Veterinary Medicines Directorate

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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Milbeworm 2.5 mg/ 25 mg Film-Coated Tablets for Small Dogs and Puppies
Milbeworm 12.5 mg/ 125 mg Film-Coated Tablets for Dogs

Date Created: 5th May 2015

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	Milbeworm 2.5 mg/ 25 mg Film-Coated Tablets for Small Dogs and Puppies Milbeworm 12.5 mg/ 125 mg Film-Coated Tablets for Dogs
Applicant	Alfamed 13ème Rue – L.I.D. 06517 Carros Cedex France
Active substance	Milbemycin Oxime Praziquantel
ATC Vetcode	QP54AB51
Target species	Dogs
Indication for use	In dogs: treatment of mixed infections by adult cestodes (tapeworms) and nematodes (roundworms) of the following species: Cestodes: *Dipylidium caninum,* *Taenia spp.,* *Echinococcus spp.,* *Mesocestoides spp*. Nematodes: *Ancylostoma caninum,* *Toxocara canis,* *Trichuris vulpis* *Toxascaris leonina,* *Crenosoma vulpis* (Reduction of the level of infection), *Thelazia callipaeda* (see specific treatment schedules under section 4.9 “Amounts to be administered and administration route”), *Angiostrongylus vasorum* (Reduction of the level of infection by immature adult (L5) and adult parasite stages; see specific treatment and disease prevention schedules under section “4.9 Amounts to be administered and administration route”). The product can also be used in the prevention

	of heartworm disease (*Dirofilaria immitis*), if concomitant treatment against cestodes is indicated.

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

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

I. SCIENTIFIC OVERVIEW

Milbeworm film-coated tablets for dogs and for small dogs and puppies have been developed as generic hybrids of Milbemax tablets for dogs and Milbemax tablets for small dogs and puppies. The reference products have been authorised in the UK since April 2003. The application is for a generic hybrid as bioequivalence could not be demonstrated. The products contain milbemycin oxime and praziquantel to be administered orally at dose of 0.5 mg/kg and 5 mg/kg respectively. The products are indicated for the treatment of mixed infections of adult cestodes and nematodes.

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[1].

The product is safe for the user and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of Product Characteristics

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTIUENTS

II.A. Composition

The product contains milbemycin oxime and praziquantel as active substances. The excipients that are used for the tablet are microcrystalline cellulose, croscamellose sodium, lactose monohydrate, starch (pregelatinised), povidone, magnesium stearate and silica hydrophobic colloidal. The coating of the tablet is made from natural poultry liver flavour, hypromellose, microcrystalline cellulose and macrogol stearate.

The container/closure system consists of an aluminium blister pack containing 2 tablets packaged in an outer carton providing 2, 4, 24 or 48 tablets. The particulars of the containers and controls performed are provided and conform to the regulation.

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

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substances are praziquantel and milbemycin oxime, established active substances. Praziquantel is described in the European Pharmacopoeia and Ph. Eur. Certificates of Suitability have been supplied for all manufacturers of this active substance. Milbemycin oxime is not described in a pharmacopeia and an Active Substance Master File (ASMF) has been provided for both manufacturers of this active substance.. 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.

The excipients described in a pharmacopeia are manufactured in accordance with the relevant Ph. Eur. monographs. The poultry liver powder is not described in a pharmacopeia and an in-house specification has been supplied. Certificates of analysis were provided for all excipients.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been justified and are considered appropriate to adequately control the quality of the product. The tests include those for identification and assay of the active substances, identification of impurities, appearance, dissolution and microbiological quality.

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.

II.F. Stability

Stability data on the active substances have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Praziquantel is manufactured in accordance with the Ph. Eur. Certificates of Suitability and the retest period is 36 months. Data were supplied for milbemycin oxime and a retest period of 24 months is supported.

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. Data were provided for batches stored at 25°C/60% RH and 30°C/65% RH, whilst in an accelerated study batches were stored 6 months at 40°C/75% RH. The data support a shelf life of 2 years for the finished product.

G. Other Information

- Shelf life of the finished product as packaged for sale is 3 years.
- This product does not require any special temperature conditions.
- Keep the blister in the outer carton.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

The active substances are milbemycin oxime and praziquantel. Milbemycin oxime is a macrocyclic lactone which has been shown in dogs and cats to prevent heartworm infection and control hookworms, roundworms and whipworms as well as killing mites. It targets glutamate-gated chloride channels found uniquely in nematodes and arthropods. Milbemycin binds to the channels and causes an increased conductance of chloride ions through the cell membrane. This hyperpolarises the cell and results in flaccid paralysis leading to death of the parasite. Macrocyclic lactones do not cross the blood-brain barrier thus making them safe to use in mammals.

