College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Meranox 25 mg/ml Oral Suspension for Pigeons

Date Created: May 2017
Updated October 2021

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0299/001/DC
Name, strength and pharmaceutical form	Meranox 25 mg/ml Oral Suspension for Pigeons
Applicant	Avimedical B.V., Abbinkdijk 1, LX Hengelo (Gld), 7255, The Netherlands
Active substance(s)	Fenbendazole
ATC Vetcode	QP52AC13
Target species	Pigeons
Indication for use	Treatment of the following gastro-intestinal nematodes in pigeons: - Ascaridia spp. (adult stages) - Capillaria spp. (adult stages)

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	A full application in accordance with Article 13 (a) of Directive 2001/82/EC as amended.
Date of conclusion of the decentralised procedure	29/03/2017
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	Belgium, Germany, Luxembourg, The Netherlands.

I. SCIENTIFIC OVERVIEW

This application was submitted in accordance with Article 13 (a) 'well-established veterinary use' of Directive 2001/82/EC as amended. Meranox 25 mg/ml Oral Suspension for Pigeons contains fenbendazole a well-known active substance authorised in the UK since 1993.

The product contains 25 mg/ml fenbendazole to be administered at a dose rate of 25 mg/kg body weight per day (0.1 ml/100 g bodyweight). This dose should be administered twice at a time interval of 14 days.

The product is indicated for the treatment of the following gastro-intestinal nematodes in pigeons:

- *Ascaridia* spp. (adult stages)
- *Capillaria* spp. (adult stages)

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released onto the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains 25 mg/ml fenbendazole and the excipients benzyl alcohol (E1519), azorubine 85% (E122), aluminium magnesium silicate, xanthan gum, propylene glycol, simethicone, sorbitan oleate, polysorbate 80 and purified water.

The container/closure system consists of Type III amber glass bottles of 10 ml, 30 ml and 50 ml closed with tamper-evident HDPE screw caps with ring and colourless LDPE syringe insert. The particulars of the containers and controls performed are provided and conform to the regulation. A 1 ml dosing syringe is supplied with each 10 mlbottle, a 1 ml and a 5 ml dosing syringe are supplied with each 30 ml or 50 ml bottle. Cardboard box containing 10 separate boxes, each containing 1 bottle.
Pack sizes:
1 x 10 ml, 10 x 10 ml.
1 x 30 ml, 10 x 30 ml
1 x 50 ml, 10 x 50 ml.
Not all pack sizes may be marketed.

The choice of the formulation and the presence of preservative are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of the preparation and combination of a number of solutions.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is fenbendazole, an established active substance described in the European Pharmacopoeia and is sourced in accordance with a certificate of suitability. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

The excipients benzyl alcohol, aluminium magnesium silicate, xanthan gum 80 mesh, propylene glycol, simethicone, sorbitan oleate, polysorbate 80 and purified water are described in a pharmacopoeia.

The specification of the excipient azorubine/carmoisine 85% complies with the requirements of Regulation 1333/2008/EC as amended in the requirements of Regulation 1333/2008/EC as amended.

II.C.4. Substances of Biological Origin

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

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

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification. Control tests on the finished product include those for appearance, homogeneity, density, pH, viscosity, particle size, microbial purity and the identification and assay of fenbendazole.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions. Batches were stored under VICH[3] conditions of 25ºC/60%RH and 40ºC/75% RH for a variety of time periods, and the results are reflected in the established shelf-life data information and storage precautions provided in the SPC.

The claim of 28 day stability after opening is based on the demonstration of stability for a batch broached and stored at 25°C/60%RH

G. Other Information

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

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf life after first opening the immediate packaging: 28 days.

Keep the bottle tightly closed.

Keep the bottle in the outer carton in order to protect from light.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

The application is submitted in accordance with 13 (a) of Directive 2001/82/EC as amended. Bibliographic references have been submitted in support of the pharmacological and toxicological data for Part III. A user risk assessment (URA) and environmental risk assessment (ERA) were been written and submitted in accordance with current guidelines.

