United Kingdom
Veterinary Medicines Directorate
Woodham Lane
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**NATIONAL PROCEDURE**

# PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

**Bravecto TriUNO Chewable Tablets for Dogs (1.27-2.5 kg)**
**Bravecto TriUNO Chewable Tablets for Dogs (>2.5-5.0 kg)**
**Bravecto TriUNO Chewable Tablets for Dogs (>5.0-10.0 kg)**
**Bravecto TriUNO Chewable Tablets for Dogs (>10-20 kg)**
**Bravecto TriUNO Chewable Tablets for Dogs (>20.0-40.0 kg)**
**Bravecto TriUNO Chewable Tablets for Dogs (>40.0-60.0 kg)**

**Date Created: April 2025**

# MODULE 1

## PRODUCT SUMMARY

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|---|---|
| Name, strength and pharmaceutical form | Bravecto TriUNO Chewable Tablets for Dogs (1.27-2.5 kg), Chewable tablet<br>Bravecto TriUNO Chewable Tablets for Dogs (>2.5-5.0 kg), Chewable tablet<br>Bravecto TriUNO Chewable Tablets for Dogs (>5.0-10.0 kg), Chewable tablet<br>Bravecto TriUNO Chewable Tablets for Dogs (>10-20 kg), Chewable tablet<br>Bravecto TriUNO Chewable Tablets for Dogs (>20.0-40.0 kg), Chewable tablet<br>Bravecto TriUNO Chewable Tablets for Dogs (>40.0-60.0 kg), Chewable tablet |
| Applicant | MSD Animal Health UK Limited, Walton Manor, Walton, Milton Keynes, Buckinghamshire, MK7 7AJ |
| Active substance | Fluralaner<br>Moxidectin<br>Pyrantel |
| ATC Vetcode | QP54AB52 |
| Target species | Dogs |
| Indication for use | For dogs with, or at risk from, mixed parasitic infestations by ticks or fleas, gastrointestinal nematodes, lungworm and/or heartworm. The veterinary medicinal product is exclusively indicated when use against ticks or fleas, one or more of the target gastrointestinal nematodes, and prevention of either heartworm or lungworm disease, are all indicated at the same time.<br><br>For the treatment of tick and flea infestations in dogs providing immediate and persistent flea (*Ctenocephalides felis* and *C. canis*) and tick (*Dermacentor reticulatus, Ixodes hexagonus*, I. *ricinus*, and *Rhipicephalus sanguineus*) killing activity for 1 month. |

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| | The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).<br><br>For reduction of the risk of infection with *Babesia canis canis* via transmission by *D. reticulatus* for 1 month. The effect is indirect due to the veterinary medicinal product's activity against the vector.<br><br>For reduction of the risk of infection with *Dipylidium caninum* via transmission by *C. felis* for 1 month. The effect is indirect due to the veterinary medicinal product's activity against the vector.<br><br>Treatment of infections with gastrointestinal nematodes of the following species: roundworms (adult stages of *Toxocara canis* and *Toxascaris leonina*), hookworms (L4, immature adult (L5) and adult stages of *Ancylostoma caninum* and adult stages of *Uncinaria stenocephala*).<br><br>Prevention of heartworm disease (caused by *Dirofilaria immitis*).<br><br>Prevention of angiostrongylosis (by reduction of the level of infection with immature adult (L5) and adult stages of *Angiostrongylus vasorum*). |

# MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

# MODULE 3

## PUBLIC ASSESSMENT REPORT

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|---|---|
| Legal basis of original application | Fixed combination application in accordance with Article 8 of Veterinary Medicine Regulations (VMRs) 2013 (Schedule 1, Para 8) as amended. |
| Date of conclusion of the procedure | 15/04/2025 |

## I. SCIENTIFIC OVERVIEW

These are fixed combination applications in Great Britain (GB) in accordance with Article 8 of Veterinary Medicine Regulations (VMRs) 2013 (Schedule 1, Para 8) as amended. The products contain active substances already used in an authorised veterinary medicine but in a new combination.