Praziquantel is a broad spectrum wormer effective against trematodes and cestodes. It is ineffective against nematodes. The mechanism of action of praziquantel has not been defined but it is suspected that the drug works by affecting Ca^{2+} homeostasis. Praziquantel is rapidly distributed through the tissues of the target helminth, altering the cell membrane permeability to calcium ions enabling an influx of Ca^{2+} and depolarising the cell. This causes muscle contractions and tetany, paralysing the parasite and resulting in expulsion and death of the parasite.

Pharmacokinetics

Milbemycin oxime is rapidly absorbed in dogs following oral administration (T_{max} = ~2 hours) and has a high bioavailability of about 80%. The compound is distributed and maximum concentrations in the tissues were seen 1-8 hours after administration. The highest concentrations were noted in the fat, liver, kidneys and lungs. In the dog the half-life of milbemycin oxime was shown to be 1-4 days, with most excreted unchanged in the faeces and some in the urine. In one study 98% of the compound was excreted within 7 days of administration.

Praziquantel is rapidly absorbed following oral administration (T_{max}[2] = 0.5-4 hours) and there is also a quick decline ($t_{1/2}$[3] = ~1.5 hours). The compound is widely distributed with maximum concentrations seen in the liver and kidneys. Praziquantel is extensively metabolised and no unmetabolised compound has been detected in the urine, faeces or bile. There is a substantial hepatic first-pass effect where praziquantel is rapidly biotransformed. Excretion of praziquantel is also fast with 90% eliminated within 2 days of administration. The main route of excretion is via the kidneys.

[2] T_{max} – time to the maximum concentration
[3] $t_{1/2}$ – elimination half-life

Toxicological Studies

The applicant has provided bibliographical data which show that milbemycin oxime has a higher toxicity profile than praziquantel, demonstrated by the lower LD_{50}[4] values and NOEL[5]. Both active substances have been shown not to cause reproductive toxicity and neither are genotoxic. Additional studies indicated the substances are non-irritant to the skin and eyes.

- Single Dose Toxicity

The data submitted indicate milbemycin oxime has a higher acute toxicity profile than praziquantel, indicated by the lower LD_{50}. In rats the LD_{50} was 863 mg/kg for milbemycin oxime and 2249 mg/kg for praziquantel. The LD_{50} for dog following intravenous (IV) administration of praziquantel was >200 mg/kg.

- Repeated Dose Toxicity

Repeat dose toxicity studies for milbemycin oxime in rats were submitted. Rats received 0, 3, 15 or 100 mg/kg/day and haematological changes were observed in the groups receiving higher doses. The NOEL was 3 mg/kg/day.

Following repeated administration of praziquantel no clinical signs of toxicity were observed in puppies receiving 5x the recommended dose (up to 55 mg/kg) on 2 occasions 14 days apart. Vomiting and diarrhoea was observed in dogs receiving up to 200 mg/kg praziquantel on 2 occasions 14 days apart. In another study dogs received either 20, 60 or 180 mg/kg/day of praziquantel. No drug related lesions were detected and an NOEL of 60 mg/kg was determined. In studies using rats, doses of 30, 100, 300 and 1000 mg/kg/day were administered with a NOEL of 33 mg/kg/day determined.

- Reproductive Toxicity, including Teratogenicity

Studies investigating the effect of milbemycin oxime on reproductive toxicity were discussed. In dogs administered 3 tablets daily before and after mating and up to one week before anticipated whelping (≥18 weeks for males and ≥30 weeks for females) no treatment related effects were seen on the health of the parent or puppies and no effects were seen on any reproductive parameters. In rats administered 300 mg/kg/day for day 7 to 17 of pregnancy clinical signs were observed in dams, including suppression of bodyweight, decreased food intake and diarrhoea. One rat died and the embryo showed delayed ossification. No abnormalities or teratogenic toxicity were seen in rats administered 3 or 30 mg/kg/day.

Praziquantel was also administered to rats, male and female, before mating until post-partum at dose rates of 30, 100 or 300 mg/kg. No effects on fertility were observed and no embryotoxic or teratogenic effects were seen. A study in dogs involved administration of praziquantel to males, 14.7 – 16.2 mg/kg twice before mating, and females, up to 26.8 mg/kg 3 times for one litter duration. No clinical effects were seen on either male or female fertility, conception rates, foetal development or during the pregnancy.

