biochemical and histopathological changes.

No clinical signs or mortality were recorded in any of the experimental animals during the study. *E. cuniculi* infection significantly reduced the final body weight of all infected animals compared to the NN group. However, the IPI group showed significantly better final weight than the ITI group. *E. cuniculi* spores were detected in urine of all infected rabbits from day 28 PC until the end of the study. High levels of specific antibodies to *E. cuniculi* were detected in sera of infected rabbits from the 21$^{st}$ day PC until the end of the study, suggesting intense spore multiplication.

Regarding haematological and biochemical results, the levels of blood lymphocytes in all the immunosuppressed rabbits significantly decreased compared with the NN group. *E. cuniculi* infection significantly enhanced serum ALT enzyme activity compared with non-infected groups while levels of AST enzyme were improved in the IPI and ITI groups compared with II group. Serum creatinine level was significantly elevated only in the II group.

On the other hand, several histopathological findings were observed in tissue specimens of organs collected from animals in the infected groups. The classic findings in rabbits were observed: chronic interstitial nephritis and granulomatous meningoencephalitis. The severity of the lesions in liver, lungs, kidneys and brain was overall higher in the II group and to a lesser extent in the ITI rabbits. A noticeable improvement was found in the IPI rabbits (e.g., less severe pulmonary and renal lesions, no significant cerebral lesions).

It can be concluded that oral administration of fenbendazole at the proposed dose given 7 days prior to an experimental infection was effective to some extent in the protection of rabbits against *E. cuniculi* infection's lesions, while when administered as a therapeutic no significant effects were observed. However, it is noted that this study was conducted in immunosuppressed rabbits and the prophylactic treatment was administered only for 7 days. In addition, this study did not evaluate clinical condition of the animals since the short time between infection and treatment (28 days) did not allow the development of clinical signs. Thus, the relevance of these data to support the efficacy claim of the product was questioned.

The applicant also cited some scientific publications as **supportive data** to document the efficacy of the product at the proposed dose.

**Meredith and Richardson (2015)[25]** stated that the microsporidium *E. cuniculi* is widespread in domestic rabbits. The diagnosis of the infection is challenging since the microorganism is difficult to isolate. A positive serological result may not be conclusive. The presumptive diagnosis involves

[25] Meredith, A. L., Richardson, J. (2015). Neurological Diseases of Rabbits and Rodents. Journal of Exotic Pet Medicine, 24(1), 21-33. https://doi.org/10.1053/j.jepm.2014.12.007.

elevated antibody levels together with relevant clinical signs. However, clinical signs are unspecific and not always present. Identification of spores in the tissues or detection in urine or CSF is not always reliable since excretion is sporadic and samples may be negative in clinically affected animals.

The objective of treatment is to reduce inflammation and prevent formation of spores. Chronic infections usually present neurological signs and when cell damage is severe treatment may not be successful. Current dosing regimens with fenbendazole in rabbits are based mainly on a single scientific study (Suter, 2001) in which a 28-day course of oral administration at 20 mg/kg once a day was recommended. This treatment is usually combined with other therapies (antibiotics, glucocorticoids, etc.). Response to treatment varies, with successful treatment depending on whether the infection is acute or chronic. Other drugs (*e.g.*, fumagillin, sparfloxacin, polyoxin D, nikkomycin Z) have been shown to have efficacy against *E. cuniculi in vitro*, but there is no information on clinical use of these agents in rabbits.

**Keeble (2011)**[26] highlighted the same issues that hamper a precise diagnosis of encephalitozoonosis and the importance of a complete neurological evaluation, although clinical signs are not always present. The recommended treatment is oral fenbendazole at 20 mg/kg/day for 28 days, together with broad-spectrum antibiotics and other therapies, such as dexamethasone and/or sedation. Once neurological signs have developed it is unlikely that these will resolve completely. Prevention of infection is difficult as the parasite is widespread in pet rabbits. Establishment of *E. cuniculi*-free breeding colonies could be an objective, but it is time-consuming and expensive. The author recommends applying a prophylactic treatment with a 28-day course of fenbendazole of all new rabbits recently acquired by owners and presented to the veterinary clinic where the animals may have been previously exposed to the parasite by contact with other rabbits at the source. This will prevent new infection and treat any infection that may have been acquired. However, it should be taken into account that this treatment will not prevent infection at a later date.

## *Overall conclusions on efficacy*

*Pharmacology*

*Pharmacodynamics*

Fenbendazole is an antiparasitic substance intended for the treatment and control of *Encephalitozoon cuniculi* in rabbits. Although not completely known, the mode of action has been sufficiently described. Fenbendazole inhibits the polymerisation of tubulin to microtubules. This interferes with essential structural and functional properties of cells.

