United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Extrontel Plus Tablets for Dogs

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Extrontel Plus Tablets for Dogs
Applicant	C&H Generics Ltd Saville House New Dock Street Galway Ireland
Active substance(s)	Praziquantel, Pyrantel, Febantel
ATC Vetcode	QP52AA51
Target species	Dogs
Indication for use	In dogs: Treatment of mixed infections by nematodes and cestodes of the following species **Nematodes:** **Ascarids:** *Toxocara canis*, *Toxascaris leonina* (adult and late immature forms). **Hookworms:** *Uncinaria stenocephala*, *Ancylostoma caninum* (adults). **Whipworms:** *Trichuris vulpis* (adults). **Cestodes:** **Tapeworms:** *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	Application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.

I. SCIENTIFIC OVERVIEW

This was a generic hybrid application submitted in accordance with Article 13(3) of Directive 2001/82/EC. The reference product for Extrontel Plus Tablets for Dogs is Drontal Plus which has been authorised since 2000. Extrontel Plus Tablets for Dogs has the same qualitative and quantitative composition in terms of the active substances and has the same pharmaceutical form as the reference product. However, bioequivalence could not be demonstrated by bioequivalence studies and therefore the application is supported by proprietary data and published literature.

Extrontel Plus Tablets for Dogs is intended for the treatment of mixed infections by nematodes and cestodes in dogs. For nematodes, the product may be used to treat the following species: Ascarids (*Toxocara canis, Toxascaris leonina* (adult and late immature forms), hookworms (*Uncinaria stenocephala, Ancylostoma caninum* (adults), whipworms (*Trichuris vulpis* (adults). For cestodes, the product may be used to treat the following species: Tapeworms *Echinococcus* species (*E. granulosus, E. multilocularis*), *Taenia* species (*T. hydatigena, T. pisiformis, T. taeniformis*), *Dipylidium caninum* (adult and immature forms).

The product is recommended to be administered at the rate of 15mg/kg febantel, 5 mg/kg pyrantel (equivalent to 14.4 mg/kg pyrantel embonate), and 5mg/kg praziquantel. This is equivalent to 1 Extrontel Plus tablet per 10 kg (22 lbs) bodyweight. The tablets are administered orally directly to the dog or disguised in food. The tablets can be divided into equal halves or quarters.

The product contains praziquantel 50 mg/tablet, pyrantel 50 mg/tablet (equivalent to 144 mg pyrantel embonate) and febantel 150 mg/tablet as active substances and excipients lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, sodium laurilsulfate and pork flavour.

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. The product is safe for the user and for the environment when used as recommended. Suitable warnings and precautions are indicated in the SPC[1]

[1] Summary of Product Characteristics.

II. QUALITY ASPECTS

A. Composition

Extrontel Plus Tablets for Dogs contain 50 mg praziquantel, 50 mg pyrantel (equivalent to 144 mg pyrantel embonate), and 150 mg febantel per tablet. The excipients are lactose monohydrate, microcrystalline cellulose, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, sodium laurilsulphate and pork flavour.

The container for this product is either individual strips composed of aluminium foil/extruded polythene containing 2, 4, 6, 8, 10, 12, 14, 16, 18 or 20 tablets, or individual blisters composed of soft temper aluminium foil and hard temper aluminium foil containing 2 or 8 tablets. The strips or blisters are contained in cartons containing either 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 30, 32, 36, 40, 42, 44, 48, 50, 52, 56, 60, 70, 80, 84, 90, 98, 100, 104, 106, 120, 140, 150, 180, 200, 204, 206, 250, 280, 300, 500 or 1000 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

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

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

Manufacturing formulae for varying batch sizes were provided. The active substances along with lactose monohydrate, microcrystalline cellulose, are sieved and granulated. The granule is dried and then blended with other portions of microcrystalline cellulose and croscarmellose sodium, colloidal anhydrous silica, and sodium laurilsulphate. Magnesium stearate is then added and the tablets are then mixed, compressed and packaged. During tablet formation, the product is checked for tablet shape, diameter, disintegration, friability, average weight, and hardness.