Bravecto TriUNO Chewable Tablets for Dogs contain fluralaner, pyrantel (as embonate), and moxidectin as the active substances. The dosage is 10-20 mg/kg of fluralaner, 0.025-0.05 mg/kg moxidectin and 5-10 mg/kg of pyrantel. In order to accommodate dogs between 1.27 and 60 kg, the product is manufactured at six different tablet sizes/strengths. The products are indicated for use in dogs with, or at risk from, mixed parasitic infestations by ticks or fleas, gastrointestinal nematodes, lungworm and/or heartworm. The veterinary medicinal product is only indicated when use against ticks or fleas and one or more of the other target parasites is indicated at the same time.

The distribution category for each product in GB is POM-V, a veterinary medicinal product subject to prescription.

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, any 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[2] 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.
[2] Efficacy – The production of a desired or intended result.

## II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

### *II.A. Composition*

The product contains fluralaner, pyrantel, and moxidectin and the excipients microcrystalline cellulose type 101, microcrystalline cellulose type 102, microcrystalline porous cellulose, croscarmellose sodium, pigment blend PB-565041 brown, sodium lauryl sulphate, hypromellose, purified water, butylated hydroxytoluene (E321), poloxamer 188, magnesium aluminometasilicate, light magnesium carbonate, anhydrous ethanol, pork liver flavour, colloidal anhydrous silica and magnesium stearate.

The container/closure system consists of aluminium foil blisters sealed with PET aluminium foil lid stock, in a cardboard box. The particulars of the containers and controls performed conform to the regulation.

The choice of the formulation and the presence of preservative are justified.

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

### *II.B. Description of the Manufacturing Method*

The product is manufactured fully in accordance with the principles of good manufacturing practice from licensed manufacturing sites. The manufacturing method consists of three phases; the preparation of fluralaner-pyrantel granules, the preparation of moxidectin granules, and finally combination of the two phases which is then compressed to form the final drug product.

The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches has been performed post-authorisation.

### *II.C. Control of Starting Materials*

The active substances are fluralaner, pyrantel, and moxidectin, which are established active substances. Moxidectin and pyrantel are supported by Certification of Suitability (CEP) certificates and fluralaner is supported by an Active Substance Master File (ASMF). The active substances are 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 choice of the excipients and their concentrations used in the formulation are appropriate. All excipients are common for the dosage form and the concentrations used are similar to those seen in other products with the same administration route. Those excipients that are compendial are appropriately controlled according to the corresponding monograph, with additional tests for desired characteristics where necessary. Pork liver flavour and pigment blend PB-565041 brown are non-compendial excipients. The same pork liver flavour has been approved for use in the UK for previous authorisations under the Bravecto trade name. Appropriate specifications for physical characteristics and desired quality attributes have been set.

Material specifications and declarations of compliance with EU material regulations were provided by the applicant.

### *II.C.4. Substances of Biological Origin*

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

## *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. 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 those appropriate for this pharmaceutical form.

## *II.F. Stability*

Stability data on the active substances have been provided in accordance with applicable regulatory guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable regulatory guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

## *G. Other Information*

The shelf life of the veterinary medicinal product as packaged for sale is 2 years. The product should not be stored above 30ºC.

# III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

Due to the legal basis of these applications the applicant provided information describing the pharmacology and toxicology of the active substances; fluralaner, moxidectin, and pyrantel.

## *III.A Safety Documentation*

### *Pharmacological Studies*

Bibliographical data has been provided describing the pharmacodynamic mode of action for each active ingredient:

*Fluralaner*
Fluralaner is an acaricide and insecticide. It is efficacious against ticks (*Dermacentor reticulatus, Ixodes hexagonus*, *I. ricinus* and *Rhipicephalus sanguineus*), and fleas (*Ctenocephalides canis* and *C. felis*) on dogs.

Fluralaner has a high potency against ticks and fleas by exposure via feeding, i.e., it is systemically active on target parasites. It is a potent inhibitor of parts of the arthropod nervous system by acting antagonistically on ligand-gated chloride channels (GABA-receptor and glutamate-receptor).

For fleas, the onset of efficacy is within 24 hours of attachment, for 30 days after the veterinary medicinal product's administration. Newly emerged fleas on a dog are killed before viable eggs are produced. An in-vitro study demonstrated that very low concentrations of fluralaner also stop the production of viable eggs by fleas.

Fluralaner reduces the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* by killing the ticks within 36 hours, before disease transmission occurs. Fluralaner reduces the risk of infection with *D. caninum* via transmission by *C. felis* by killing the fleas within 24 hours, before disease transmission occurs.