[4] LD_{50} – The dose that kills half the population
[5] NOEL – No observable effect level

The studies provided indicate neither milbemycin oxime nor praziquantel causes reproductive toxicity. No evidence of embryotoxicity, teratogenicity or foetotoxicity was observed and fertility and reproductive performance appeared not to be affected following administration of milbemycin oxime and praziquantel.

- Mutagenicity

Milbemycin oxime was determined not to be genotoxic. A bacterial reverse mutagenicity test was performed on milbemycin oxime and chromosome aberration tests showed the active did not induce revertant colonies or increase the number of cells with chromosomal abnormalities.

A number of studies were provided for praziquantel including tissue-mediated mutagenicity study, dominant lethal test in mice, micronucleus test, spermatogonial test, host mediated assay, cell mediated assay and DNA-damage in human blood cells. All the tests showed negative for any mutagenic effects of praziquantel.

- Carcinogenicity

No data were submitted for milbemycin oxime. However based on the genotoxicity tests the active substance is not expected to be a carcinogen. Studies were provided for praziquantel in hamsters and rats which showed no long term toxic or carcinogenic effects of praziquantel.

Studies of Other Effects

Skin Irritation

The applicant has provided a skin corrosivity study that was conducted using a reconstituted three-dimensional human skin model and the final formulation of the test product. The product was ground to a powder and 25 mg was applied to the skin. A negative control, distilled water, and a positive control, 8 N potassium hydroxide, were used. The results showed that the test product produced no corrosive effects and had a relative mean tissue viability of 95% following 3 minutes exposure and of 102% after 60 minutes of exposure.

In a second skin irritation study the test product was applied to the reconstituted skin model and cell viability was determined by mitochondrial dehydrogenase activity. A negative control, sterile Dulbecco's Phosphate Buffered Saline (DPBS) with magnesium and calcium, was used. The positive control for this study was 5% Sodium Dodecyl Sulphate (SDS) in distilled water. The results showed the test product was non-irritant and had a mean tissue viability of 96% after 15 minutes exposure.

Eye Irritation

An eye irritation study was also performed. Using the closed chamber method bovine eyes were exposed to the test product in a 20% solution, a negative control comprised of physiological saline and a positive control, imidazole in a 20% solution. The change in opacity for each cornea and the *in vitro* irritation scores were calculated. The mean irritation score for the test product was calculated as 2.66 and the product was classed as non-irritant.

As no valid *in vitro* method is yet available to confirm the results in the BCOP[6] study, a limit *in vivo* test was conducted on three female White Rabbits. Rabbits were given 0.1 g of the test product in one eye. All animals were observed for 72 hours after dosing and treated eyes were examined using a fluorescein solution. An irritant effect was observed but no corrosive effects were seen. No mortality or clinical signs of toxicity were seen. All animals showed initial conjunctival redness (mean scores ≤1.33) and the changes were fully reversed within 7 days. The product was classed as non-irritant to eyes.

Skin Sensitisation

A skin sensitisation study was conducted in mice. The animals were administered the product, a negative control (DMSO vehicle) or a positive control (1% phenylenediamine in DMSO) via topical administration to the dorsal surface of the ear for 3 consecutive days. The potential of the product to induce contact hypersensitivity was determined using a local lymph node assay. On Day 6 the mice were given titrated methyl thymidine and auricular lymph nodes were excised and pooled for analysis. The proliferative response of lymph node cells was counted as radioactive disintegrations per minute per lymph node and expressed as the Stimulation Index (SI).

No evidence of erythema or skin thickening was seen following treatment. The SI for the test product was ≤1.1 whilst for the positive control it was 7.5. The product is considered not to cause skin sensitisation.

Observations in Humans

Milbemycin oxime is not used in human medicine however praziquantel has been used to treat trematode and cestode infections in humans for 35 years. The side effects of praziquantel are well documented and often relate to effects from dying parasites. The most common side effects include a headache, nausea, anorexia, epigastric pain, diarrhoea, fever, myalgia and dizziness. The frequency and severity of side effects is directly correlated with the level of infection. In humans 30-60% of patients experience one or more side effects but they are normally transient and disappear within 24 hours. Praziquantel has also been shown to be safe in children 1-5 years old and in pregnant or lactating women.

User Safety

The applicant has provided a user safety assessment in compliance with the relevant guideline which shows that the most likely routes of exposure are dermal and through accidental ingestion. The risk to the user from dermal exposure is negligible due to the film coating of the tablet. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- Wash hands after use.