*Pharmacokinetics*

Several limitations were identified regarding the pharmacokinetic profile of the active substance in rabbits. No information about the proposed formulation was provided neither of the proposed dosage regimen. In addition, none of the references submitted provided information about when fenbendazole crosses the blood-brain barrier or reaches the eye. This issue could impact the expected efficacy of the product since clinical encephalitozoonosis is likely to result in neurological and/or ocular symptoms. In addition, no information was provided at repeated doses. Furthermore, the role of the caecum as a reservoir was not discussed. All these deficiencies were requested to be discussed further.

[26] Keeble, E. (2011). Encephalitozoonosis in rabbits –what we do and don't know. In Pract, 33, 426-435.

*Development of resistance and related risks to animals*

The references submitted provided information about the mechanism of resistance and the different genotypes of *E. cuniculi* and its impact on the efficacy of fenbendazole. In addition, the applicant proposed different warnings in the product information to inform about the prudent use of the product. Nevertheless, some changes in the product information needed to be considered, specially based on the use of the product as an antimicrobial. In line with the antimicrobial GL, available and relevant information, such as 'Resistance appears to be characterized by a loss of high affinity BZ-parasite tubulin interactions and a corresponding increase in lower affinity interactions', needed to be included in Section 4.2.

*Dose determination and confirmation*

The dose of 20 mg/kg of fenbendazole is used in most of the publicly available scientific references submitted but no other justification than the reference to the publication by Suter (2001) was found, neither was other data related to the minimum effective dose (in vitro or in vivo) found. The same issue was noted in relation to the treatment duration. A treatment duration of 28 days was usually found in the references submitted however, no explanation for this time was found.

In addition, the effect of albendazole in controlling encephalitozoonosis was questioned based on introduction of modern diagnostic methods used in combination with experimental infections, indicating reactivation of the infection after treatment termination and spreading within host body to an extent like that seen before treatment. These issues could question the proposed dose regimen.

All of the above was raised prior to withdrawal of the application.

*Tolerance in the target animal species*

The information submitted were mainly related to the toxicology and possible adverse effects of fenbendazole. Nevertheless, this information was considered limited since most of the references did not provide information about posology nor provided information in different target species.

Although it was acknowledged that the applicant included different warnings on the product information consistent with the references provided, these were considered incomplete and of limited value for the veterinary practitioner.

*Clinical trials*

The applicant did not perform clinical studies with the candidate product, and the clinical part of the dossier was supported with bibliographic documentation. However, only a few of these publications provided were considered to be relevant, in some way, for the assessment, due to different limitations of the data.

From the provided published scientific references, a certain degree of protective effect of fenbendazole could be expected when administered prior to an (induced) *E. cuniculi* infection. This protection was measured in terms of absence of *E. cuniculi*-specific antibodies and absence of isolation of the pathogen from the brain tissue, as well as prevention of severe haematological, biochemical and histopathological lesions. However, references provided showed limitations that made it difficult to form a robust interpretation of the results.

Efficacy of fenbendazole as a treatment when the disease had already been diagnosed was evaluated in different published scientific references. From these, it could be deduced a certain positive effect of fenbendazole in some cases of clinical disease, especially with (non-severe) neurological symptoms, for the reduction of severity of the signs, but only at a short-term. Nevertheless, the provided data had several limitations and lacked relevant information and thus

the reliability of the results was questioned.

Overall, the provided published scientific references did not fully allow to draw robust conclusions on the efficacy of the candidate product for the claimed indication at the proposed dosing scheme. Neither the prophylactic effect nor the therapeutic efficacy could be considered to have been demonstrated in a reliable way according to the current requirements, especially if it is considered that fenbendazole will be used as an antimicrobial substance.

Taking into account what is stated in the above-mentioned guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 guideline, the omission of comprehensive clinical documentation, including confirmatory clinical trial, could be accepted when, based on the information provided in the pre-clinical part, it is reasonable to conclude that the product is safe for the target population when administered at the recommended treatment dose, and it is expected to be effective for the proposed indication at the proposed dose. That does not seem to be the case, since major concerns were raised in the preclinical part of the report. Thus, the applicant should justify the absence of pivotal clinical data obtained with the candidate product, taking into account that no dose determination/confirmation studies or target animal safety studies were conducted and consequently, neither the pre-clinical nor the clinical documentation allowed to adequately document the safety and efficacy of the product at the proposed dose for the claimed indication.