C. Control of Starting Materials

The active substances are praziquantel, pyrantel, and febantel. These are established active substances and are all described in the European Pharmacopoeia. All three active substances are manufactured in accordance with an Active Substance Master File (ASMF). Febantel is also manufactured in accordance with a European Pharmacopoeia Certificate of Suitability. The active substances specifications are considered adequate to control the quality of the materials. All excipients comply with the European Pharmacopoeia.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

A declaration has been provided stating that the finished product complies with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products. The suppliers of the active substances and have provided declarations that their materials are not derived from animal origin. Lactose monohydrate falls outside the scope of the guideline; however, the suppliers of lactose monohydrate have declared that the milk used for production of lactose is derived from healthy animals. The suppliers of all other excipients have declared that their materials are free from TSE risk material or derived from vegetable and mineral origin.

E. Control on intermediate products

There are no tests on intermediate products.

F. 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. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification. Tests include those for appearance, identification, dissolution, assay of active substance content and uniformity of dosage units.

G. Stability

Stability data on 3 batches of the active substance praziquantel, 3 batches of the active substance febantel, and numerous batches of the active substance pyrantel embonate have been provided in accordance with the applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on 4 batches of the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product when stored under the approved conditions. Tests include those for appearance, disintegration, identification, dissolution and related substances. All results were satisfactory.

H. Other Information

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years
Discard any unused divided tablets.
This veterinary medicinal product does not require any special storage conditions.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

A number of published references were submitted for praziquantel, pyrantel and febantel with regard to pharmacological studies. These data were originally provided for the UK authorised product Vet Worm Plus Tablets, which was the reference product for Drontal Plus Tablets.

Pharmacodynamics

In this fixed combination, pyrantel and febantel act against all relevant nematodes (ascarids, hookworms, and whipworms) in dogs. In particular, the activity spectrum covers *Toxocara canis*, *Toxascaris leonina*, *Uncinaria stenocephala*, *Ancylostoma caninum* and *Trichuris vulpis*.

This combination shows synergistic activity in the case of hookworms and febantel is effective against *T. vulpis*. The spectrum of activity of praziquantel covers all important cestode species in dogs, in particular *Taenia* spp., *Dipylidium caninum*, *Echinococcus granulosus* and *Echinococcus multilocularis*. Praziquantel acts against all adult and immature forms of these parasites.

Praziquantel is very rapidly absorbed through the parasite's surface and distributed throughout the parasite. Both in vitro and in vivo studies have shown that praziquantel causes severe damage to the parasite integument, resulting in the contraction and paralysis of the parasites. There is an almost instantaneous tetanic contraction of the parasite musculature and a rapid vacuolization of the syncytial tegument. This rapid contraction has been explained by changes in divalent cation fluxes, especially calcium.

Pyrantel acts as a cholinergic agonist. Its mode of action is to stimulate nicotinic cholinergic receptors of the parasite, induce spastic paralysis of the nematodes and thereby allow removal from the gastrointestinal system by peristalsis.

Within the mammalian system, febantel undergoes ring closure, forming fenbendazole and oxfendazole. It is these chemical entities which exert the anthelmintic effect by inhibition of tubulin polymerisation. Formation of microtubules is thereby prevented, resulting in disruption of structures vital to the normal functioning of the helminth. Glucose uptake in particular is affected, leading to depletion in cell ATP[2]. The parasite dies upon exhaustion of its energy reserves, which occurs 2 – 3 days later.

[2] Adenosine triphosphate

Pharmacokinetics

Perorally administered praziquantel is absorbed almost completely from the intestinal tract. After absorption, the drug is distributed to all organs. Praziquantel is metabolized into inactive forms in the liver and secreted in bile. It is excreted within 24 hours to more than 95% of the administered dosage. Only traces of non-metabolised praziquantel are excreted. Following administration of the product to dogs, peak plasma concentrations of praziquantel were achieved by approximately 2.5 hours.

The pamoate salt of pyrantel has low aqueous solubility, an attribute that reduces absorption from the gut and allows the drug to reach and be effective against parasites in the large intestine. Following absorption, pyrantel pamoate is quickly and almost completely metabolized into inactive metabolites that are excreted rapidly in the urine.

Febantel is absorbed relatively rapidly and metabolized to a number of metabolites including fenbendazole and oxfendazole, which have anthelmintic activity. Following administration of the product to dogs, peak plasma concentrations of fenbendazole and oxfendazole were achieved by approximately 7-9 hours.

Toxicological Studies

The applicant provided a number of references to support this section.