[6] Bovine Cornea Opacity Permeability

- In the event of accidental ingestion of the tablets, particularly by a child, seek medical advice immediately and show the package leaflet or the label to the doctor.

Environmental Safety

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the product will be administered for individual treatment of companion animals and the risk of environmental exposure is minimal. No environmental warnings or information are therefore required as the product is safe for the environment when used as directed.

IV CLINICAL DOCUMENTATION

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics
A literature review was provided and the pharmacodynamics of both active substances have been previously characterised. Milbemycin oxime is a macrocyclic lactone and targets the glutamate-gated chloride ion channels causing an influx of Cl^-, hyperpolarising the cell, leading to flaccid paralysis and death of the parasite. Praziquantel is an acylated pyrazino-isoquinolone derivative and the exact method of action is not known. It is suspected that praziquantel alters membrane permeability to Ca^{2+} resulting in cell depolarisation, which causes muscle contraction, tetany and death of the parasite.

Pharmacokinetics
The pharmacokinetics of the active substances was covered in a literature review. In addition pharmacokinetic studies were supplied for the proposed formulation.

Bioequivalence
The first study was a bioequivalence study comparing the pharmacokinetic profiles of the test products with the reference products following oral administration. The study used 12 healthy male dogs that had not been treated with a similar product in the preceding 6 weeks. The dogs were divided into 2 groups; Group A received the reference product followed by the reference product whilst Group B were given the test product before the reference product. There was a 42 day washout period between treatments. Dogs were observed for general health and signs of adverse reactions after treatment. Blood samples were taken before treatment, half an hour after treatment and at regular intervals post-treatment for 15 days.

Blood samples were analysed to determine the plasma concentrations of milbemycin oxime and praziquantel. The pharmacokinetic parameters measured included C_{max}[7], T_{max}, elimination half-life and AUC[8]. Parameters were exposed to statistical analysis using ANOVA and the 90% confidence interval (CI) was determined for the means.

The results showed a similar pharmacokinetic profile for the test and reference product. For milbemycin oxime the mean (± standard deviation) AUC was 19249 (±5000) µg/l*h for the reference product and for the test product was 20333 (±4793) µg/l*h. The mean C_{max} was 538 (± 158) µg/l for the reference product and 543 (± 151) µg/l for the test product. T_{max} was 2.4 (± 3.1) h for the reference product and 2.8 (± 3.1) h for the test product. The 90% CI of the ration of the means was determined for the AUC as 0.99 – 1.13, falling within the predefined limits 0.80 – 1.25, and for C_{max} as 0.86 – 1.18 which again was within the limits 0.80 – 1.25. Bioequivalence was demonstrated for milbemycin oxime.

The pharmacokinetic parameters were determined for praziquantel. The mean AUC was 3444 (±1523) µg/l*h for the reference product and 3544 (±1292) µg/l*h for the test product. For the reference product and test product the C_{max} was 1507 (±755) µg/l and 1487 (±531) µg/l*h whilst the T_{max} was 1.1 (± 1.1) h and 1.5 (± 1.3) h respectively. Again the 90% CI was determined for the ratio of the means and bioequivalence was accepted if the confidence interval fell within the predefined limits of 0.80 – 1.25. For AUC the 90% CI was 0.91 – 1.27 and for C_{max} 0.72 – 1.53. Bioequivalence was not accepted for praziquantel.

A second bioequivalence study was provided. This study used 20 male dogs and followed the same protocol as the previous study but included a 35 day washout period between treatments. Blood samples were again taken and analysed. The results showed bioequivalence could be accepted based on AUC data for both milbemycin oxime and praziquantel (90% CI within 0.80 – 1.25) but data for the C_{max} meant bioequivalence could not be accepted. The studies demonstrated a similar pharmacokinetic profile for both the test and reference products and provide supportive evidence of the safety of the products. Whilst bioequivalence was demonstrated for one pivotal parameter, AUC, the data for C_{max} was highly variable and bioequivalence could not be accepted.

Dissolution

A dissolution study was also provided to compare the dissolution profiles of the tablets for dogs and the tablets for small dogs and puppies. The tablets were placed in 3 different dissolution media with pH 3, 4.5 and 7.5 for the study. The solution was sampled at 5, 10, 15, 30, 45 and 60 minutes for pH 3 and 4.5, for pH 7.5 sampling also included 90 and 120 minutes.

