ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

(Reference Member State)

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Cestem Flavoured Tablets for Medium and Small Dogs
Cestem Flavoured Tablets for Large Dogs

PuAR correct as of 13/06/2018 when RMS was transferred to NL.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0359/001/MR UK/V/0359/002/MR
Name, strength and pharmaceutical form	Cestem Flavoured Tablets for Medium and Small Dogs Cestem Flavoured Tablets for Large Dogs
Applicant	Ceva Animal Health Ltd
Active substance(s)	Febantel, pyrantel embonate, praziquantel
ATC Vetcode	QP52AA51
Target species	Dogs
Indication for use	Treatment of mixed infections by adult cestodes and nematodes 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* spp., *Taenia* spp., *Dipylidium caninum* (adult and immature forms).

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 (hybrid) application in accordance with Article 13(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	15th September 2010.
Date product first authorised in the Reference Member State (MRP only)	19th June 2009.
Concerned Member States for original procedure	Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Estonia, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, The Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain

I. SCIENTIFIC OVERVIEW

These are hybrid applications based on two reference products, Drontal Plus tablets and Drontal Plus XL tablets. Drontal Plus XL is a Line Extension of Drontal Plus. Cestem Flavoured Tablets for Medium and Small Dogs and Cestem Flavoured Tablets for Large Dogs contain febantel (150 mg/525 mg), pyrantel as pyrantel embonate (50 mg/175 mg) and praziquantel (50 mg/175 mg). All active ingredients have a well established use.

The indication for use of the product is for the treatment of mixed infections in dogs caused by adult cestodes and nematodes of the following species: Nematodes, ascarids: *Toxocara canis*, *Toxascaris leonina* (adult and late immature forms). Hookworms, *Uncinaria stenocephala*, *Ancylostoma caninum* (adults), and whipworms, *Trichuris vulpis* (adults). Cestodes, tapeworms: *Echinococcus* spp., *Taenia* spp., *Dipylidium caninum* (adult and immature forms).

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 Summary of Product Characteristics (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 benefit/risk analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The products contain the active substances, febantel, praziquantel and pyrantel embonate. The products contain the excipients liver powder flavour, tablet grade inactive yeast, sodium laurilsulfate, croscarmellose sodium, povidone K30, anhydrous colloidal silica, cellulose microcrystalline, magnesium stearate and maize starch. The choice of the formulation and the absence of preservative are justified.

The container system is comprised of a polyamide-aluminium PVC or aluminium blister pack containing 2 or 4 tablets in 1 or 2 blisters, 12 blisters of 4 tablets, or 24 blisters of 2 tablets. Not all pack sizes may be marketed The particulars of the containers and controls performed are provided and conform to the regulation.

The products are an established pharmaceutical form and the development of them is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The active substances, a portion of liver powder, a portion of maize starch and croscarmellose sodium are mixed and sieved prior to formation into a granulate. Dried granules are then sieved and mixed with the remainder of the constituents, before being compressed into tablets. The tablets are then placed into pre-formed blisters.

In-process checks include the recording of dissolution times, mixing times, mesh sizes, drying temperature and residual moisture.

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. Validation of the manufacturing process were carried out on a suitable number of batches

C. Control of Starting Materials

The active substances are febantel, praziquantel and pyrantel embonate. All are monographed in the European Pharmacopoeia (Ph. Eur.) and all are established active substances. 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 have been provided.

The use of both praziquantel and febantel is covered by a certificate of suitability, and an in-house specification was considered acceptable for pyrantel embonate.

Excipients monographed in the Ph. Eur. are sodium laurelsulphate, silica colloidal anhydrous, maize starch, croscarmellose sodium, povidone K30, cellulose microcrystalline and magnesium stearate. Excipients not monographed in a pharmacopoeia are inactived yeast and liver powder flavour. Specifications were provided for both of these excipients.