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that fenbendazole acts by interfering with the energy metabolism of the nematode.

Fenbendazole inhibits the polymerisation of tubulin to microtubules. This interferes with essential structural and functional properties of the cells of helminths, such as formation of the cytoskeleton, formation of the mitotic spindle and the uptake and intracellular transport of nutrients and metabolic products. Fenbendazole is effective and has a dose dependent effect on adult stages.

The applicant has also provided bibliographical data which show that after oral administration fenbendazole is only partially absorbed. Following absorption, fenbendazole is rapidly metabolised in the liver mainly to its sulphoxide (oxfendazole) and further to its sulphone (oxfendazole sulphone). Fenbendazole and its metabolites are distributed throughout the body, reaching highest concentrations in the liver. The elimination of fenbendazole and its metabolites occurs primarily via the faeces.

Toxicological Studies

The applicant has provided bibliographical data which show that no adverse reactions have been detected when the product is administered at the recommended dose. The safety of the veterinary medicinal product has not been established during lay.

- Single Dose Toxicity

Fenbendazole was shown to be of low acute toxicity. Oral LD_{50} values in laboratory rats and mice were greater than 10 000 mg/kg.

- Repeated Dose Toxicity

Results indicated that no treatment related effects were observed in a repeated-dose toxicity study in rats at doses of up to 2500 mg/kg bw/day for 30 days. In a 90 day study, daily doses up to 1600 mg/kg bw/day were increased to 2500 mg/kg from over the duration of the study. Tremors were observed in some rats, there were no other treatment-related effects.

- Reproductive Toxicity, including Teratogenicity:

In a 3-generation study rat study, doses of over 45 mg/kg fenbendazole resulted in diarrhoea, reduced bodyweight gain and pathological changes in the liver in the parent animals. At the same doses, reductions in fertility, survival and growth of the neonates during lactation were also seen. The NOEL[4] for maternal and reproductive toxicity was 15 mg/kg bw/day.

In a teratogenicity study in rats, mated females were given daily oral fenbendazole at various doses during gestation. There was no evidence of maternal toxicity, foetotoxicity or teratogenicity at any dose level.

In mated rabbits dosed with fenbendazole, an increase in delayed ossification was observed in one group. The NOEL was calculated at 25 mg/kg bw/day, the next lowest dose.

Additional data included showed there were no treatment related effects in the offspring of dogs, pigs, sheep and cattle when administered fenbendazole at various times during gestation. In addition, fenbendazole had no effect in testicular function tests in sheep and horses.

- Mutagenicity:

Mutagenicity data available for fenbendazole indicate that it is not genotoxic. Febantel and oxfendazole also show no clear evidence of genotoxicity.

- Carcinogenicity:

No treatment related effects were observed in mice treated with fenbendazole for 2 years. In rats high doses of fenbendazole, including in-utero, resulted in effects on survival and bodyweight gain. 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.

Observations in Humans

Fenbendazole is not authorised for use in human treatment, however in a case where healthy male subjects were given oral doses of fenbendazole, with and

[4] No observed effect limit

without food, no relevant changes in blood clinical chemistry parameters were seen.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that there are potential exposure risks during administration of the product.

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

- This product may be toxic to humans after ingestion.
- This product may cause hypersensitivity (allergy) reactions.
- People with known hypersensitivity to fenbendazole should avoid contact with the veterinary medicinal product.
- Avoid contact with skin, eyes and mucous membranes.
- In case or skin and/or eye contact, immediately rinse with plenty or clean water.
- Due to the risk or accidental ingestion, never leave a loaded syringe unattended.
- In case or accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- Wash hands after use.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP[5] guidelines.

Phase I:

The assessment concluded at question 3 of the VICH decision tree. The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

The disposal advice in the SPC is: 'Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements'. As the product is not an ectoparasiticide, no environmental warnings or risk mitigation measures are provided on the SPC.

