ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
MUTUAL RECOGNITION
(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Drontal Oral Suspension for Puppies

PuAR correct as of 18/05/2018 when RMS was transferred to IE. Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0286/001/MR
Name, strength and pharmaceutical form	Drontal Oral Suspension for Puppies
Applicant	Bayer plc Animal Health Division Bayer House Strawberry Hill Newbury Berkshire RG14 1JA
Active substances	Febantal Pyrantel (as pyrantel embonate)
ATC Vetcode	QP52AF02
Target species	Dogs
Indication for use	For the treatment of roundworm infections in puppies and young dogs up to one year of age caused by: Ascarids: *Toxocara canis* *Toxascaris leonina* Hookworms: *Ancylostoma caninum* *Uncinaria stenocephala* Whipworm: *Trichuris vulpis*

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual Recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	26 March 2008
Date product first authorised in the Reference Member State (MRP only)	17 April 1998
Concerned Member States for original procedure	Austria Estonia Finland France Germany Iceland Ireland Latvia Lithuania Norway Spain

I. SCIENTIFIC OVERVIEW

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 slight reactions observed are indicated in the SPC.
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 of the product was demonstrated according to the claims made in the SPC.
The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains 15.00 mg febantel and 14.40 mg pyrantel embonate per millilitre and excipients: sodium propionate, sodium benzoate, sodium dihydrogen phosphate dihydrate, sorbitan mono-oleate, povidone K25, polysorbate 80, docusate sodium, bentonite, citric acid anhydrous, ponceau 4R (E124), xanthan gum, propylene glycol and purified water.

The container/closure system comprises a white high density polyethylene bottle (50ml or 100ml) with a white polypropylene screw closure. To facilitate dosing, a 5 ml blunt-ended plastic syringe is supplied within the outer carton. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation and 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.

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 the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substances are pyrantel (as pyrantel embonate) and febantel. Both active substances are supported by data have been provided in the form of a European Drug Master File (EDMF). It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified.

All the excipients with the exception of ponceau 4R(E124) are the subject of monographs in the European Pharmacopoeia and are provided to that standard. The ponceau 4R(E124) used must comply with European standards for materials for food and pharmaceutical use. Supplier's certificate of analysis, and checks on appearance and an identity test provide support of appropriate quality.

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

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

E. Control on intermediate products

There are no intermediate products. The suspension is not stored or transported in bulk.

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.
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.

The white, high density polyethylene containers for the product are required to comply with a test for identity of the material of construction and with mechanical tests of diameter of mouth, wall thickness, volume and permeability (leakage). The white, high density polyethylene closures are subjected to tests of identity, colour, diameter of seal and, again, permeability (leakage). Appropriate information regarding the quality control of the packaging has been provided.

G. Stability

Stability data on both 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.
Results recent production batches tested in compliance with VICH requirements for 5 years at 25°C/60%RH and 6 months at 40°C/75%RH. A shelf life of 5 years without restriction on temperature of storage is considered justified. No data are available on stability in light, but the active substances are not markedly light-sensitive and the pack is opaque. As the product is to be presented in a carton, exposure is likely to be limited. This is considered acceptable.

Data were presented on a 100 ml pack of the product from which samples have been repeatedly removed over a 10-week period. No changes in appearance,

pH or assays of active substances or preservatives were noted and an in-use shelf-life of ten weeks have therefore been justified.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life
Shelf-life of the veterinary medicinal product as packaged for sale: 5 years
Shelf-life after first opening the immediate packaging: 12 weeks

Special precautions for storage
Do not use after expiry date.
This unopened veterinary medicinal product does not require any special storage conditions. After opening, store the product at a temperature not exceeding 25 ºC.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has conducted studies which show the effects of febantel in *in vitro* and *in vivo* models. Within the mammalian system febantel undergoes structural changes forming fenbendazole and oxfendazole, (ring formations). It is these chemical entities which exert the anthelmintic effect by inhibition of tubulin polymerization. Formation of microtubules is prevented, resulting in disruption to 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.

Pyrantel, belongs to the tetrahydropyrimidine type. Its mode of action is to stimulate nicotinic cholinergic receptors inducing spastic paralysis and thereby allowing the expulsion of immobilised parasites from the gastro-intestinal (GI) system. Published studies have been provided to support this.

The applicant has also provided bibliographical data which show that after oral application of the recommended dose of 1 ml/kg bodyweight (corresponding to 14.4mg/kg pyrantel embonate and 15 mg/kg febantel) maximum serum concentrations for febantel were found between 1 and 6 hours with a C_{max}[1] of 0.019 mg/l two hours after dosing. As febantel as a pro-drug is metabolised to fenbendazol which is further converted to oxfendazole, these metabolites were also measured. C_{max} of febendazole was 0.130 mg/l after 3 hours and C_{max} of oxfendazole was 0.157 mg/l at about 5 hours after application. The C_{max} of pyrantel (measured as pyrantel base) was 0.084 mg/l 2.5 hours after dosing in each target species.