Single Dose Toxicity
Praziquantel is of low toxicity in a wide variety of species. Oral LD_{50}[3] in rabbit is approximately 1050 mg/kg. Acute toxicity studies in dogs were limited by emesis, which occurred at 100 mg/kg. No deaths occurred at oral doses up to 400 mg/kg.

Pyrantel is very well tolerated in various species. LD_{50} value in rats and dogs was >5000 and >690 mg/kg respectively.

Febantel is of low toxicity. LD_{50} in rabbits was 1250 mg/kg and in dogs and other laboratory species was >10,000 mg/kg.

Repeated Dose Toxicity

Praziquantel
Praziquantel has low toxicity when given repeatedly to laboratory species and dogs orally. The administration of up to 180 mg/kg daily for 13 weeks led to no drug related effects in dogs. Doses of 5x and 10x the recommended dose of 5 mg/kg given twice at 2 week intervals led to occasional vomiting and diarrhoea but mostly there were no effects. In rats of up to 1000 mg/kg /day for 4 weeks or 250 mg/kg / week for 104 weeks led to no drug related effects.

[3] Dose that kills half (50%) of the animals.

Pyrantel
Pyrantel when administered to dogs at 207 mg/kg for up to 90 days produced no drug related morphological changes. In young greyhounds, repeated doses of 5 mg/kg produced an initial decline in serum alkaline phosphatase which then stabilised and remained constant at maturity. In another study, adverse effects occurred in dogs administered 50 mg/kg/day for 90 days, but no adverse effects occurred at 20 mg/kg/day.

Febantel
Doses of 4x - 8x the recommended dose daily for 10 days can cause transient diarrhoea in horses. Data on the metabolite fenbendazole showed no toxic signs in dogs given 250 mg/kg/day for 30 days or 125 mg/kg/day for 90 days.

Reproductive Toxicity
The applicant has submitted a review of published literature to support this section.

Praziquantal
There was no effect on fertility, conception, foetal development or pregnancy in dogs at doses up to 26.8 mg/kg during critical stages of reproduction. In 3-generation and other fertility tests, there was no effect in laboratory species at doses up to 300 mg/kg, except diarrhoea and salivation in some pregnant dams.

Pyrantel
No teratogenicity, foetotoxicity or toxic effects on fertility, gestation, viability or lactation were found in rats when treated at up to 90 mg/kg/day from day 14 prior to mating. No adverse effects on foetuses occurred in rabbits dosed from day 7 – 17 of gestation with up to 90 mg/kg/day but an increase in the incidence of resorption was seen. Following treatment of pregnant bitches at various intervals after breeding to cover the major period of organogenesis, and males treated from 2 – 127 days prior to service, no teratogenic or other effects were observed. Extensive clinical studies on dogs including pregnant and lactating bitches have not revealed any evidence of toxic effects.

Febantel
Febantel and its metabolite oxfendazole are teratogenic in rats at doses of 50 – 100 mg/kg. In sheep febantel is teratogenic at doses of 45 mg/kg given on day 17 of pregnancy. Pregnant mares given 2x the recommended dose, from 40 days before conception to 148 days after, delivered normal foals. No evidence of teratogenicity has been found in dogs and a variety of other species.
Mutagenicity

Praziquantel
A number of published references were provided which indicated that praziquantel is not mutagenic.

Pyrantel
From the CVMP Summary Report for pyrantel embonate (EMEA/CVMP MRL Summary Report), it was noted that pyrantel can not be considered as a mutagenic compound.

Febantel
Many benzimidazoles are known to have effects on mitosis, causing aneuploidy but mutagenicity data from febantel, fenbendazole and oxfendazole showed no clear evidence of genotoxicity. Although fenbendazole and other metabolites led to positive results in the mouse lymphoma forward mutation study, this occurred only in the presence of metabolic activation. Fenbendazole produced negative results in 2 *in vitro* and 2 *in vivo* mutagenicity tests.

Carcinogenicity

Praziquantel
Published oral toxicity studies in rats and hamsters were provided which indicated that no treatment-related effects in tumour incidence, latency and multiplicity occurred when praziquantel was given orally at doses of 0, 100 and 250 mg/kg body weight once weekly for 104 or 80 weeks.

Pyrantel: The long term feeding studies in rats (93 weeks) and dogs (2 years) using the tartrate concluded that the NOEL[4] was 3 mg/kg/day for both species.

Febantel: No reports were provided.

