United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Ridaworm Wormer Granules 888 mg for Adult Dogs (Fenbendazole)

Date Created: January 2017

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Ridaworm Wormer Granules 888 mg for Adult Dogs (Fenbendazole)
Applicant	C&H Generics Ltd. c/o Michael McEvoy and Co. Seville House New Dock Street Galway Ireland
Active substance	Fenbendazole
ATC Vetcode	QP52AC13
Target species	Dogs
Indication for use	For the treatment of immature and mature stages of *Toxocara canis* and *Taenia hydatigena*

MODULE 2

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

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	A generic hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	2 December 2016

I. SCIENTIFIC OVERVIEW

This was a generic hybrid application submitted in accordance with Article 13(3) of Directive 2001/82/EC. The reference product was Panacur Granules 22.2% w/w which has been marketed in the UK since 1998.

A combination of proprietary studies and bibliographical data were provided to show that the product is essentially similar to the reference product.

The indications are for the treatment of immature and mature stages of *Toxacara canis* and *Taenia hydatigena.*

The product is administered orally, sprinkled on food. For the routine treatment of adult dogs a dosage of 100 mg/kg is recommended. This equates to approximately 1 whole sachet per 8 kg bodyweight. The sachet cannot be divided or stored for future use.

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species, any reactions observed are indicated in the SPC.[1] The product is safe for the user 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 CONSTITUENTS

II.A. Composition

The product contains the active fenbendazole 888.8 mg and excipients lactose monohydrate, povidone K30 and sodium lauryl sulphate.

The container system consists of paper foil sachets. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of formulation and the absence of preservatives are justified.

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

II.B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The manufacturing method consists of standard procedures for the manufacture of granules.

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 substance described in the European Pharmacopoeia. 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 are monographed in the European Pharmacopoeia. Acceptable Certificates of Analysis were provided.
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.

II.C.4. Substances of Biological Origin

Certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Control tests on the finished product include: appearance, identification and assay of fenbendazole, sieve analysis, uniformity of dosage, moisture content and microbial purity.

II.F. Stability

Stability data on the active substances 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 25°C/60% RH and 40°C/75% RH for a variety of time periods, and the results are reflected in the established shelf-life data information provided in the SPC.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Store in a dry place.
Add to feed immediately before administration. Discard any remaining medicated feed.

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

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

This is a generic hybrid application according to Article 13 (3). Bioequivalence with the reference product could not been demonstrated therefore a user risk assessment was required.

The pharmacokinetic aspects of this product are similar to the reference product.

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

III.A Safety Documentation

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that:

- The product can cause irritation to the skin, eyes and lungs.
- Direct contact with the skin should be kept to a minimum.

Therefore the user warnings in the SPC are appropriate:

- Avoid inhalation of granule dust.
- Wash hands after use.
- Avoid contact with the eyes. In case of accidental eye contact, irrigate the eyes with plenty of clean water. If irritation persists, seek medical advice.

The data provided only supports the use of whole sachets for specific animal bodyweights; therefore the product is not suitable for use in cats.

Environmental Safety

A phase I ERA was carried out in accordance with the VICH guidelines.

The disposal advice provided in the SPC is adequate and the products are not expected to pose a risk for the environment when used as recommended.

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.

IV CLINICAL DOCUMENTATION

The applicant has conducted studies and provided bibliographical data to show that the product is essentially similar to the reference product.

IV.I. Pre-Clinical Studies

Pharmacology

The applicant has provided literature to demonstrate the pharmacodynamic properties of fenbendazole in dogs and cats. The user safety data provided only supports the use of whole sachets for specific animal bodyweights; therefore it was decided that as this product is only available in a 4 g sachet it is not suitable for use in cats, who would typically need less than a whole sachet per animal.

Fenbendazole is a member of the benzimidazole family of anthelmintics and has been in veterinary use for a number of years. It acts against parasites by disrupting the formation of microtubules by binding to tubulin in the parasites intestinal cells hence preventing the absorption of glucose, and as a result the parasites are gradually starved to death. Fenbendazole displays preference for parasitic as opposed to mammalian tubulin; this appears to be due to the fact that the formation of the parasitic tubulin-fenbendazole complex is more favourable kinetically under physiological conditions than the mammalian complex.

Studies were conducted to assess pharmacokinetic parameters in dogs and cats administered either the investigational product or an authorised reference product containing the same active substance. Results suggested similarity; however, bioequivalence was not investigated in accordance with current CVMP guidance.