*Moxidectin*
Moxidectin, a semisynthetic derivative of nemadectin, belongs to the milbemycin group of macrocyclic lactones (avermectins being the other). Milbemycins and avermectins have a common mode of action that is based on the binding of ligand-gated chloride channels (glutamate-R and GABA-R). This leads to an increased membrane permeability of nematode and arthropod nerve and/or muscle cells for chloride ions and results in hyperpolarisation, paralysis and death of the parasites. Binding of glutamate-gated chloride channels, which are specific to invertebrates and do not exist in mammals, is considered the main mechanism for the anthelmintic and insecticidal activity. Moxidectin has parasiticidal activity against a range of internal and external parasites including nematodes (*Toxocara canis, Toxascaris leonina, Ancylostoma caninum* and *Uncinaria stenocephala*),

lungworm (*Angiostrongylus vasorum*) and heartworm (*Dirofilaria immitis*). Moxidectin lacks substantial efficacy against fleas and ticks.

*Pyrantel*
Pyrantel belongs to the class of tetrahydropyrimidines and targets nicotinic acetylcholine channel receptors (nAChRs). Selectivity of pyrantel for invertebrate nAChRs is based on high-affinity binding to specific nematode receptor subtypes and a subsequent agonistic mode of action leading to a depolarizing neuromuscular block, which causes muscle contraction, paralysis, and subsequently death of the parasites. Pyrantel lacks activity against muscarinic mAChRs. Pyrantel is an anthelmintic with parasiticidal activity against gastrointestinal parasites (including *T. canis, T. leonina, A. caninum* and *U. stenocephala*).

The applicant has also provided bibliographical data which show the main pharmacokinetic features of each of the active ingredients:

*Fluralaner*
Fluralaner is readily and rapidly absorbed systemically following oral dosing, reaching mean maximum concentrations in plasma within 17.7 hours (Tmax) after administration. Fluralaner is slowly eliminated from plasma (half-life of approximately 12 days) via biliary excretion and elimination through the faeces. A fed state of the dog increases the extent of absorption of fluralaner.

*Moxidectin*
Moxidectin is readily and rapidly absorbed systemically following oral dosing, reaching mean maximum concentrations in plasma within 3 hours (Tmax) after administration. Moxidectin is slowly eliminated from plasma (half-life of approximately 16 days) via biliary excretion and elimination through the faeces.

*Pyrantel*
Pyrantel is poorly absorbed, and the absorbed portion has a Tmax of 1.5 hours and half-life of 6 hours. Pyrantel is eliminated through faeces and the small, absorbed portion is eliminated mainly via urine.

The pharmacokinetic profiles of fluralaner, moxidectin and pyrantel are not affected by co-administration.

### *Toxicological Studies*

The applicant has provided data which show the following for each active substance:

*Fluralaner*

- Single Dose Toxicity:
  - The $LD_{50}$ of fluralaner after single oral treatment in rats is >2000 mg/kg.
- Repeated Dose Toxicity
  - The oral no observable adverse effect level (NOAEL) in 4-week study in rats was the highest dose level tested of 600 mg/kg/day.
  - The oral NOAEL in a 13-week study in rats was the highest dose level tested of 400 mg/kg/day.
  - The oral no observable effect level (NOEL) in a 52-week study in dogs was 1 mg/kg/day.
- Reproductive Toxicity:
  - The oral NOEL for reproduction and development in rats is 50 mg/kg/day.

*Moxidectin*

- Single Dose Toxicity:
  - The oral $LD_{50}$ in mice is 84 mg/kg.
  - The oral $LD_{50}$ in rats is 106 mg/kg.
- Repeated Dose Toxicity
  - The oral NOEL in mice in a 4-week study was 6.9 mg/kg/day.
  - The oral NOEL in rats in a 13-week study was 3.9 mg/kg/day.
  - The oral NOEL in dogs in a 4-week study was 0.5 mg/kg/day.
  - The oral NOEL in dogs in a 13-week study was 0.3 mg/kg/day.
  - The oral NOEL in dogs in a 52-week study was 1.15 mg/kg/day.
- Reproductive Toxicity:
  - The oral NOEL for reproduction in rats is 0.41 mg/kg/day.