The results showed that at pH 3, 4.5 and 7.5 >85% of the praziquantel and the milbemycin oxime was dissolved within 15 minutes for both tablets. The study showed the dissolution profiles of the products were similar and it was concluded that bioequivalence could be accepted between the tablet strengths.

[7] C_{max} – maximum plasma concentration
[8] AUC – Area Under the Curve (concentration curve)

Tolerance in the Target Species

A literature review was submitted, in addition to bioequivalence and dose confirmation studies, in support of target animal safety. The use of milbemycin oxime and praziquantel individually and in combination was covered. The two actives have different mechanisms of action and literature supports the conclusion that interactions between praziquantel and milbemycin oxime are highly unlikely. The use of these two actives in combination has been permitted and is established in veterinary medicine.

The literature indicates both actives are safe for use in the target species. The most commonly observed adverse reactions include vomiting, lethargy and diarrhoea. A number of references were supplied for studies using milbemycin oxime in collies. Milbemycin oxime is a macrocyclic lactone like avermectins which are not well tolerated in collies. The review indicates collies are not likely to experience adverse events at the proposed dose but adverse reactions may occur at high doses. Studies also demonstrated the combination product is well tolerated during pregnancy and lactation but a specific study has not been performed therefore administration is still based on a benefit/risk assessment by the veterinarian.

Based on the literature review and the supportive evidence from the other studies submitted it was concluded that milbemycin oxime and praziquantel re safe to use in combination as directed. Whilst bioequivalence was not demonstrated the pharmacokinetic profile of the test product is similar to the reference product, therefore the same warnings and precautions are considered acceptable. The product literature accurately reflects the type and incidence of adverse effects which might be expected.

Resistance

A bibliography was provided and looked at resistance to macrocyclic lactones and praziquantel. Milbemycin oxime is a macrocyclic lactone, resistance to this class was first observed in sheep and goats but has now also been detected in cattle parasites. Studies indicate that the nematodes contain multiple forms of the glutamate-gated ion channels that are the target of avermectin/ milbemycin anthelmintics. These different forms of the channels can have different sensitivity to current drugs. The review also covered milbemycin in dogs. A study showed milbemycin has a very high efficacy against *Dirofilaria immitis* (~99%) but that the dogs were not 100% cleared of the parasite. High prevention rates are considered essential for this parasite due to the severity of the disease it causes.

Literature relating to praziquantel resistance in food producing species was also provided. Resistance to both milbemycin oxime and praziquantel has not yet been identified in dogs. Adequate warnings and precautions appear on the product literature.

- In order to develop an effective worm control programme local epidemiological information and the living conditions of the dog should be

taken into account and therefore it is recommended to seek professional advice.
- Parasite resistance to any particular class of anthelmintic may develop following frequent, repeated use of an anthelmintic of that class.

IV.II. Clinical Documentation

Laboratory Trials

The applicant has conducted dose confirmation studies and provided bibliographical data to support the claims made in the SPC. Dose determination studies were not provided as an appropriate dose rate has been established for the reference product.

The dose confirmation studies, included below, were conducted for the parasites *Dipylidium caninum*, *Ancylostoma caninum*, *Toxicara canis* and *Trichuris vulpis.* The use of these parasites was to provide a representation of cestodes, hookworms, ascarids and whipworms. In the dose confirmation studies animals received an appropriate dose of milbemycin oxime and praziquantel based on their weight, a range of doses were used including several lower doses. The studies indicated that the test products were effective (>90% efficacy) against the selected parasites. The test product, 594.06 tablets, used in the study was equivalent to Milbeworm 12.5 mg/ 125 mg tablets and Milbeworm 2.5 mg / 25 mg tablets.

Bibliographic data was also supplied in support of the remaining claims against specific parasites that were not tested in dose confirmation studies.

Echinoccocus granulosus
Literature was summarised and studies provided for the *E. granulosus*. As this parasite is considered to pose a threat to public health the effectiveness of a product should be close to 100%. A large amount of evidence was supplied that indicates praziquantel is effective against cestodes, in particular two recent studies show 100% efficacy against *E. granulosus* at a dose of 5 mg/kg praziquantel. All studies provided showed >98% effectiveness against this cestode. In addition the 5 mg/kg dose of praziquantel is well-recognised and a well-established dose for treatment of *E. granulosus.* As no apparent resistance has been identified it was concluded that the efficacy against *E. granulosus* has been sufficiently demonstrated.