Fenbendazole is only partly absorbed from the intestine and reaches maximum plasma concentration in dogs 4 - 9 hours after oral administration. Its metabolites are distributed throughout the body but highest concentrations are found in the liver. It is metabolised mainly by enzymes of the cytochrome P-450 system in the liver. The major oxidative metabolite is fenbendazole sulfoxide which is further metabolised to fenbendazole sulfone. The metabolites are predominantly excreted via the faeces.

Tolerance in the Target Species

The applicant has conducted target animal tolerance studies using multiples (2x and 3x) of the recommended dose in dogs and cats. All doses were administered orally. Full physical examinations of the animals were conducted at intervals following treatment. No adverse effects were seen.

Resistance

The information provided suggests that resistance in the target species has not been documented or published.

Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials

The applicant provided study reports for clinical trials conducted in dogs and cats. The efficacy data supports the use in cats, however the user safety data provided only supports the use of whole sachets for specific animal bodyweights; therefore, as this product is only available in a 4 g sachet which is not a dose appropriate for most cats, it is not suitable for use in cats.

Study title	Clinical trial for Zerofen 22.2% granules in the treatment of Toxacara canis infestation in the dog Chanelle Pharmaceuticals Manufacturing Ltd.
Objectives	To examine the efficacy of Zerofen 22.2% granules (fenbendazole 220 mg/g) in the treatment of T. canis infestation in the dog.
Test site(s)	Veterinary Teaching Hospital, University College Dublin, Ireland
Test Product	Zerofen 22.2% Granules (Chanelle Pharmaceuticals Manufacturing Ltd.) administered at 50 mg/kg PO for three days with food
Control product/placebo	Panacur 22.2% Granules (Hoechst Pharmaceuticals Ltd.) administered at 50 mg/kg PO for three days with food
Animals	18 puppies from four litters. Breeds as follows: Litter 1: Weimeraner (n=4) Litter 2: Collie cross-breed (n=8) Litter 3: Terrier cross-breed (n=4) Litter 4: Dachshund (n=2)
Eligibility Criteria	Fully weaned and clinically healthy. No history of anthelmintic treatment or vaccination.
Outcomes/endpoints	Faecal quantitative and qualitative analysis (McMaster and Sugar Flotation Techniques, respectively). Samples collected prior to treatment and then daily for seven days post-treatment. Animals were observed during the study period and for an additional month for any potential adverse effects. Worm counts were conducted at the end of the study.
Randomisation	Randomised
Blinding	Partially blinded
Statistical method	A significant or absolute reduction in faecal egg count by Day 7 was considered as efficacious treatment.
RESULTS	

Outcomes for endpoints	100% faecal egg count reduction by Day 7 post treatment for Zerofen and Panacur groups (although in many cases 0 egg counts were recorded within 48 hours of treatment)
DISCUSSION	Zerofen 22.2% Granules was 100% effective in reducing positive faecal egg counts in naturally-occurring cases of T. canis infestation in puppies. Confirmed with worm counts.

Study title	Clinical trial for Zerofen 22.2% granules in the treatment of Toxacara canis infestation in the pregnant bitch Chanelle Pharmaceuticals Manufacturing Ltd.
Objectives	To examine the efficacy of Zerofen 22.2% granules (fenbendazole 220 mg/g) in the treatment of T. canis infestation in the pregnant bitch
Test site(s)	Veterinary Teaching Hospital, University College Dublin, Ireland
Test Product	Zerofen 22.2% Granules (Chanelle Pharmaceuticals Manufacturing Ltd.) administered at 25 mg/kg PO daily from D40 of pregnancy until 2 days after whelping (with food)
Control product/placebo	Panacur 22.2% Granules (Hoechst Pharmaceuticals Ltd.) administered at 25 mg/kg PO daily from D40 of pregnancy until 2 days after whelping (with food)
Animals	16 pregnant bitches of various breeds and ages
Eligibility Criteria	Vaccinated and clinically healthy. Pregnancy confirmed with ultrasound scan at around day 35 of pregnancy prior to study.
Outcomes/endpoints	Faecal quantitative and qualitative analysis (McMaster and Sugar Flotation Techniques, respectively). Samples collected prior to treatment and then at approximately D 55 - 60 of pregnancy and then weekly from three to six weeks post-partum. Animals were observed during the study period for any potential adverse effects.
Randomisation	Randomised
Blinding	Partially blinded
RESULTS	
Outcomes for endpoints	83.3 - 100% faecal egg count reduction from week three to week six post-partum (Sugar Flotation Technique) 0 - 8 eggs per gram faeces from week three to week six post-partum (McMaster Technique)
DISCUSSION	Zerofen 22.2% Granules was effective in preventing positive faecal egg counts in bitches in late pregnancy and the early post-partum period.