All the above-mentioned bring into question what the most relevant therapeutical application of this product under real field conditions could be and whether a reasonable expectation of effectiveness could be assumed for the claimed indications. The applicant was asked to further justify the claimed indication (i.e. treatment and control of protozoan parasites in rabbits infected with *E. cuniculi*) since the term 'control' was not well defined and did not seem to be appropriate, and how the provided published scientific references could reliably support the efficacy for the intended use of the product at the proposed dosing scheme. Also, the applicant was requested to make clear what group of patients would be expected to benefit from the treatment.

# Part 5 – Benefit-risk assessment

## *Introduction*

Cunitraxx was an oral suspension containing the active substance fenbendazole. The active substance is well-known.

Fenbendazole is an antiparasitic belonging to the benzimidazole-carbamate group, which inhibits the polymerisation of tubulin to microtubules. This interferes with essential structural and functional properties of cells.

The product was intended for use in rabbits (non-food producing) for the treatment and control of protozoan parasites in rabbits infected with *Encephalitozoon cuniculi*. However, at the time of the application, rabbits were considered a food producing species, as Regulation (EU) 2019/6 was not considered to include a basis to treat them otherwise. Consequently, the restriction to non-food producing rabbits was not accepted and the applicant was requested to adjust the application to take this into account. The proposed dose of 20 mg fenbendazole per kg body weight per day, with the product to be administered orally for 28 consecutive days remained to be confirmed.

The application was submitted under Article 23 of Regulation 2019/6 - limited market. Reduced data requirements therefore apply and were considered in the assessment. These reductions relate to efficacy data.

## *Benefit assessment*

## Direct benefit

The proposed benefit of Cunitraxx was its efficacy in the treatment and control of protozoan parasites in rabbits infected with *Encephalitozoon cuniculi*, which was based solely on bibliographic data.

However, at the time of withdrawal of the application concerns remained about the correct dose/tolerance/efficacy, which precluded CVMP from drawing firm conclusions. Though fully acknowledging the clinical relevance and the severity of clinical encephalitozoonosis and acknowledging the fact that this was an Article 23 marketing authorisations application, the benefit of the product in the treatment of clinical encephalitozoonosis was strongly questioned.

## Additional benefits

*Quality*

A number of other concerns were raised in relation to the quality part of the dossier. No final conclusion could be drawn on the quality of the product as those issues remained to be satisfactorily addressed.

*Risks for the target animal*

Major concerns were raised in relation to the safety part of the dossier. No final conclusion could be drawn either on target animal safety until those issues were satisfactorily addressed.

*Risk for the user*

The most severe risk was deemed to be accidental ingestion by a child. Appropriate warnings needed to be included in the SPC. Moreover, the applicant was requested to confirm that the "resistant cap" was child-resistant, otherwise additional risk mitigation measure(s) needed to be implemented.

Hypersensitivity reactions, as well as adverse local effects, both due to the active substance and some excipients needed to also be taken into account in the product information.

A number of concerns were raised. No final conclusion could be drawn on user safety until those issues were satisfactorily addressed.

*Risk for the environment*

Cunitraxx was not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal was included in the SPC and PL.

*Resistance*

Lack of efficacy of fenbendazole in the treatment and control of encephalitozoon in rabbits (non-food producing) infected with *Encephalitozoon cuniculi* were reported for genotype 3. Concerns were raised relating to the potential for resistance to the proposed dosage.

## *Risk management or mitigation measures*

Risk management or mitigation measures needed to be considered pending additional information from the applicant.

*User safety*

User safety risks were identified, mainly the risks associated with exposure in children. Moreover, the applicant needed to confirm that the "resistant cap" was child-resistant, otherwise additional risk mitigation measure(s) needed to be implemented.

Also, hypersensitivity reactions, as well as adverse local effects, both due to the active substance and some excipients needed to also be taken into account in the product information

A number of concerns were raised and no final conclusion could be drawn on user safety.

The warnings proposed by the applicant to be included in the SPC were not fully in line with the risks identified. Therefore, the applicant had been requested to review the proposed mitigation measures.

*Environmental safety*

As the product was intended to be used in non-food producing animals no unacceptable risk for the environment was identified.

*Resistance*

Prudent use advice as recommended in the revised CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005) needed to be included, as appropriate, as well as any specific risk management recommendations for the antimicrobial product under consideration.

## *Evaluation of the benefit-risk balance*

At the time of submission, the applicant applied for the following indication: Treatment and control of protozoan parasites in rabbits infected with *Encephalitozoon cuniculi*.

In the presence of major and other concerns, no conclusions could be taken on the benefit-risk balance of the application.

## *Conclusion*

Based on the original data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) considered that the application for Cunitraxx was not approvable since "major objections" had been identified which precluded a recommendation for marketing authorisation. At the time of withdrawal of the application no conclusions could be taken on the benefit-risk balance of the application.