Observations in Humans

Praziquantel
Praziquantel is used in humans for the treatment of schistosomiasis and cestode infections. There are no serious short-term or long-term side-effects associated with the use praziquantel.
Pharmacokinetic data in man showed that radiolabelled praziquantel is rapidly and almost completely metabolised. Following oral administration of C-praziquantel at doses of 14 - 46 mg/kg body weight the radioactivity was eliminated from serum with a half life of approximately 4 hours. The major metabolites in serum and urine were isolated and identified as predominantly hydroxylation derivatives of praziquantel, containing one or two hydroxy groups. Doses up to 50 mg/kg body weight in man were well tolerated with no clinically relevant changes. Therapeutic doses in man range from single oral dose of 5 mg/kg body weight to 60 mg/kg body weight, multiple oral doses of 3 x 25 mg/kg body weight for up to 3 days, to 50-60 mg/kg body weight for 15 days.

Pyrantel:
Pyrantel has been used in human medicines for over 20 years. It is normally administered as pamoate salt at oral doses of 10 to 20 mg/kg/ body weight /day for 1 to 3 days. The reported adverse effects in humans in case of overdose include gastro-intestinal disturbances, central nervous system effects and skin reactions. The values of serum asparatate aminotransferase and serum alanin aminotransferase were elevated in 1.8% of patients.

Febantel:
Febantel is not used in human medicine, nor its metabolites fenbendazole and oxfendazole.

[4] No observed effect level

User Safety

The applicant has provided a satisfactory user risk assessment, identifying the users of the product and the potential routes of exposure for the operator. The risks have been identified and appropriate warnings are included in the SPC and product literature. These are:

- 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.

Other precautions
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.

Ecotoxicity

The products are only intended for administration to dogs. A Phase I environmental risk assessment was satisfactorily carried out in accordance with VICH and CVMP guidelines. Data provided have demonstrated that exposure of these products to the environment will not be extensive and the assessment can end at Phase 1.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The applicant provided published data for praziquantel, pyrantel and febantel. In this fixed combination, pyrantel and febantel act against all relevant nematodes (ascarids, hookworms, and whipworms) in dogs. In particular, the activity spectrum covers *Toxocara canis*, *Toxascaris leonina*, *Uncinaria stenocephala*, *Ancylostoma caninum* and *Trichuris vulpis*. This combination shows synergistic activity in the case of hookworms and febantel is effective against *T. vulpis*.

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Within the mammalian system, febantel undergoes ring closure, forming fenbendazole and oxfendazole. It is these chemical entities which exert the anthelmintic effect by inhibition of tubulin polymerisation. Formation of microtubules is thereby prevented, resulting in disruption of structures vital to the normal functioning of the helminth. Glucose uptake in particular is affected, leading to depletion in cell ATP. The parasite dies upon exhaustion of its energy reserves, which occurs 2 – 3 days later.

Pharmacokinetics:
Perorally administered praziquantel is absorbed almost completely from the intestinal tract. After absorption, the drug is distributed to all organs. Praziquantel is metabolized into inactive forms in the liver and secreted in bile. It is excreted within 24 hours to more than 95% of the administered dosage. Only traces of non-metabolised praziquantel are excreted. Following administration of the product to dogs, peak plasma concentrations of praziquantel were achieved by approximately 2.5 hours.

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Tolerance in the Target Species of Animals

The applicant submitted bibliographic references and conducted one tolerance study in puppies using Extrontel Plus Tablets for Dogs. A suitable number of dogs of various sizes were divided into different groups and dosed accordingly. No indication of toxicity or intolerance was found. The study concluded that Extrontel Plus Tablets for Dogs was well tolerated when administered at does up to five times the recommended treatment dose or when administered at the recommended treatment dose for up to three days.

Resistance

The available information suggested that the active substances in Extrontel Plus Tablets for Dogs are effective against target canine pathogens with limited reports of resistance. The product has the same composition, in terms of active substances as the reference product, and the proposed conditions of use are identical. Therefore, it is assumed that Extrontel Plus Tablets for Dogs are unlikely to present any greater risk for resistance emergence than that posed by the reference product.

IV.B Clinical Studies

The product has the same composition, in terms of active substances as the reference product, and the proposed conditions of use are identical. The applicant has submitted an extensive bibliographic data to support the efficacy of the individual active substances when used individually or in combination. This is considered acceptable and 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 for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

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)