Echinoccocus multilocularis
Studies were discussed that demonstrated the efficacy of 5 mg/kg praziquantel against *E. multilocularis*. The efficacy was >99.99% in the submitted studies and a treatment claim is considered acceptable.

Taenia species
Literature was provided in support of a claim for the *Taenia* species that infect dogs. Humans are not intermediate hosts for this species therefore treatment efficacy of >90% can be accepted. A recent study conducted in line with current

EU guidelines showed 100% efficacy of 5 mg/kg praziquantel against *Taenia* species. The combined findings of all the studies demonstrate the effectiveness of praziquantel against *Taenia* species and a claim against these parasites is accepted.

Mesocestoides species
Evidence to support the efficacy of praziquantel was provided. Again studies showed an efficacy of 100% against *Mesocestoides* species with 5 mg/kg praziquantel and the claim could be accepted.

Angiostrongylus vasorum and *Crenosoma vulpis*
Evidence was provided to support SPC claims for *Angiostrongylus vasorum* and *Crenosoma vulpis*. The efficacy of 0.5 mg/kg milbemycin oxime against these species was demonstrated and the claims could be accepted.

Dose confirmation studies:

Study title	Dose confirmation study for an orally administered anthelmintic formulation, 594.06 tablets, against *Dipylidium caninum* in naturally infected dogs
Objectives	To confirm the efficacy of orally administered anthelmintic formulation, 594.06 tablets, against *D. caninum* in naturally infected dogs.
Test site(s)	Single centre, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Milbemycin oxime and praziquantel tablets administered either one 12.5 mg/ 125 mg tablet or two 2.5 mg/ 25 mg tablets once orally.
Control product/placebo	Negative control, animals were untreated.
Animals	20 dogs were included in the study, 9 males and 11 females, weighing 5.24 – 20.42 kg. Inclusion criteria: • demonstrated infection with *D.caninum* at least once during the seven-day acclimatisation period • reasonably good health as judged by a veterinarian • cooperative with study procedures Exclusion criteria: • treatment with an anthelmintic by any route within 10 days prior to the onset of the acclimatisation period • pregnant
Outcomes/endpoints	Following treatment the *D. caninum* scoleces were

	identified and counted. The counts determined the effectiveness of the test product. Clinical examinations were performed throughout the study.
Randomisation	Dogs were randomly assigned to groups.
Blinding	Single blind; investigator.
Method	Dogs were enrolled in the study and had a 7 day acclimatisation period. During this time faecal examinations were performed to determine positive diagnosis of *D. caninum* infection. All animals were treated with an ectoparasiticide. On Day 0 dogs in the treatment group received the test product and monitored closely for clinical normality for the first 4 hours. Clinical examinations continued throughout the study. On Day 10 necropsy the gastrointestinal (GI) tract was examined from stomach to rectum. *D. caninum* scoleces were identified and counted.
Statistical method	The difference in parasite counts between the control and treated groups were analysed using ANOVA. Significance was set at 5%.
RESULTS	
Outcomes for endpoints	The results showed fewer scoleces were identified in the GI tract of treated dogs than the untreated dogs. The mean count for the control group was 23.2 whilst for the treatment group it was 0. This indicated 100% efficacy of the test product and the difference was statistically significant (P = 0.0002). No abnormal conditions or adverse reactions were observed following administration of the test product.
DISCUSSION	The study concluded that efficacy of the test product was demonstrated against adult *D. caninum*. The effectiveness of treatment compared with no treatment resulted in >90% effectiveness.

Study title	Dose confirmation study for an orally administered anthelmintic formulation, 594.06 tablets, against *Ancylostoma caninum* in naturally infected dogs
Objectives	To confirm the efficacy of orally administered anthelmintic formulation, 594.06 tablets, against *A. caninum* in naturally infected dogs.
Test site(s)	Single centre, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Milbemycin oxime and praziquantel tablets administered one 12.5 mg/ 125 mg tablet, one or two