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

A format 3 declaration, and declarations by the suppliers of each active substance and of the yeast used in the products have been provided citing that 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 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. 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 are tests for appearance, mean mass, dimensions, resistance to crushing, identity, uniformity of dosage, subdivision of tablets, water content, dissolution, assay at release and during shelf life, impurities and microbial count.

G. 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 relating to two batches of finished product, stored according to VICH[1] guidelines at long-term and accelerated conditions were submitted.

[1] VICH – International Co-operation on Harmonisation of Technical Requirements for Registration of Veterinary Products.

Febantel was slightly sensitive to oxidising and acid conditions and sensitive to heat. Praziquantel was slightly sensitive to oxidation and heat, and pyrantel was sensitive to alkaline conditions.

Data for both products were obtained under accelerated conditions at 40ºC/75% RH for six months and under long-term conditions at 25ºC/60% RH for thirty-six months. Results determined the shelf-life at thirty-six months.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life after first opening the blister pack is seven days. Any halved tablets should be returned to the blister and used within seven days.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Bioequivalence between product and reference product was established for praziquantel and therefore results of pharmacological and toxicological tests were not required for this active substance. Appropriate data were submitted for febantel and pyrantel embonate.

III.A Safety Testing

Pharmacological Studies

A number of published references were submitted for pyrantel embonate, febantel and praziquantel with regard to pharmacological studies.

Pharmacodynamics

Published references were submitted for pyrantel embonate and febantel:-

Pyrantel Embonate

A CVMP[2] report (EMEA/MRL/491/198.1998), was submitted describing pyrantel embonate as a nicotinic acid. Pyrantel embonate is a potent agonist against the acetylcholine receptors on the muscle cells of nematodes. Spike activity and contraction is increased via membrane depolarisation, culminating in expulsion of the parasite.

A second reference described the synergistic effect of pyrantel and fenbendazole on *Toxocara canis,* (Melhorn *et al*, Parasitol. Res, 90, ppS151-

[2] CVMP – The Committee for Medicinal Products for Veterinary Use.

S153. 2003). The combination of the two drugs was demonstrated to be more effective in killing the target worms. A third reference enforced previous conclusions on the synergistic effects of pyrantel and fenbendazole.

Febantel

Three published references were submitted for febantel. The first was a CVMP report, EMEA/MRL/867/03 (1998), describing the metabolism into fenbendazole, a benzimidine anthelmintic. Two further references described the action of anthelmintics.

Pharmacokinetics

Two published references were presented for each active substance:-

Praziquantel

A publication from Dayan, Acta Tropica, 86, pp 141-159. (2003), describing oral administration to the rat, dog and monkey, highlighted that between 75% and 100% of praziquantel is absorbed in the body, with maximum serum concentration occurring at between 30 minutes and 2 hours. Rapid and extensive metabolism was found to occur in the liver. No adverse effects were seen to be due to the co-administration of other drugs. A second published reference from the CVMP summary Report for praziquantel, EMEA/MRL/141/96 (1998) described a radio-labelling assay, with praziquantel delivered intravenously at 2 mg/kg or orally at 10 mg/kg bodyweight. This assay demonstrated the rapid elimination of praziquantel from all species observed.

Pyrantel Embonate

CVMP Summary Report EMEA/MRL/491/98 (1998), described a single oral administration of radioactively labelled pyrantel embonate at 10 mg/kg bodyweight in rats. Rapid excretion occurred after extensive metabolism in the liver. A second reference described pyrantel embonate as exhibiting the highest anthelmintic activity, compared to other salts.

Febantel

CVMP Summary Report EMEA/MRL/867/03 (1998), described the absorption of febantel, with about 20% to 30% of an oral dose excreted in the urine in rat and 20% in sheep.

A second published reference, (Woodward KN, WHO Food Additives Series 29), found that 70% of a dose of febantel was excreted in the bile after intravenous and intraduodenal dosing. Febantel is metabolised in the liver into its associated metabolites, with the liver and kidney identified as key target tissues for metabolites in different species.

