United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Ridaworm Plus Tablets for Dogs
VetUK Dog Wormer Flavoured Tablets
Rofectan Plus Tablets for Dogs
Beaphar WORMclear Tablets for Dogs

Date Created: May 2015

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Ridaworm Plus Tablets for Dogs VetUK Dog Wormer Flavoured Tablets Rofectan Plus Tablets for Dogs Beaphar WORMclear Tablets for Dogs
Applicant	C&H Generics Ltd c/o Michael McEvoy and Co Seville House New Dock Street Galway, Ireland
Active substance	Praziquantel, pyrantel embonate, febantel
ATC Vetcode	QP52AA51
Target species	Dogs
Indication for use	In dogs and puppies: treatment of gastrointestinal roundworms, tapeworms, hookworms, and whipworms of the following species: **Ascarids:** *Toxocara canis*, *Toxascaris leonina* (adult and late immature forms). **Hookworms:** *Uncinaria stenocephala*, *Ancylostoma caninum* (adults). **Whipworms:** *Trichuris vulpis* (adults). **Tapeworms (cestodes):** *Echinococcus* species, *(E. granulosus, E. multilocularis), Taenia* species *(T. hydatigena, T. pisiformis, T. taeniformis), Dipylidium caninum* (adult and immature forms).

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Generic 'hybrid' applications in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

These applications were submitted in accordance with Article 13 (3) of Directive 2001/82/EC, as amended by 2004/28/EC for 'hybrid' applications. The reference product is Drontal Plus, which has been authorised in the UK for more than 10 years.

The products are indicated for use in dogs with the following gastrointestinal tapeworms and roundworms in dogs and puppies
Roundworms (nematodes):
Ascarids: *Toxocara canis*, *Toxascaris leonina* (adult and late immature forms).
Hookworms: *Uncinaria stenocephala*, *Ancylostoma caninum* (adults).
Whipworms: *Trichuris vulpis* (adults).
Tapeworms (cestodes): *Echinococcus* species, *(E. granulosus, E. multilocularis), Taenia* species *(T. hydatigena, T. pisiformis, T. taeniformis), Dipylidium caninum* (adult and immature forms).

The products are 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 products 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 per tablet, praziquantel 150mg, pyrantel embonate 144 mg and febantel 50mg. The excipients are lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, sodium laurilsulfate and pork flavour.

The container/closure system consists of individual strips composed of aluminium foil 30 µm/30 gsm extruded polythene, containing 2, 4, 6 or 8 tablets.

or

Individual blisters composed of 45 µm, soft temper aluminium foil and 25 µm hard temper aluminium foil, containing 2 or 8 tablets.

The strips or blisters are packed into cartons containing 2, 4, 6, or 8 tablets. Not all pack sizes may be marketed.

The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the formulation and the absence of preservative are justified. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guideline.

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

The manufacturing process consists of a simple granulation and compression technique. The results of a process validation study using three production-scale batches were provided.

II.C. Control of Starting Materials

The active substances are praziquantel, pyrantel and febantel, established substances described in the European Pharmacopoeia (Ph. Eur). The active substances are manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications, which included reference to relevant certificates of suitability have been provided.

II.C.4. Substances of Biological Origin

Scientific data and/or 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:

- The suppliers of the active substances have provided declarations that their materials are not derived from animal origin and no intermediates or auxillary agents are used in the manufacturing process.
- The supplier of lactose monohydrate has certified that "The milk used for production of lactose derives from healthy animals and is collected as milk for human consumption". This is considered adequate as these types of products are excluded from the guideline.
- The supplier of magnesium stearate has certified that their material is of vegetable and mineral origin.

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. Tests on the finished products include those on appearance, identification of the active substances and associate by-products. Additional testing includes identification of the pork flavour, friability, weight, dissolution, uniformity of dosage, 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. Data were provided for tests performed under VICH[3] guidelines. For two sites producing praziquantel, retest periods of 36 months and 60 months were deemed acceptable.

Likewise, for both pyrantel embonate and febantel, from results of tests performed under VICH test conditions, a retest period of 60 months was considered acceptable.

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

For the finished product as packaged for sale, appropriate VICH testing resulted in a shelf-life of 5 years being considered acceptable.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 5 years.

This veterinary medicinal product does not require any special storage conditions.

Discard any unused divided tablets immediately.

Do not remove tablets from strip packaging until required for use.

Keep blister in outer carton.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

These were generic 'hybrid' applications according to Article 13 (3), whereby bioequivalence with a reference product could not be established. Pharmacological data and user safety data were obtained from published literature.

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

Praziquantel
The active substance is a pyrazinoisoquinoline which causes paralysis of the target parasite, leading to death.

Pyrantel
The active substance is an imidazothiazole derivative, which acts by causing a neuromuscular block within the nicotinic receptors of the target parasite.

Febantel
The active substance is a probenzimidazole, which acts by binding to tubulin, with resulting interference to the cell membrane and microtubule structure, while also affecting glucose metabolism and transport.

Pharmacokinetics

Praziquantel
The active substance is quickly metabolised in the dog, among other species, and is excreted via the bile, urine, and gastro-intestinal tract mucosae. Metabolites are likely present in the excreta.

Pyrantel embonate

The active substance is poorly absorbed from the gastro-intestinal tract in dogs, leading to a large amount of efficacious activity in the large intestine. Absorbed pyrantel embonate is broken down into several metabolites and eliminated via the faeces. Approximately half of the drug excreted in this manner is unchanged.

Febantel
Pharmacokinetic properties in dogs have not been specifically studied, although the profile is considered to be similar to that seen in other species. The metabolites of febantel are active, and thus data on one of these metabolites, fenbendazole, were presented. Variation in administration and formulation can affect the absorption of the active substance. Full elimination takes place within 3-7 days of administration.