	2.5 mg/ 25 mg tablets once orally.
Control product/placebo	Negative control, animals were untreated.
Animals	20 dogs were included in the study, 7 males and 13 females, weighing 1.35 – 18.81 kg. Inclusion criteria: • demonstrated infection with A. *caninum* (egg count ≥200 per gram) at least once during the seven-day acclimatisation period • reasonably good health as judged by a veterinarian • cooperative with study procedures Exclusion criteria: • treatment with an anthelmintic by any route within 10 days prior to the onset of the acclimatisation period • pregnant
Outcomes/endpoints	Following treatment the *A. caninum* nematodes were identified and counted. The counts determined the effectiveness of the test product. Clinical examinations were performed throughout the study.
Randomisation	Dogs were randomly assigned to groups.
Blinding	Single blind; investigator.
Method	Dogs were enrolled in the study and had a 7 day acclimatisation period. During this time faecal examinations were performed to determine positive diagnosis of *A. caninum* infection. A faecal egg count of at least 200 per gram using the quantitative McMaster technique was seen in all dogs. On Day 0 dogs in the treatment group received the test product and monitored closely for clinical normality for the first 4 hours. Clinical examinations continued throughout the study. On Day 7 the gastrointestinal (GI) tract was examined from stomach to rectum. *A. caninum* nematodes were identified and counted using microscopy.
Statistical method	The difference in parasite counts between the control and treated groups were analysed using ANOVA. Significance was set at 5%.
RESULTS	
Outcomes for endpoints	The results showed fewer nematodes were identified in the GI tract of treated dogs than the untreated dogs. The mean count for the control group was 55.5 whilst for the treatment group it was 2.7. This was calculated

	to show 95.10% efficacy of the test product and the difference was statistically significant (P < 0.0001). No abnormal conditions or adverse reactions were observed following administration of the test product.
DISCUSSION	The study concluded that efficacy of the test product was demonstrated against adult A. *caninum*. The effectiveness of treatment compared with no treatment resulted in >90% effectiveness.

Study title	Dose confirmation study for an orally administered anthelmintic formulation, 594.06 tablets, against *Toxocara canis* in naturally infected dogs
Objectives	To confirm the efficacy of orally administered anthelmintic formulation, 594.06 tablets, against *T. canis* in naturally infected dogs.
Test site(s)	Single centre, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Milbemycin oxime and praziquantel tablets administered one or two 2.5 mg/ 25 mg tablets once orally.
Control product/placebo	Negative control, animals were untreated.
Animals	18 dogs were included in the study, 6 males and 12 females, weighing 1.86 – 8.81 kg. Inclusion criteria: • demonstrated infection with *T. canis* (egg count ≥300 per gram) at least once during the seven-day acclimatisation period • reasonably good health as judged by a veterinarian • cooperative with study procedures Exclusion criteria: • treatment with an anthelmintic by any route within 10 days prior to the onset of the acclimatisation period • pregnant
Outcomes/endpoints	Following treatment the *T. canis* nematodes were identified and counted. The counts determined the effectiveness of the test product. Clinical examinations were performed throughout the study.
Randomisation	Dogs were randomly assigned to groups.
Blinding	Single blind; investigator.

Method	Dogs were enrolled in the study and had a 7 day acclimatisation period. During this time faecal examinations were performed to determine positive diagnosis of *T. canis* infection. A faecal egg count of at least 300 per gram using the quantitative McMaster technique was seen in all dogs. On Day 0 dogs in the treatment group received the test product and monitored closely for clinical normality for the first 4 hours. Clinical examinations continued throughout the study. On Day 7 the gastrointestinal (GI) tract was examined from stomach to rectum. *T. canis* nematodes were identified and counted using microscopy.
Statistical method	The difference in parasite counts between the control and treated groups were analysed using ANOVA. Significance was set at 5%.
RESULTS	
Outcomes for endpoints	The results showed fewer nematodes were identified in the GI tract of treated dogs than the untreated dogs. The total mean count for the control group was 27.9 whilst for the treatment group it was 0.1. This was calculated to show 99.60% efficacy of the test product and the difference was statistically significant ($P < 0.0001$). No abnormal conditions or adverse reactions were observed following administration of the test product.
DISCUSSION	The study concluded that efficacy of the test product was demonstrated against adult *T. canis*. The effectiveness of treatment compared with no treatment resulted in >90% effectiveness.

Study title	Dose confirmation study for an orally administered anthelmintic formulation, 594.06 tablets, against *Trichuris vulpis* in naturally infected dogs
Objectives	To confirm the efficacy of orally administered anthelmintic formulation, 594.06 tablets, against *T. vulpis* in naturally infected dogs.
Test site(s)	Single centre, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Milbemycin oxime and praziquantel tablets administered one or two 2.5 mg/ 25 mg tablets once orally.
Control product/placebo	Negative control, animals were untreated.
Animals	20 dogs were included in the study, 8 males and 12 females, weighing 4.48 – 20.36 kg.

