ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

X-Spectra Flavoured Tablets for Medium and Small Dogs (UK)
Cestem F tablets for dogs [FR]

X-Spectra Flavoured Tablets for Large Dogs
Cestem F XL tablets for dogs [FR]

PuAR correct as of 12/06/2018 when RMS was transferred to FR.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0413/001/MR UK/V/0413/002/MR
Name, strength and pharmaceutical form	X-Spectra Flavoured Tablets for Medium and Small Dogs X-Spectra Flavoured Tablets for Large Dogs
Applicant	Ceva Animal Health Ltd Unit 3 Anglo Office Park White Lion Road Amersham Buckinghamshire HP7 9FB
Active substance(s)	Praziquantel, febantel and pyrantel (as embonate)
ATC Vetcode	QP52AA51
Target species	Dogs
Indication for use	Treatment of mixed infections by adult cestodes and nematodes of the following species: <u>Nematodes</u>: Ascarids: *Toxocara canis*, *Toxascaris leonina* Hookworms: *Uncinaria stenocephala*, *Ancylostoma caninum* Whipworms: *Trichuris vulpis* <u>Cestodes</u>: Tapeworms: *Taenia* spp., *Dipylidium caninum*

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	Hybrid application in accordance with Article 13 (3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	23rd November 2011.
Date product first authorised in the Reference Member State (MRP only)	26th November 2010.
Concerned Member States for original procedure	France.

I. SCIENTIFIC OVERVIEW

These are hybrid applications submitted under Article 13 (3) of Directive 2001/82/EC as amended. Data submitted were identical to that provided for the original National procedure, which were identical to Mutual Recognition Procedures for the Nationally authorised products Cestem Flavoured Tablets for Medium and Small Dogs, and Cestem Flavoured Tablets for Large Dogs. The reference products were cited as Drontal Plus and Drontal Plus XL Tablets, authorised in the UK since June 1989 and August 2002 respectively. The products are indicated for the treatment of mixed infections by adult nematodes of the following species: ascarids, (*Toxocara canis, Toxascaris leonina*, hookworms, (*Uncinaria stenocephala, Ancylostoma caninum*), whipworms, (*Trichuris vulpis*, adult), and cestodes of the following species: tapeworms (*Taenia* spp., and *Diplylidium caninum*).

Active substance quantities in X-Spectra Tablets for Medium and Small Dogs are: febantel 150 mg, pyrantel (as embonate) 50 mg and praziqiantel 50 mg. Dose rates are half a tablet per 3-5 kg bodyweight, one tablet for 5-10 kg bodyweight, one and a half tablets for 10-15 kg bodyweight and two tablets for 15-20 kg bodyweight. For X-Spectra Tablets for Large Dogs, the quantities are: febantel 525 mg, pyrantel (as embonate) 175 mg and praziquantel 175 mg. Dose rates are half a tablet per 17.5 kg bodyweight, one tablet for >17.5-35 kg bodyweight, one and a half tablets for >35-52.5 kg bodyweight, and two tablets for >52.5-70 kg bodyweight. The generic and reference products carry the same recommendations. The products can be administered to dogs with or without food.

The products are produced and controlled using validated methods and tests which ensure the consistency of the products released on the market. It has been shown that the products can be safely used in the target species, the slight reactions observed are indicated in the SPC[1]. The products are 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 products 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 praziquantel, febantel and pyrantel embonate and 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 applicant aimed for comparability of tablet strengths and compositions, between product and reference product. It was shown that milled active substances produced a dissolution profile in the products that matched those of the reference products. Palatability of the products to dogs was proven, and slight adjustment of the formulation was then required to improve ease of divisibility of the tablets. A wet granulation process was used to improve the compression characteristics of the products, which have an internal and external phase. Oval punches were selected in order to improve the halving of the tablets. The absence of preservative is justified.

The particulars of the containers and controls performed are provided and conform to the regulation. Packaging materials consist of polyamide-aluminium-PVC/aluminium blister packs.

The products are of an established pharmaceutical form and their 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.

[1] SPC – Summary of Product Characteristics.

C. Control of Starting Materials

The active substances are praziquantel, febantel and pyrantel established active substances described in the European Pharmacopoeia (Ph. Eur). 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.

Active substance 1

A Certificate of Suitability (CEP) was received for praziquantel. The raw material specification of the applicant includes testing in line with the monograph described in the European Pharmacopoeia. Satisfactory batch analysis was provided for three batches of the substance.

Active substance 2

A CEP was provided for febantel. The applicant's raw material specification includes testing as described in the Ph. Eur, and satisfactory data were received for three batches of the substance.

Active substance 3

A European Drug Master File (EDMF) was provided for pyrantel embonate. All data were satisfactory. The applicant uses an in-house specification, and data provided for three batches of the active substance were satisfactory.

Excipients described in the Ph. Eur are sodium laurilsulfate, anhydrous colloidal silica, maize starch, croscarmellose sodium, povidone K30, cellulose microcrystalline and magnesium stearate. Excipients not cited in a pharmacopoeia are yeast flavour and liver powder aroma. In-house specifications for these substances were acceptable.

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. A format 3 declaration was provided.

E. Control on intermediate products

Not applicable.

F. Control Tests on the Finished Product

Tests performed on the final product include those for appearance, mass, dimension, identity, water content, assay at release, and assay during shelf-life, impurities and microbial count.

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.

G. Stability

Active substances

A CEP assigns a retest period of 36 months for febantel stored in a low density polyethylene bag, within a black low density polyethylene bag, held in a high density polyethylene drum.

For praziquantel, a CEP was provided specifying a retest period of 2 years for material stored in double polyethylene bags within an iron drum.