*Pyrantel Embonate*

- Single Dose Toxicity:
  - The oral $LD_{50}$ in mice is >2000 mg/kg, i.e. not toxic.
  - The oral $LD_{50}$ in rats is >2000 mg/kg, i.e. not toxic
  - The oral $LD_{50}$ in dogs is >2000 mg/kg, i.e. not toxic
- Repeated Dose Toxicity:
  - The oral lowest observable adverse effect level (LOAEL) in the rat in a 13-week study was 35 mg/kg/day.
  - The oral NOEL in the dog in a 13-week study was 35 mg/kg/day.
- Reproductive Toxicity:
  - The oral NOEL for reproduction in rats is 30 mg/kg/day (study for pyrantel tartrate, whose bioavailability is expected to be higher than that of the embonate salt).

None of the active substances are considered to be genotoxic or carcinogenic.

### *Studies of Other Effects*

The applicant has provided bibliographical data which show that the product could be potentially irritating to the skin and eyes and that pyrantel embonate is potentially sensitizing. Appropriate information regarding this appears in the product literature.

### *Observations in Humans*

Bibliographical information was provided which show that:

- Fluralaner has been developed exclusively for veterinary use.
- Moxidectin was approved by the US Food and Drug Administration (FDA) in 2018 for the treatment of onchocerciasis (river blindness).
- Pyrantel has been used in human medicine for more than 40 years.

The absorption of pyrantel is considered relatively low in humans when administered orally, and the receptors for each active substance are largely specific to invertebrates and not exhibited as strongly in mammals.

### *User Safety*

A user risk assessment was provided in compliance with the relevant guideline which shows that the product is not expected to pose an unacceptable risk to the user, if used as directed.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

- Accidental ingestion of a tablet by a child may cause symptoms such as headache or nausea.
- Keep tablets in the original packaging until use in order to prevent children from getting access to the product and ensure that if the tablet is administered via the dog's feed, that it is fully consumed.
- In case of accidental ingestion by a child, seek medical advice immediately and show the package leaflet or the label to the physician.
- The product may cause skin or eye irritation.
- Should skin or eye irritation occur, rinse the affected area with water. If irritation persists, seek medical advice.
- Pyrantel may cause hypersensitivity reactions. People with sensitivity to pyrantel should avoid contact with the product. If symptoms such as a skin rash occur, seek medical advice.
- Do not eat, drink, or smoke while handling the product.
- Wash hands after use.

### *Environmental Safety*

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

**Phase I:**
The product will only be used in non-food animals and as a result environmental exposure will be low. A Phase II ERA was not required.

Appropriate environmental safety warnings are listed in the production literature. The products are not expected to pose an unacceptable risk to the environment if used as directed.

## IV. CLINICAL DOCUMENTATION

The applicant has provided bibliographical data to show the pharmacodynamics of the active substances in the products and completed studies to evaluate the pharmacokinetics of the products.

### *IV.I. Pre-Clinical Studies*

### *Pharmacology*

The applicant has provided bibliographical data describing the pharmacodynamic properties of the active substances. Fluralaner is a potent inhibitor of arthropod GABA and GluCl receptors, acting predominantly by exposure through ingestion by fleas and ticks. Conversely, moxidectin is a positive modulator of these receptors, whereas pyrantel acts via a distinct signalling pathway.

The applicant has conducted four studies to evaluate the pharmacokinetic properties of the products. This included one pivotal pharmacokinetic study and one pivotal target animal safety study.

The pivotal GLP-compliant pharmacokinetic study investigated single administrations of the products, relative to comparative single-substance products, and to intravenous fluralaner and moxidectin, in dogs. Three doses of the products were evaluated, corresponding to 0.5x, 1x and 2x the maximum recommended dose. The single-substance products were administered at the maximum recommended dose. The intravenous doses of fluralaner and moxidectin were 0.25x and 10x the maximum recommended doses, respectively. Systemic exposure to each active substance was detected at all oral doses investigated, following administration of either single-substance or fixed combination formulations. Based on the AUC and $C_{max}$ ratios, it was concluded that there were no major differences in systemic exposure between the fixed combination and the respective single-substance formulations.

In the pivotal GLP-compliant target animal safety study, 8-week-old dogs were orally administered the products seven times, at monthly intervals. The study provided data on the accumulation of the active substances, following consecutive monthly administrations of the products at 1x, 3x and 5x the maximum recommended dose. The results concluded that, following six consecutive monthly administrations of the products at the maximum recommended dose (1x), accumulation of fluralaner was observed up to and including the $6^{th}$ monthly administration. Additionally, moxidectin accumulated up to, and including, the $5^{th}$ monthly administration, when steady state was observed. Pyrantel does not accumulate at the maximum recommended dose, when applying a monthly treatment interval.