Toxicological Studies

Bioequivalence between the products and reference products was demonstrated for praziquantel, and therefore toxicological studies were not required for this active substance. Suitable published references were provided for pyrantel embonate and febantel. This was considered acceptable.

Other Studies

Single Dose Toxicity

Reference was made to the CVMP Summary Report for pyrantel embonate, EMEA/MRL/491/98 (1998). In this report, the oral LD_{50}[3] was described as being above 2000 mg/kg bodyweight in rats, mice and dogs. This represents low oral toxicity. For febantel, the LD_{50} was >10,000 mg/kg bodyweight in rats, mice and dogs, again via the oral route.

Repeated Dose Toxicity

The CVMP Summary Report, EMEA/MRL/491/98 (1998) was cited for pyrantel embonate. Here, repeated dose toxicity studies resulted in the establishment of a NOEL[4] of 35 mg/kg bodyweight/day in rats and dogs.

The published reference from Woodward KN, WHO Food Additives Series 29, was presented for febantel. Groups of male and female rats were given oral doses of the active substance of between 0 and 125 mg/kg for three months. No adverse effects attributable to treatment occurred. Increased liver weights were noted in animals given the highest dose, with fatty infiltration of the liver seen in several high dose rats. The NOEL was established as 50 mg/kg bodyweight/day. A further study was performed in dogs. Animals were given oral doses of between 0 and 180 mg/kg bodyweight/day. Animals given higher doses exhibited reductions in haematocrit, haemoglobin and erythrocyte count. A related study demonstrated that no adverse effects were seen at between 5 or 10 mg/kg bodyweight/day, establishing the NOEL at 10 mg/kg bodyweight/day. A further study established NOEL at 5 mg/kg bodyweight/day.

Reproductive Toxicity

From the CVMP Summary Report for pyrantel embonate EMEA/MRL/491/98 (1998), it was noted that no significant difference was seen between two groups of rats, (one control group), with regard to adverse effects on reproductivity. For febantel, the published reference Woodward KN, WHO Food Additives Series 29 was cited, in which the NOEL for rats with regard to adverse reproductive effects was 10 mg/kg bodyweight/day.

[3] LD_{50} – Median lethal dose.
[4] NOEL – No Observed Effect Level.

CVMP Summary Report EMEA/MRL/867/03, (1998), concluded that no adverse effects with regard to reproductive performance occurred at 5-10 mg/kg bodyweight/day.

Embryotoxicity, foetotoxicity (including teratogenicity)

From the CVMP Summary Report for pyrantel embonate EMEA/MRL/491/98 (1998), it was noted that no adverse effects were noted in rats and rabbits in doses up to 90 mg/kg bodyweight/day.

From the published reference Woodward KN, WHO Food Additives Series 29, for febantel, it was noted that no teratogenic effects were seen in male and female rats at doses up to 50 mg/kg bodyweight/day. The NOEL was established as being 10 mg/kg bodyweight/day. A further study noted no adverse effects at doses of 30 mg/kg bodyweight/day in female rats. In conclusion, it was found that the NOEL for maternal toxicity and teratogenicity is between 22 mg and 30 mg febantel/kg bodyweight/day.

Mutagenicity

From the CVMP Summary Report for pyrantel embonate EMEA/MRL/491/98 (1998), it was noted that pyrantel can not be considered a mutagenic compound. CVMP Summary Report EMEA/MRL/867/03, (1998), concluded that there is no evidence of mutagenicity for febantel.

Carcinogenicity

From the CVMP Summary Report for pyrantel embonate EMEA/MRL/491/98 (1998), long-term feeding studies in rats and dogs, the NOEL for rats fed between 0 and 115 mg/kg bodyweight/day was established as being 3 mg/kg bodyweight/day based on haematology results and some organ weights. In dogs, A NOEL of 3 mg/kg bodyweight/day was established in animals given between 0 and 30 mg/kg bodyweight/day, based on serum alkaline aminotransferase values and increased liver weight.

