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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Simparica Trio (EMEA/V/C/004846, EMA/VRA/0000221746)

INN: Sarolaner / Moxidectin / Pyrantel embonate

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Zoetis Belgium (the applicant), submitted to the European Medicines Agency (the Agency) on 27 June 2024 an application for a variation requiring assessment for Simparica Trio.

1.2. Scope of the variation

Variation requested	
G.I.7.a	Addition of a new therapeutic indication or modification of an approved one.

To add a new therapeutic indication for the treatment of the lungworm *Angiostrongylus vasorum* and to amend the contact details to report suspected adverse events provided in the package leaflet.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1, Part 4

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

Simparica Trio is currently authorised for use in dogs with, or at risk from, mixed external and internal parasitic infestations. The veterinary medicinal product is exclusively indicated when use against ticks, fleas or mites and gastrointestinal nematodes is indicated at the same time. The VMP provides concurrent efficacy for the prevention of angiostrongylosis, heartworm disease and thelaziosis. The proposed variation is to add a new therapeutic indication for the treatment of angiostrongylosis (by killing adult *Angiostrongylus vasorum*). Additionally, the applicant has proposed an amendment to the contact details provided in the package leaflet.

Simparica Trio is a fixed-combination product containing the active substances sarolaner, moxidectin and pyrantel (as pyrantel embonate) and is presented as a chewable tablet with six different strengths available. The recommended minimum treatment dose is 1.2 mg sarolaner/kg, 0.024 mg moxidectin/kg and 5 mg pyrantel/kg bodyweight, to be administered orally. The currently authorised dose rate is also proposed for the new indication.

Angiostrongylosis (lungworm), caused by the nematode *Angiostrongylus vasorum,* is an important clinical disease in dogs in Europe. *A. vasorum* is most prevalent in Central and Northern Europe, having a variable distribution with hyperendemic foci surrounded by lower prevalence areas. The distribution is mainly linked to wildlife presence, as red foxes and other wild canids act as a natural reservoir of canine lungworm. Wild canids do not develop protective immunity following *A. vasorum*

infection and may act as a continuous source of environmental contamination. Next to wild canids, the relevance of sub-clinically infected dogs in the spread of infection has been highlighted. Dogs travelling to endemic areas may also introduce the parasite in "free" areas upon their return. Immuno-diagnosis of parasite antigen and specific antibodies indicate prevalence rates consistently between 0.5% - 3% in canine populations in Europe.

To support the proposed additional treatment claim, one laboratory dose confirmation study and one clinical trial were conducted. Both studies were conducted within the European Union using the commercial formulation of Simparica Trio, and in accordance with VICH GCP standards.

The laboratory dose confirmation study was conducted in Ireland and involved dogs with induced infections of *A. vasorum*. The study was performed in accordance with the requirements provided in the VICH GL19: Efficacy of anthelmintics: Specific recommendations for canines (EMA/CVMP/VICH/835/1999), although it is noted that EMA and VICH guidance do not provide recommendations specific for *A. vasorum*. However, it is stated that efficacy of such veterinary medicinal products should be at least 90% when calculated and interpreted using the procedure described in Section 4.2 of VICH GL7.

Twenty-three laboratory Beagles were included in this study. Sixty-three days or more prior to treatment, test animals were inoculated orally with infective L3 larvae of *A. vasorum*. An adequate infection with the target parasite was confirmed by positive faecal examination for *A. vasorum* larvae on Days -4, -3 or -2. All dogs receiving treatment with IVP or placebo at Day 0 met the inclusion criteria. The primary efficacy variable was adult worm counts after necropsy, which was calculated as the sum of the whole male and female counts and the fragment counts. The secondary efficacy variables included post-treatment faecal and lung larval counts, percentage of consolidated lung area, and lung lesion severity scores.