### *Tolerance in the Target Species*

The applicant has conducted four controlled target animal tolerance studies using multiples of the recommended dose of the products in the target species and a fluralaner only product.

The pivotal controlled, long term safety study administered 1x, 3x, and 5x the proposed dose of the final formulation to 32 Beagle puppies. The results support the safety of the proposed product at the maximum dose over a 6-month period. Toxicokinetic evaluations showed that the study was sufficiently long for steady state to have been achieved and that a margin of safety was supported

The applicant also submitted additional supporting data, including peer reviewed publications, concerning the margin of safety of moxidectin in ivermectin-sensitive Collies. Overall, the data supplied are taken to be supportive of the safety of the proposed maximal doses of fluralaner, moxidectin, and pyrantel.
The product literature accurately reflects the type and incidence of adverse effects which might be expected.

### *Resistance*

The applicant provided studies and submitted a review to detail the potential for resistance of the active substances. The studies collectively support the potential for resistance development in several of the target parasites proposed for the products and against the commonly used antiparasitic substances in veterinary medicine.

No reports of resistance to fluralaner were identified and this substance has showed continued effectiveness even in the presence of resistance to other active substances (e.g. fipronil or ivermectin).

Resistance to moxidectin was reported in the US for *Dirofilaria immitis*, however, this active remains the optimal active substance available for the prevention of this disease and resistance levels are lower than for other active substances available.

For gastrointestinal nematode infections, pyrantel is shown to be effective and well-established for the indications proposed by the applicant.

The relevant product SPCs reflect the guidance to ensure prudent use of this fixed combination product.

## *IV.II. Clinical Documentation*

### *Laboratory Trials*

The applicant has conducted dose determination and confirmation studies to demonstrate efficacy at the recommended dosage for the product's indications in the target species.

### *Dose confirmation studies:*

***Ticks***
The applicant provided a review of previous studies to demonstrate that *Rhipicephalus sanguineus* can be considered as the relevant dose-limiting tick species of those targeted by the products.

The applicant submitted two GCP-compliant studies that demonstrated suitable efficacy against *R. sanguineus*.

Both studies administered target dosages of 10 mg fluralaner/kg + 0.025 mg moxidectin/kg + 5.0 mg pyrantel/kg to 30 puppies. The trials were randomised and controlled with one group remaining untreated. The studies concluded that the product was safe and, at day 31, following a single oral treatment, one study showed 100% reduction in live ticks and the second 99.3% reduction.

***Fleas***
Based on data submitted by the applicant, it was concluded that 24 hours post-treatment, or 24 hours after weekly reinfestations for up to 7 weeks, insecticidal efficacy of the products is consistently ≥95%.

One study submitted, administered 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0 mg/kg pyrantel orally to 30 puppies. The objective was to confirm the prevention of infestation of *C. felis* in puppies for at least 30 days following a single treatment. The study was GCP-compliant and controlled, with one group remaining untreated. The primary efficacy criterion was live flea count, and the products demonstrated at least 99.8% insecticidal efficacy at 24 hours post-treatment and/or serial re-infestation, for up to 30 days post-treatment.

***Gastrointestinal Nematodes***
<u>*Ancylostoma caninum* (adults)</u>
In two, GCP-compliant studies, submitted by the applicant, the products demonstrated 99.3% efficacy and 100% efficacy against adult *A. caninum.* The products were given at the target dose of 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0 mg/kg pyrantel.

<u>*Ancylostoma caninum* (L4 & L5 larvae)</u>
In relation to the L4 larval stage of *A. caninum*, three studies submitted by the applicant show that the products demonstrated 93.1%, 99.9%, and 97.9% efficacy, at the target dose of 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0

mg/kg pyrantel. These three canine studies were all GCP-compliant, randomised and controlled.

In relation to the immature adult (L5) larval stage of *A. caninum*, the same studies demonstrated 98.3%, 100%, and 97.9% efficacy, at the target dose of 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0 mg/kg pyrantel.