	Inclusion criteria: • demonstrated infection with *T. vulpis* (egg count ≥60 per gram) at least once during the seven-day acclimatisation period • reasonably good health as judged by a veterinarian • cooperative with study procedures Exclusion criteria: • treatment with an anthelmintic by any route within 10 days prior to the onset of the acclimatisation period • pregnant
Outcomes/endpoints	Following treatment the *T. vulpis* nematodes were identified and counted. The counts determined the effectiveness of the test product. Clinical examinations were performed throughout the study.
Randomisation	Dogs were randomly assigned to groups.
Blinding	Single blind; investigator.
Method	Dogs were enrolled in the study and had a 7 day acclimatisation period. During this time faecal examinations were performed to determine positive diagnosis of *T. vulpis* infection. A faecal egg count of at least 60 per gram using the quantitative McMaster technique was seen in all dogs. On Day 0 dogs in the treatment group received the test product and monitored closely for clinical normality for the first 4 hours. Clinical examinations continued throughout the study. On Day 7 the gastrointestinal (GI) tract was examined from stomach to rectum. *T. vulpis* nematodes were identified and counted using microscopy.
Statistical method	The difference in parasite counts between the control and treated groups were analysed using ANOVA. Significance was set at 5%.
RESULTS	
Outcomes for endpoints	The results showed fewer nematodes were identified in the GI tract of treated dogs than the untreated dogs. The total mean count for the control group was 89.2 whilst for the treatment group it was 8.2. This was calculated to show 96.70% efficacy of the test product and the difference was statistically significant ($P < 0.0001$). No abnormal conditions or adverse reactions were

	observed following administration of the test product.
DISCUSSION	The study concluded that efficacy of the test product was demonstrated against adult *T. vulpis*. The effectiveness of treatment compared with no treatment resulted in >90% effectiveness.

A Dose confirmation study was provided to add a treatment claim for Toxascaris Leonina

Study title	Dose confirmation study for an orally administered anthelmintic formulation, 594.06 tablets, against *Toxascaris leonina* in experimentally infected dogs
Objectives	To confirm the efficacy of orally administered anthelmintic formulation, 594.06 tablets, against *Toxascaris leonina* in experimentally infected dogs.
Test site(s)	Single centre, third country.
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	Milbemycin oxime and praziquantel tablets 12.5 mg/ 125 mg tablet.
Control product/placebo	Negative control, animals were untreated.
Animals	38 dogs were included in the study, given anthelmintic treatment at day -91 and inoculated 7 days later with 500 *T. leonina* eggs. 15 dogs were excluded as not positive to *T. leonina* during acclimatisation. 3 further animals excluded as having lowest egg counts. 20 dogs (10 male 10 female) then allocated to groups. The animals were separated by gender and ranked with gender from lowest to highest mean pre-treatment egg count per gram of faeces. Then blocked into 10 replicates of 2. (Negative control or test product).
Outcomes/endpoints	Following treatment the *T. leonina* worms were identified and counted. The counts determined the effectiveness of the test product. Clinical examinations were performed throughout the study. The test product was considered effective if: • At least 6 animals in the control group were infected with *T. leonina* (+5 worms at necropsy). • The difference in parasite counts between the treated and control group were statistically significant ($p < 0.05$) using ANOVA (ln(n+1) transformation of data). • The calculated efficacy was 90% or higher, based on geometric means.
Randomisation	Dogs were randomly assigned to groups.
Blinding	Single, blind (study staff), parallel design.

Method	Animals in the test product group were dosed once orally after food, according to the SPC.
Statistical method	The difference in parasite counts between the control and treated groups were analysed using ANOVA. Significance was set at 5%.
RESULTS	
Outcomes for endpoints	Significantly lower ($p<0.001$) numbers of parasites were seen from treated dogs as opposed to non-treated dogs. No adverse reactions due to the test product were seen. 90% effectiveness against *T. leonina* was observed.
DISCUSSION	Effectiveness against *T. leonina* was adequately demonstrated.

A publication was supplied in support of the addition of a treatment claim for *Thelazia callipaeda*. 55 client-owned dogs naturally infected with *T. callipaeda* were given a minimum dose of 0.5 mg/kg milbemycin oxime, with overall efficacy of the treatment noted as being 98.2%. These data in addition to the observed demonstrated efficacy of the active substance against other nematodes, and in line with similar pharmacokinetics seen with similar formulation provide sufficient data for the indication.

Field Trials

As this is a generic hybrid application submitted according to Article 13 (3) of Directive 2001/82/EC as amended, and due to the established use of the reference product and the supportive data included above, the results of field trials were not 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)