Primary efficacy results, based on adult worm counts, showed a reduction in geometric mean counts compared to the placebo-treated group of 98.3% in T02 with a single dose of IVP, and 99.6% in T03 with two doses of IVP. The adult worm counts were significantly lower in both T02 ($P < 0.0001$) and T03 ($P < 0.0001$) than in the placebo-treated group. The geometric mean adult worm counts in T03 were significantly lower compared to T02 ($P = 0.0466$). Arithmetic mean adult worm count was 164.0 in T01, 6.3 in T02 and 1.1 in T03. The percentage reduction in arithmetic mean adult worm count compared to the placebo-treated group was 96.2% in T02 with a single dose of IVP and 99.3% in T03 with two doses of IVP.

With regards to the secondary efficacy variables, the reduction in geometric mean faecal larvae counts compared to the placebo-treated group was >90% in both T02 and T03 from Week 3 until the end of the study, with 100.0% in T02 in Weeks 5 and 6 and 99.5% in Week 8 and 100% reduction in T03 for Weeks 5, 6 and 8. Geometric mean lung larvae counts were 27050.6, 1.43, and 0.00 in the placebo, T02 and T03 groups respectively. The percentage reduction in geometric mean lung larvae counts compared to the placebo group was 100.0% for both T02 and T03.

Mean percent lung consolidation was 56.3% in the placebo-treated group, 12.9% in T02 and 15.4% in T03. Mean sum of lung lesion severity scores was 15.9 in the placebo-treated group, 4.9 in T02 and 3.5 in T03.

The GCP compliant clinical trial, conducted in client-owned dogs in Denmark and Italy, was performed in accordance with VICH GL7 and GL19. The study was conducted to evaluate the safety and efficacy of Simparica Trio as a monthly treatment for up to two months in the treatment of patent infections with *Angiostrongylus vasorum* in dogs presented as veterinary patients in these endemic regions.

103 (53 female, 50 male) client-owned dogs were allocated randomly to one of two treatment groups; IVP (Simparica Trio; T01; n=66) or positive control product (Advocate Spot On T02; n=37). Dogs were confirmed to be positive for *A. vasorum* larvae in faecal samples tested by the Baermann method prior to enrolment. A number of test animals presented with clinical signs consistent with angiostrongylosis. Treatments were administered on Day 0 (Visit 1) and again on Day 30 (Visit 2) if the dog was positive for *A. vasorum* larvae at that timepoint. Dogs that were found to be negative at Day 30 (Visit 2) completed the study at that timepoint. Prior to each study visit, three faecal samples were collected and tested at a central laboratory for the presence of *A. vasorum* larvae using the Baermann method.

The enrolled dogs represented various breeds, with a broad range of ages and bodyweights included in the study population.

The primary efficacy variable was assessed as the percent reduction in faecal larvae counts at Day 30 compared to baseline (percent efficacy). Non-inferiority of Simparica Trio compared to Advocate Spot On was assessed. The rate of treatment successes (as defined by a reduction of baseline faecal larvae counts by ≥90%) was also determined, at Day 30 and Day 60. Non-inferiority of Simparica Trio compared to Advocate Spot On was also assessed for this criterion at each time point.

Non-inferiority of Simparica Trio compared to Advocate Spot On (positive control) was assessed for the primary efficacy criterion. However, due to four dogs (2 IVP, 2 control) showing a significant increase in faecal larvae counts between Day 0 and Day 30, no meaningful results could be presented. Faecal larvae counts were nonetheless reduced by ninety percent or more in 90.9% of dogs in the Simparica Trio-treated group at Day 30 (Visit 2) and 98.5% of dogs at Day 60 (Visit 3), compared to the Advocate Spot On-treated group where 91.9% of the dogs met the success criteria at Day 30 and 97.3% at Day 60. Based on this endpoint, the study successfully met the non-inferiority criteria at both Day 30 and Day 60; the lower bound of the confidence interval for the difference in success rates was -0.006 and 0.012, respectively. Given that the observed rise in faecal larval counts between Day 0 and Day 30 affected an equal number of animals in both groups, the applicant's rationale in using an alternative approach to demonstrate non-inferiority for Simparica Trio can in this case be accepted.