*Toxocara canis* (adults)
The applicant submitted two studies that showed the products demonstrated 92.6% and 97.49% efficacy against adult *T. canis* at the target dose of 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0 mg/kg pyrantel. Both studies were GCP-compliant, randomised and controlled.

*Toxascaris leonina* (adults)
The applicant provided sufficient data to support the efficacy of the products against adult *T. leonina* at the target dose of 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0 mg/kg pyrantel. A GCP-compliant study included 30 dogs and was randomised and blinded. It compared the treatment group to a negative control group with the primary criterion for the effectiveness being the number of worms recovered at the end of the study. The study demonstrated 99.4% efficacy.

*Uncinaria stenocephala* (adults)
In two studies submitted by the applicant, the products demonstrated 99.8% and 100% efficacy against adult *U. stenocephala* at the target dose of 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0 mg/kg pyrantel. Both GCP-compliant, controlled studies were performed on dogs. The assessment criterion was recording a reduction of worm burden in the treated group at the end of the study.

***Heartworm***
*Dirofilaria immitis*
The applicant submitted two dose confirmation studies for *D. immitis* efficacy. The products demonstrated 96.6%, 99.0% and 100% efficacy in the first study after one, two and three consecutive monthly doses, respectively, and 100% efficacy in the second after a single dose. In both GCP-compliant studies, the target dose of 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0 mg/kg pyrantel was administered to dogs. In the studies the products were compared to an untreated control.

***Lungworm***
*Angiostrongylus vasorum*
The applicant submitted two studies for dose confirmation against *A. vasorum.* The products demonstrated 99.98% and 99% efficacy in these studies at the target dose of 10 mg/kg fluralaner + 0.025 mg/kg moxidectin + 5.0 mg/kg pyrantel. Both studies were GCP-compliant, negatively controlled and performed in dogs.

## *Field Trials*

Nine clinical field trials were submitted in support of clinical documentation. Three of these were considered as pivotal trials and were randomised, controlled, blinded, and GCP-compliant studies. Two were performed in the EU (and Albania), and the third was conducted in the United States, in accordance with Committee for Veterinary Medicinal Products (CVMP) Scientific Advice.

***Fleas and Ticks***
The pivotal flea and tick field trial was conducted in the European Union, across various geographical zones and climactic regions (Germany, France, Portugal and Spain) in accordance with EMEA/CVMP/EWP/005/20000-Rev4*.

The species, breeds, sex and neuter status of the animals included were considered to be homogeneous between treatment groups and representative of the target population.

Pre-treatment manual flea and tick counts were performed, indicating adequate pre-treatment infestation and tick species identification was provided.

Efficacy calculations were based on manual live flea and tick counts performed at set intervals pre- and post-treatment. Efficacy assessments indicate >98% efficacy against ticks and >97% against fleas. A non-inferiority assessment was performed in the pivotal EU flea and tick study.

***Nematodes***
The pivotal gastrointestinal nematode field trial was conducted in Albania, Bulgaria, Greece and Italy. The nematode species identified in pre-treatment faecal analysis represent those species of clinical importance/risk to the canine population in GB.

The species, breeds, sex and neuter status of the animals were considered to be homogenous between treatment groups and representative of the target population. Faecal egg counts (FECs) were performed, at set intervals pre- and post-treatment.

In this study, primary efficacy assessments indicate >99% efficacy when calculated based on the percentage reduction in FECs from pre-treatment.

***Heartworm***
The pivotal clinical trial to support heartworm prevention was performed in the USA, with the applicant demonstrating how USA generated data is relevant to Europe. However, given the overall low prevalence of *D. immitis*, the results were considered supportive and interpreted in conjunction with the data submitted for dose determination and dose confirmation.

Animals included in this study were treated once a month with either the products or a control product for 11 consecutive months. At visits 1, 5, 7, 9, and 12, all animals were tested for heartworm using antigen and microfilaria testing. Blood and urine samples were collected for clinical pathology testing at visits 1, 7 and 12. Primary efficacy calculations were based on the number and percent of animals positive for heartworm on antigen and microfilaria tests on day 330 (± 2 days).

None of the animals treated with the products were positive for heartworm on day 330 (± 2 days).

***Lungworm***
In accordance with CVMP scientific advice a field study for the indication “prevention of angiostrongylosis” was not required due to very low incidences of *A. vasorum.* As two studies for dose confirmation were submitted this is acceptable.

## 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 of the products is favourable.

# 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)