For pyrantel embonate, data were provided showing results of long-term stability tests of up to 60 months. Testing was generally performed at 25°C/60%RH in containers representative of commercial packaging. A further set of data related to active substance stored at 40°C/75%RH for 12 months. No adverse effects were seen. The active substance is unaffected by heat (105°C/6 months), but sensitive to strong acid, alkaline or oxidative conditions. A retest period of 5 years was justified. Results for micronized pyrantel embonate reflected the results shown above.

Finished Product

Two batches of each strength of product were tested under VICH[2] conditions. Febantel was shown to be slightly sensitive to oxidising and acid conditions and very sensitive to heat. Pyrantel was very sensitive to alkaline conditions, and praziquantel was slightly sensitive to oxidation and heat.

Products were stored under accelerated conditions (40°C/75%RH/ 6 months), and under long-term condition at 25°C/60%RH for 36 months). A small increase was seen in a pyrantel impurity, but no other changes were noted. Shelf-life of the products as packaged for sale is 3 years.

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

In-Use

Unused half tablets should be discarded.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf-life:
Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.

Special precautions for storage:
This veterinary medicinal product does not require any special storage conditions

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

Bioequivalence with the reference products could not be demonstrated for all three active substances, therefore this application was classified as a hybrid application. Bioequivalence data were presented for praziquantel, therefore it was not necessary for the applicant to provide the results of pharmacological and toxicological studies for this active substance. Data were submitted for febantel and pyrantel embonate. A number of published references were submitted for pharmacological studies.

III.A Safety Testing

Pharmacological Studies

Pharmacodynamics

A published reference was submitted for pyrantel embonate, from CVMP Summary Report EMEA/MRL/491/98(1998). The active substance is classified as a nicotinic agonist, with a potent effect at the acetylcholine receptors within the muscle cells of nematodes. Membrane depolaristaion increases spike activity and contraction, producing a prolonged spastic paralysis of the worms, ending in expulsion of the parasite from the host.

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

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

Data were submitted for 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.

For pyrantel embonate, a 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.
For febantel, a 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.

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

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

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.

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.

Other Studies

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 products identical to those cited in this application; X-Spectra Flavoured Tablets for Medium and Small Dogs and X-Spectra 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

[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.

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 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 X-Spectra 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 X-Spectra Flavoured Tablets for Medium and Small Dogs and X-Spectra 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

[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.

dogs are of zoonotic concern. Adequate warnings and precautions appear on the product literature.

IV.B Clinical Studies

Laboratory Trials

The applicant conducted two dose confirmation studies.

Dose confirmation studies:

Study 1

Study title	Controlled randomised study to evaluate and compare the efficacy of a test article (C558) containing 50 mg praziquantel, 150 mg febantel and 50 mg pyrantel embonate with a reference product Drontal Plus Flavour, containing the same amount of active substances, against natural infections of *T. canis* in dogs.
Objectives	To confirm the efficacy of the test product against natural infections of *T.canis*, when compared to Drontal Plus Flavour and an untreated control group.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP) and VICH.
Test Product	C558, synonymous with X-Spectra Flavoured Tablets for Medium and Small Dogs, delivered at half a tablet/5 kg bodyweight..
Control product/placebo	Reference product – Drontal Plus Flavour Negative control - Untreated controls.
Animals	8 dogs per group, various breeds and ages.
Outcomes/endpoints	Determine the efficacy of the test product as compared to the reference product, up to Day 8.
Randomisation	Randomised.
Blinding	Blinded.
Method	Parallel arm study. Animals were given tablets once daily, and egg counts were performed post-mortem at Day 8.
Statistical method	Differences in egg count were analysed by ANOVA, with the significance level p = 0.05.
RESULTS	
Outcomes for endpoints	For *T. canis*, there was a statistically significant difference between the proportions of animals with zero worms in both treated groups compared to the controls. There was no significant difference in efficacy between the test product and reference product. No treatment-related adverse effects were noted.
DISCUSSION	The test product was shown to be effective against the target parasite.

Study 2

Study title	To evaluate and compare the efficacy of a test article (C558) containing 50 mg praziquantel, 150 mg febantel and 50 mg pyrantel embonate with a reference product Drontal Plus Flavour, containing the same amount of active substances, against concurrent natural *T. vulpis* and *U. stenocephala* infections in dogs.
Objectives	To confirm the efficacy of the test product against natural infections of *T. Vulpis* and *U. Stenocephala*, when compared to Drontal Plus Flavour and an untreated control group.
Test site(s)	Single centre.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP).
Test Product	C558, synonymous with X-Spectra Flavoured Tablets for Medium and Small Dogs, delivered at 1 tablet/10 kg bodyweight.
Control product/placebo	Reference product – Drontal Plus Flavour Negative control - Untreated controls.
Animals	8 dogs per group, various breeds and ages.
Outcomes/endpoints	Determine the efficacy of the test product as compared to the reference product, up to Day 7.
Randomisation	Randomised.
Blinding	Blinded.
Method	Parallel arm study. Animals were given tablets once daily, and egg counts were performed post-mortem at Day 7.
Statistical method	Differences in egg count were analysed by ANOVA, with the significance level p = 0.05.
RESULTS	
Outcomes for endpoints	For *U. stenocephala*, there was no statistically significant difference between worm counts for the two treated groups, but there was a statistical difference between both treated groups and the control group. For T*. vulpis*, there was no statistically significant difference between worm counts for the two treated groups, but there was a statistical difference between both treated groups and the control group.
DISCUSSION	The test product was shown to be effective against the target parasites.

The studies conducted supported the claims in the authorised SPC, in compliance with the requirements laid out in the appropriate Guideline.

Field Trials

Data from previous field trials were pertinent to 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. The products, when used as directed, were shown to be effective against the specified target species.

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)