[1] C_{max} = maximum concentration

Toxicological Studies

The applicant has conducted the following laboratory studies:

Single Dose Toxicity

The applicant has provided company studies as evidence of the acute toxicity of febantel in rat, mouse, rabbit and dog. A summary of the findings was provided: Decreased motor activity was seen at the lower toxic doses, with diarrhoea occurring at higher doses. No skin irritation was noted in the dermal toxicity test. A range of values for LD_{50} studies between 335->10000 mg/kg body weight in the 4 different laboratory species (routes of administration also varied) and show a relatively wide margin of safety between acute lethal dose and pharmacologically effective doses.

In pyrantal embonate again a wide range of values for LD_{50} studies between 535->24000 mg/kg bw in mice and rats (routes of administration also varied) and show a wide margin of safety between acute lethal dose and pharmacologically effective doses

Single dose safety data on the combination of febantel and pyrantel embonate have also been provided. This gives adequate information to conclude that the toxicity of both active ingredients in mammals is low and that the toxicity is not increased by the combination. Oral doses of the formulated product at a level of 1276 mg febantel and 1224 mg pyrantel embonate /kg body weight in rats had no adverse effects. Dermal doses of formulated product at a level of 2550 mg febantel and 2450 mg pyrantel embonate /kg body weight in rats had no adverse effects.

Repeated Dose Toxicity

The applicant has provided studies in rats, mice and dog for repeat dose administration. In rats and mice, fatty infiltration of the liver was the predominant adverse effect and a NOEL of 50 µg/kg body weight per day could be established for this effect in the study in rats. A NOEL of 6 mg/kg body weight per day for repeat dose toxicity of febantel was established from the 1-year study in dogs.

The applicant has provided published one oral studies in rats and data reporting repeat dose studies in dogs. The rat study indicated no adverse effects up to daily doses of 3000 mg/kg/d for 3 months. The details given for the dog study suggest that 200 mg/kg/d is not harmful to dogs.

Reproductive Toxicity

For febantel a two generation study in rats was been provided. Rats of both sexes were treated from 100 days before the first mating until the second generation were 28 days old. No toxicologically significant effects on reproductive performance were found in doses up to 500 ppm in the diet. At the 100 and 500 ppm dose levels, general maternal and foetal toxic effects (liver damage and impaired weight gain) were observed. The NOEL for these effects was 20 ppm (equivalent to about 2 mg/kg bw/d).

No studies in pyrantel embonate were provided.

Embryotoxicity/foetotoxicity (inc. teratogenicity)
A toxicity study was carried out in which groups of pregnant female rats were given daily oral doses of on days 6-15 of gestation. Maternal toxicity (reduced body weight gain) was observed at 100 mg/kg bw. 100 m/kg bw was also foetotoxic causing an increased incidence of resorptions and reduced foetal weights. The NOEL for maternal toxicity and teratogenicity was 30 mg/kg bw/day.

The potential reproductive toxicity, including foetotoxicity and teratogenic potential of pyrantel embonate remains unclear from the studies in experimental animals.

Mutagenicity
The mutagenicity data available for febantel, fenbendazole and oxfendazole show no evidence of genotoxicity although no specific tests for aneugenicity have been conducted.

A limited range of mutagenicity tests for pyrantel embonate in bacterial and mammalian systems have been provided. One conclusion made in an expert report was that pyrantel embonate does not posses mutagenic or genotoxic, although it was also considered not possible to determine the genotoxic potential of pyrantel embonate from the information provides, although the studies provided do not indicate a particular cause for concern.

Carcinogenicity
A combined chronic/reproductive toxicity/carcinogenicity study of febantal in rats and a 21-month toxicity/carcinogenicity study in mice have been presented. There was no evidence of carcinogenic potential in either species.

No studies on the carcinogenic potential of pyrantel embonate have been carried out by the applicant or could be found in published literature. These however are not considered necessary for the safety evaluation of the product.

Other Studies
No specific studies for febantal or pyrantel embonate have been carried out. The repeat dose studies gave no indication of adverse effects on the tissues and organs of the immune system.

Studies on eye irritation and skin sensitisation by the formulated product were provided. The data were sufficient to indicate that the formulated product will be of low or non-irritancy to skin and eye and is unlikely to lead to sensitisation reactions.

The applicant has also provided studies in dogs on simultaneous administration of Drontal Plus (which contains praziquantel in addition to febantel and pyrantel embonate) with enrofloxacin, ampicillin, xylazine, ketamine, dexamethasone 21-

orthophosphate and N-butyl-O-tropylscopinium hydroxide and metamizole. No interactions were found.

Observations in Humans
Febantel has not been used in humans, so no information is available.