Study title	Clinical trial for Zerofen 22.2% granules in the treatment of Taenia hydatigena infestation in the dog Chanelle Pharmaceuticals Manufacturing Ltd.
Objectives	To examine the efficacy of Zerofen 22.2% granules (fenbendazole 220 mg/g) in the treatment of T. hydatigena infestation in the dog.
Test site(s)	Veterinary Teaching Hospital, University College Dublin, Ireland
Test Product	Zerofen 22.2% Granules (Chanelle Pharmaceuticals Manufacturing Ltd.) administered at a single dose of 100 mg/kg PO with food
Control product/placebo	Panacur 22.2% Granules (Hoechst Pharmaceuticals Ltd.) administered at a single dose of 100 mg/kg PO with food
Animals	18 Beagles
Eligibility Criteria	Vaccinated and clinically healthy. Bathed in amitraz on arrival.
Outcomes/endpoints	Faecal quantitative and qualitative analysis (McMaster and Sugar Flotation Techniques, respectively). Samples collected prior to treatment and then daily for seven days post-treatment. Animals were observed during the study period and for an additional month for any potential adverse effects.
Randomisation	Randomised
Blinding	Partially blinded
Statistical method	A significant or absolute reduction in faecal egg count by Day 7 was considered as efficacious treatment.
RESULTS	
Outcomes for endpoints	100% faecal egg count reduction by Day 7 post treatment for Zerofen and Panacur groups (although in many cases 0 egg counts were recorded within 48 hours of treatment)
DISCUSSION	Zerofen 22.2% Granules was 100% effective in reducing positive faecal egg counts in naturally-occurring cases of Taenia hydatigena infestation in dogs. Confirmed with worm counts.

Study title	Clinical trial for Zerofen 22.2% granules in the treatment of Toxacara cati infestation in the cat Chanelle Pharmaceuticals Manufacturing Ltd.
Objectives	To examine the efficacy of Zerofen 22.2% granules (fenbendazole 220 mg/g) in the treatment of T. cati infestation in the cat
Test site(s)	Veterinary Teaching Hospital, University College Dublin, Ireland
Test Product	Zerofen 22.2% Granules (Chanelle Pharmaceuticals Manufacturing Ltd.) administered at 50 mg/kg PO daily for three consecutive days. Treatment was 60 days

	after induced infection with T. canis eggs
Control product/placebo	Panacur 22.2% Granules (Hoechst Pharmaceuticals Ltd.) administered at 50 mg/kg PO daily for three consecutive days. Treatment was 60 days after induced infection with T. canis eggs There was also a negative control group that did not receive any treatment.
Animals	16 purpose-bred Domestic Short Hair kittens (aged six weeks old at inclusion)
Eligibility Criteria	Vaccinated and clinically healthy. Treated with a proprietary anthelmintic prior to artificial infection, one week post-inclusion.
Outcomes/endpoints	Faecal quantitative and qualitative analysis (McMaster and Flotation Techniques, respectively). Samples collected prior to treatment and then daily for seven days post-treatment. Animals were observed during the study period for any potential adverse effects. Worm counts were conducted at the end of the study.
Randomisation	Randomised
Blinding	Partially blinded
RESULTS	
Outcomes for endpoints	100% faecal egg count reduction by Day 7 post treatment for Zerofen and Panacur groups (although in many cases 0 egg counts were recorded within 48 hours of treatment)
DISCUSSION	Zerofen 22.2% Granules was 100% effective in reducing positive faecal egg counts in artificially-induced cases of T. cati infestation in kittens. Confirmed with worm counts.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The overall conclusion was that the product in its current presentation, of a 4 g sachet, is suitable for use in dogs but not in cats.

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 for use in dogs is favourable.

The data provided only supports the use of whole sachets for specific animal bodyweights; therefore it was decided that, as this product is only available in a 4 g sachet, it is not suitable for use in cats because cats would typically require a lower dosage than 4g per animal.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

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

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

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

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