It was considered that the action of the three active substances together would provide an efficacy profile similar to that of the reference product.

Toxicological Studies

The applicant provided bibliographical data:

- Single Dose Toxicity

All three active substances are of low toxicity. For praziquantel, no deaths in dogs occur in oral doses of up to 400 mg/kg. The LD_{50}[4] in rabbits is approximately 1050 mg/kg. For pyrantel pamoate, the LD_{50} in dogs is in the region of >690 mg/kg, and >5000 mg/kg in rats. For febantel, the LD_{50} in rabbits is approximately 1250 mg/kg, and in dogs >10,000 mg/kg.

- Repeated Dose Toxicity

From published studies, it was noted that toxicity was minimal on repeat dosing in dogs.

- Reproductive Toxicity, including Teratogenicity:

From published studies, it was noted that no effect was seen on reproduction in dogs.

- Mutagenicity

From published studies, it was noted that no mutagenic effect was seen in dogs.

- Carcinogenicity (if necessary):

From published studies, it was noted that no carcinogenic effect was seen in dogs.

[4] LD_{50} – Dose at which half a test population is deceased.

Observations in Humans

From published data submitted, it was noted that praziquantel and pyrantel are used in human medicine, with no significant side effects observed. Febantel is not used in human medicine.

User Safety

A user risk assessment was provided in compliance with the relevant guideline. Eye irritation can occur with use of praziquantel and with extended use of febantel. Complications can occur with the use of lactose monohydrate, which may cause adverse reactions in the presence of deficiency of the intestinal enzyme lactase. Microcystalline cellulose and magnesium stearate are commonly used in food and pharmaceutical production, and may cause a laxative effect at high levels, and magnesium stearate may additionally cause mucosal irritation. Colloidal anhydrous silica is commonly used in products and is not considered to be toxic. Croscarmellose sodium is commonly used and is generally considered to be non-toxic, with large amounts causing a laxative effect. Sodium lauryl sulphate is commonly used and is moderately toxic, generating irritation effects to eyes and skin. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product, and reflect those of the reference product:

In case of accidental ingestion, seek medical advice and show the package leaflet to the physician.
In the interests of good hygiene, persons administering the tablets directly to the dog, or by adding them to the dog's food, should wash their hands afterwards.

Echinococcosis represents a hazard for humans. As echinococcosis is a notifiable disease to the World Organisation for Animal Health (OIE), specific guidelines on the treatment and follow-up, and on the safeguard of persons, need to be obtained from the relevant competent authority.

Environmental Safety

The assessment was in accordance with VICH and CVMP guidelines.

Phase I:

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. Disposal advice given in the SPC is consistent with that of the reference product.

IV CLINICAL DOCUMENTATION

Bioequivalence for all active substances although accepted was not demonstrated. Proprietary data and product literature was used to supplement the application.

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics

Praziquantel
The active substance is a pyrazinoisoquinoline, of which the levo (-) isomer causes muscular paralysis in schistosomes. It is thought that a depolarising effect occurs within the cells of the target parasite.

Pyrantel embonate
The active substance is an imidazothiazole with broad-spectrum activity against nematodes. As a cholinergic agonist, the active substance induces a neuromuscular blockade via excitation at the nicotinic receptors.

Febantel
Febantel is a probenzimidazole with a broad spectrum of activity against nematodes. Activity is via the conversion of the active substance to fenbendazole and oxfendazole, and acts by binding to tubulin, resulting in interference to microtubule and membrane structure and glucose metabolism. The generation of energy is then compromised by the inhibition of fumarate reductase.

Pharmacokinetics

Praziquantel
The active substance is rapidly and extensively absorbed, with significant first-pass metabolism observed. Elimination is also rapid, and occurs via the urine, gastro-intestinal tract and bile. Praziquantel crosses the placenta and may be found in the foetus only in very small amounts, with similar profiles seen for pharmacokinetic data between animals and humans.

Pyrantel embonate
There is low absorption of pyrantel embonate from the gastro-intestinal tract, with a large amount remaining active in the large intestine. Inactive metabolites are quickly eliminated in the faeces, with approximately half of the active substance remaining as unchanged active substance.

Febantel

Specific studies with regard to the dog have not been provided, but the metabolic pathway appears similar in all studied species. The active metabolites fenbendazole and oxfendazole are among several produced. Studies presented on the active metabolites showed variation for results in dogs, with complete elimination occurring within 3 – 7 days.

A published study and an *in vivo* study performed by the applicant were submitted, describing use of the active substances in combination. Although bioequivalence was not directly established, published references and a dissolution study also performed by the applicant contributed to the overall conclusion that the proposed product and the reference product were essentially similar.

Tolerance in the Target Species

The applicant has conducted a pivotal controlled target animal tolerance study using multiples of the recommended dose in the target species, in order to support the application with regard to target animal safety and any questions with regard to metabolites remaining from the active substances when used in combination. It was found that in a suitably conducted trial that the proposed product was well-tolerated when used at up to 5 times the recommended dose.

Resistance

The bibliography provided suggests that when used at the recommended dose, the proposed product is no more likely to present a greater risk for the emergence of resistance in target organism than the reference product. No cases of resistance were noted for praziquantel or febantel. Some resistance to pyrantel by *Toxocara canis* and *Ancylostoma caninum* has been noted in the USA and Australia when used at a lower dose than that of the proposed product. Adequate warnings and precautions appear on the product literature.

IV.II. Clinical Documentation

Laboratory Trials/Field Trials

The applicant has provided extensive bibliographical data which show that when used as recommended, efficacy of the active substances when used alone or in combination as in the proposed product can be assured. No further data were required.

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(s) is favourable.