Some product literature on the human use and adverse reactions of pyrantel embonate has been provided. Pyrantel, as embonate and other salts, has been used as an anthelmintic for many years in human medicine. The normal therapeutic dose is 10 mg/kg/d for 1-3 days. Adverse effects were reported in 20% of patients and included gastro-intestinal effects, central nervous system effects and skin reactions. The causative agent for skin reactions (urticaria and dermatitis) has been proposed to be derived from the parasites or Cochineal Red used in the formulation.

Studies on Metabolites, Impurities, Other Substances and Formulation.
The applicant makes reference to a report concerning cochineal red A (Ponceau 4R, E124) is an EC-approved colorant for use in medicines, food and cosmetics. This excipient may cause allergic reactions in sensitive individuals, however, E124 is used in a number of other veterinary medicinal products and the Suspected Adverse Reaction Surveillance Scheme do not indicate a particular problem.

User Safety
The applicant has provided a user safety assessment in compliance with the relevant guideline which concludes that use of Drontal Puppy Suspension will not present any undue risk for users of the product and no special warning phrases are required, however the warning to “wash hands after use” is on the SPC and product literature.

Ecotoxicity
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology
The applicant has referred to a number of references concerning the mode of action of anthelmintics. The applicant has demonstrated that pyrantel acts as an agonist at the nicotinic acetylcholine receptors of nematodes and the benzimidazoles (metabolites of febantel) act to selectively bind β tubulin of parasites and inhibit microtubule formation. It is also clear that pyrantel pamoate is poorly absorbed from the GI tract, a property that contributes to its selective action on gastrointestinal nematodes. The major proportion of an administered

dose is reported to be recovered in the faeces. It is noted that the effect of the action of nicotinic substances and also of depolarising muscle relaxants is increased when using pyrantel. It is also assumed that the neuromuscular blocking piperazine can antagonise the spastic, paralysing action of pyrantel in parasites. This leads to the conclusion that concomitant administration of pyrantel and piperazine should be avoided. This is reflected in the SPC.

In relation to pharmacokinetics the applicant has provided further literature references. These demonstrate that the actives are not well absorbed and are largely excreted via the faeces in the dog and the synergism between pyrantel and febantel has been clearly documented This synergism justifies the combination of the actives and the dose of each active included in the final formulation taken forward to clinical trials. The applicant has also demonstrated that the toxicity profile of each active is not adversely affected by their use in combination and that good efficacy might be expected of such a combination against nematodes

Tolerance in the Target Species of Animals

The Applicant has provided references to studies which address target species tolerance. A couple of studies demonstrated basic tolerance of the combination although the data captured were limited. Some more thorough studies performed provide evidence of the target species safety of the final formulation at doses up to 10 x overdose on one occasion and a single dose on 3 repeated occasions in puppies as young as 2 weeks of age. Another study demonstrates that the combination of febantel and pyrantel in these proportions, even at 10 x overdose, had no effect on the growth or development of young dogs. This study was performed using Drontal Tablets, not Drontal Oral Suspension; however the inclusion of praziquantel in tablet form is only likely to have made the safety testing more stringent. It is reasonable to assume that the combination of febantel and pyrantel in Drontal Oral Suspension would not adversely affect the growth and development of young dogs treated with it.

Resistance

A number of references to known mechanisms of resistance to benzimidazoles and pyrantel in helminths in ruminants and horses have been provided. An expert states that a recent literature search has revealed no reports of emergence or development of resistance to febantel in canine helminths. Out of the references provided there is only incidence of resistance to pyrantel in a canine parasite reported, this being in New Zealand. There are no reports of resistance of canine helminths to pyrantel within the EU. This is supported by the periodic safety update report submitted, which shows that there have been no reports of lack of efficacy since Drontal Puppy Suspension has been marketed. It has been demonstrated adequately that Drontal Puppy Suspension does not pose a serious risk to emergence of anthelmintic resistance in canine parasites.

IV.B Clinical Studies

Laboratory Trials

Dose determining

Several references have been provided which provide evidence of the efficacy of the combination against *Toxocara canis* infections against natural immature and mature *Ancylostoma caninum* infestations in dogs at the dose rates proposed.

Dose confirmation

A reference to a study provides a clear demonstration of the synergism between febantel and pyrantel embonate against the named parasites in the dog. It also provides justification of the dose combination selected by the applicant and confirmation of the clinical efficacy of those doses.

Field Trials

A study provided demonstrates a high level of efficacy of the proposed product against *Toxocara canis, Trichuris vulpis, Ancylostoma caninum* and *Uncinaria stenocephala.* These results are supported by the large body of supportive data which the applicant has also provided

The tolerance to the product was also excellent in the field studies. Mild signs such as vomiting and diarrhoea were very rarely seen and were self limiting. There were no signs related to local intolerance reported.

Efficacy against *Toxascaris leonina* has been demonstrated in a number of further references. Although the final formulation of the proposed product was not used in these references, the formulations were sufficiently similar to assume that efficacy against this parasite would not be significantly different than reported in these papers.

The claims on the SPC are fully supported and the warnings included are considered sufficient for this product.

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 risk benefit 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)