[5] The Committee for Medicinal Products for Veterinary Use

IV CLINICAL DOCUMENTATION

The application is submitted in accordance with 13 (a) of Directive 2001/82/EC as amended. Bibliographic references have been submitted in support of the pharmacological and toxicological data for Part IV.

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided bibliographical data information describing the pharmacodynamic and pharmacokinetic properties of the active substance.

Pharmacodynamic properties

Fenbendazole is an anthelmintic belonging to the benzimidazole-carbamate group. It acts by interfering with the energy metabolism of the nematode.
Fenbendazole inhibits the polymerisation of tubulin to microtubules. This interferes with essential structural and functional properties of the cells of helminths, such as formation of the cytoskeleton, formation of the mitotic spindle and the uptake and intracellular transport of nutrients and metabolic products. Fenbendazole is effective and has a dose dependent effect on adult stages.

Pharmacokinetic particulars

After oral administration fenbendazole is only partially absorbed. Following absorption, fenbendazole is rapidly metabolised in the liver mainly to its sulphoxide (oxfendazole) and further to its sulphone (oxfendazole sulphone).
Fenbendazole and its metabolites are distributed throughout the body, reaching highest concentrations in the liver. The elimination of fenbendazole and its metabolites occurs primarily via the faeces.

Tolerance in the Target Species

A target animal safety study and bibliographical data were provided which show that the proposed dose of 25 mg/kg bw/day is well tolerated in pigeons.

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

Resistance

The information provided suggests that there is currently no resistance reported to benzimidazoles in the parasites of the target species listed for the proposed product. However, resistance in other species (mainly ruminants) is well documented as are potential resistance mechanisms. Clearly, use of the proposed product has the potential to result in resistance in the targeted parasites through similar mechanisms. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has conducted dose determination and confirmation studies which show that a dose of 25 mg/kg/day is effective in the target species.

Dose confirmation study:

Study title	A dose determination/confirmation study in pigeons with a fenbendazole containing suspension, administered orally at 2 dosages
Objectives	To evaluate the efficacy against *Capillaria* and safety of a fenbendazole containing suspension administered orally two times at a time interval of 14 days.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Meranox 25 mg/ml at a dose rate of 25 mg/kg or 50 mg/kg.
Control product/placebo	Placebo.
Animals	20 male and female pigeons with bodyweights ranging from 300 – 550g. Inclusion criteria: Infection with *Capillaria* spp. as determined by identification of eggs in the faeces. An additional pre-existing *Ascaridia* spp. infection was allowed. Exclusion criteria: Any clinical condition or medication administered to the animal that might adversely interfere with the purpose or conduct of the study.
Outcomes/endpoints	Efficacy of the Test Item was evaluated on the basis of the number of adult worms in the intestines.
Randomisation	Randomised
Blinding	Blinded
Method	General health was monitored daily. Outcomes were measured by blood sampling, faecal sampling and necropsy.
Statistical method	Safety of the product was based on measured parameters was based on differences between control and treatment groups and development of these parameters during treatment. Statistical comparisons were based on ANOVA and/or normal or paired student t-tests. Where appropriate, clinical findings, macroscopic and microscopic findings were compared using Fisher's exact test.
RESULTS	
Outcomes for	Results of the post-mortem worm counts suggest that

endpoints	the product is highly efficacious, since all birds administered the test product had counts of zero worms.
DISCUSSION	The applicant has provided evidence to support *Capillaria* spp. as the dose-limiting parasites in pigeons and therefore efficacy against *Ascaridia* spp. can be extrapolated. It can be concluded that Meranox 25 mg/ml, when administered according to the proposed dosing regimens, is sufficiently efficacious against both *Capillaria* and *Ascaridia* spp.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics the benefit/risk profile of the product is favourable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Heads of Veterinary Medicines Agencies website (www.HMA.eu).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

Summary of change **(Application number)**	**Approval date**
C.I.9.a.Change in the QPPV and/or QPPV contact details and/or back up procedure C.I.9.d.Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH (NL/V/0299/001/IA/001/G)	22 November 2019
RMS change from UK to NL	28 November 2018