From the published reference Woodward KN, WHO Food Additives Series 29, for febantel, it was noted that no carcinogenic effects were seen.

Observations in Humans

Praziquantel

Praziquantel is commonly used for the treatment of schistosome and liver fluke infections. The recommended dose is 3 doses of 20 mg/kg on one day, at 4-6 hour intervals. Adverse, usually transient reactions include: malaise, headache, bloody diarrhoea, dizziness, arrhythmias, abdominal discomfort, convulsion, myalgia, somnolence vertigo, vomiting and rarely, urticaria. Hypersensitivity reactions are rare. It is considered that there is a very low potential for adverse effect in pregnant women or the unborn child.

Pyrantel Embonate

This active substance has been established for human use for many years. The dose is usually given as pamoate salt at doses of 10-20 mg/kg bodyweight/day for 1 to 3 days. Side effects may include: mild to moderate gastrointestinal disturbance, headache, dizziness, drowsiness, insomnia, rash, vomiting and elevated liver enzymes.

Febantel

Febantel is not used in human medicines.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guidelines. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product:-

- Wash hands after administration to the animal.
- In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
- People with known hypersensitivity to any of the ingredients should avoid contact with the veterinary medicinal product.

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)

For praziquantel, bioequivalence was demonstrated for both Cestem Flavoured Tablets for Medium and Small Dogs and Cestem Flavoured Tablets for Large Dogs as compared to Drontal Plus XL, no further data were required for this active substance.

IV.A Pre-Clinical Studies

Pharmacology

Pharmacodynamics

The applicant provided bibliographical data for pyrantel embonate and febantel. For pyrantel embonate, three studies showed that prolonged spastic paralysis of worms resulted in expulsion from the host. A synergistic effect occurred between fenbendazole and pyrantel embonate resulting in high damage to parasites occurred, and a degree of efficacy was seen in dogs when the three active substances pertinent to the current product were used in combination. Essentially, depolarisation occurs in the neuromuscular membrane resulting in spastic paralysis. For febantel, published references were submitted outlining the efficacy of the active substance with regard to dose rate, metabolism and action. Febantel is a pro-drug, with efficacy induced after metabolism in the liver to active metabolites. The mode of action is chiefly via inhibition of tubulin within the parasite.

Pharmacokinetics

Most broad-spectrum anthelmintics affect parasites in the gut and in other body locations. Efficacy and dosage are dependent on route of administration, formulation, bioavailability, pattern of metabolism and pharmacokinetic behaviour. Minimum effective plasma concentrations have not been established.

After oral administration with praziquantel to laboratory species, a published reference described peak plasma concentrations being reached between 0.5 to 2 hours. The majority of the remainder of praziquantel was eliminated in the urine. A study of radio-labelled pyrantel embonate in dogs demonstrated that peak plasma concentrations were reached 4 to 6 hours after dosing. Excretion was primarily in the faeces. A further study found that bioavailability of fenbendazole was increased in dogs, when the active substance was given in food. Increasing the dose from 20 mg/kg bodyweight to 100 mg/kg bodyweight did not increase C_{max}[5] or AUC[6], possibly because of the poor solubility of fenbendazole and the short gut transit time in this species. It is likely that the drug is excreted before full absorption can take place. It was thought likely that

[5] C_{max} – The maximum (or peak) concentration that a drug achieves in the tested area after the drug has been administered and prior to the administration of a second dose.
[6] AUC – Area Under the (dose concentration versus time) Curve.

this accounted for variability seen in the bioequivalence study performed in dogs for febantel for these applications.

A bioequivalence study comparing a single oral dose of Cestem Flavoured Tablets for Large Dogs with the reference product Drontal Plus XL was conducted in dogs. A suitable number of animals were divided into groups and treated with either product or reference product. Both products contained 175 mg praziquantel, 175 mg pyrantel embonate and 525 mg febantel. The daily dose rate was 15 mg/kg febantel and 5 mg/kg pyrantel and praziquantel. The study design was a balanced 2 x 2 cross-over, with a wash-out period of 6 days. Plasma samples were taken at appropriate time-points, with HPLC[7] being used to determine active substances and/or metabolites. The 90% confidence limit for all relevant AUC values were predicted to be between 0.8 and 1.25, with a Cmax confidence limit between a range of 0.70 and 1.43. For T_{max}[8], the absolute differences between the means (Test-Reference) were predicted to be within the range of approximately 20% of the mean for the reference product. Bioequivalence was established for essential parameters, but it was not possible to determine equivalence between pyrantel, fenbendazole and oxfendazole, as variability between animals was high. This was likely to be due to the low absorption of pyrantel and febantel. Additional dose confirmation studies ultimately supported the claims in the SPC. Dissolution studies were performed comparing Cestem Flavoured Tablets for Medium and Small Dogs, and Cestem Flavoured Tablets for Large Dogs, to Drontal Plus and Drontal Plus XL respectively. Dissolution profiles between products and reference products were comparable.

Tolerance in the Target Species of Animals

As product and reference product were considered bioequivalent with regard to praziquantel, no further data were required for this active substance. For febantel and pyrantel embonate, results from published data referred to in the Safety section (Section III), were considered appropriate. In addition, tolerance data from two GLP[9] studies were submitted for the reference product. Results are reflected in the SPC, which states that occasional vomiting may be seen in very young animals.

Resistance

In general, in cats and dogs, there are a large number of untreated animals which contribute to the stasis of anthelmintic susceptibility. The active ingredients in the products cited in this application elicit different modes of action, therefore limiting the development of resistance. A prophylactic approach to the worming of dogs is recommended, as helminth infections in dogs are of zoonotic concern. Adequate warnings and precautions appear on the product literature.

[7] HPLC - High Performance Liquid Chromotography.
[8] T_{max} – The amount of time after administration of a drug when the maximum plasma concentration is reached, when the rate of absorption equals the rate of administration.
[9] GLP – Good Laboratory Practice.

IV.B Clinical Studies

Laboratory Trials

Two dose confirmation studies were submitted. First, a controlled, randomised study to evaluate and compare the efficacy of Cestem Flavoured Tablets for Medium and Small Dogs and Cestem Flavoured Tablets for Large Dogs to Drontal Plus Flavour against natural infections of *Toxocara canis* was performed. A suitable number of dogs of various sizes, divided into three groups, (one negative control group), were given half a tablet per 5 kg bodyweight/day. Statistical analysis was performed on data obtained from worm counts, with worm numbers low in both treated groups. No significant difference in efficacy was noted between the two products tested, and there were no adverse reactions attributable to the products.

A second study compared the efficacy of Cestem Flavoured Tablets for Medium and Small Dogs and Cestem Flavoured Tablets for Large Dogs to Drontal Plus Flavour against natural infections of *Trichuris vulpis* and *Uncinaria stenocephala*. This was a randomised, parallel arm, blinded, controlled efficacy study in which a suitable number of animals of different sizes were divided into three groups (one negative control group), and were given either the test product or the reference product. Half a tablet was given per kg bodyweight/day. Statistical analysis was performed on data obtained from worm counts, with worm numbers low in both treated groups. No significant difference in efficacy was noted between the two products tested, and there were no adverse reactions attributable to the products.

Field Trials

Data from previous field trials pertinent this application, in addition to supportive published references were submitted. These data, submitted for the three established active substances were considered satisfactory evidence with regard to the use of pyrantel at a dose rate of 5 mg/kg, used in combination with febantel and praziquantel.

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)