Compared to pre-treatment group mean faecal larvae counts, oral administration of Simparica Trio resulted in a geometric mean percent reduction of 96.7% on Day 30 and 99.1% on Day 60 while the Advocate Spot On treatment had a 96.9% reduction on Day 30 and an 85.6% reduction on Day 60.

With regard to safety, the IVP appears to have been generally well-tolerated by dogs across both studies. The majority of adverse clinical signs observed can be attributed to clinical manifestations of angiostrongylosis or pre-existing medical issues. One animal in the laboratory dose confirmation study was observed to have experienced significant (>10%) weight loss between day -2 pre-treatment and day 27 post-treatment, which was considered most likely a result of parasite burden; no definitive relationship with treatment administration was demonstrated. The product information literature pertaining to safe use in the target species is considered to be adequate in its current state, with SPC section 3.3 containing a contraindication against use in animals with hypersensitivity to the active substances or any of the excipients, and the other observations (e.g. vomiting, lethargy) which were considered to be treatment-related included in the table in SPC section 3.6. However, it is noted that a potential case of hypersensitivity reaction to the test product (DO05) was identified during the clinical trial. The applicant has acknowledged that the observations in this dog are suggestive of a delayed-type hypersensitivity reaction based on the temporal relationship with administration of Simparica Trio (signs were observed from 8 days after the first administration and 1 day after the second one). The pharmacovigilance data obtained by the applicant from the EMA DWH would suggest that hypersensitivity reactions have been only extremely rarely reported for Simparica Trio. However, in future, the MAH is expected to implement a signal detection methodology that includes the relevant appropriate VeDDRA terms (e.g., including but not limited to "anaphylaxis") to enhance identification

of cases of hypersensitivity reactions and indicate whether a causal relationship with the product is present in these cases. Nonetheless, the CVMP can accept that at present it is not necessary to include hypersensitivity reactions as a possible adverse event in section 3.6 of the SPC based on available data.

It is noted that the applicant has conducted only one GLP-compliant dose confirmation study, whereas VICH GL7 recommends a minimum of 2 such studies should be provided. However, considering the totality of evidence derived from the results of the single dose confirmation study and clinical trial provided, the CVMP can accept that Simparica Trio is efficacious when used in dogs for the treatment of *Angiostrongylus vasorum*. Non-inferiority for Simparica Trio has been satisfactorily demonstrated against the centrally authorised VMP Advocate Spot-On, which is approved for use in the treatment of angiostrongylosis in the target species. Furthermore, based on the clinical trial data provided, Simparica Trio has been shown to be efficacious for the proposed indication in endemic regions within the European Union. According to VICH GL19, dose confirmation studies should be conducted using naturally or artificially infected animals. Where possible, at least one study should be conducted in naturally infected animals – this criterion has been fulfilled by the accompanying clinical trial. The *A. vasorum* strain used in the laboratory dose confirmation study originated from faecal samples collected in Switzerland in 2019.

The recommended dose rate for Simparica Trio will remain unchanged as a result of this variation, and appropriate guidance is given in relation to treatment of *A. vasorum* (including the need for re-examination and potentially a second administration after 30 days) in the proposed SPC. Section 3.9 contains the following advice, which the CVMP considers appropriate:

"*Treatment of angiostrongylosis (caused by Angiostrongylus vasorum):*

A single dose should be administered. A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment."

With this variation, the applicant is also implementing changes to the list of contact details to report suspected adverse events in section 16 of the package leaflet. This is considered acceptable.

3. Benefit-risk assessment of the proposed change

This product is authorised for the treatment of tick (*Ixodes hexagonus, Ixodes ricinus, Rhipicephalus sanguineus* and *Dermacentor reticulatus*) and flea (*Ctenocephalides felis* and *Ctenocephalides canis*) infestations, for the treatment of sarcoptic mange (*Sarcoptes scabiei* var. *canis)* and demodicosis (*Demodex canis*), for the treatment of gastrointestinal roundworm and hookworm infections (*Toxocara canis, Ancylostoma caninum, Toxascaris leonina* and *Uncinaria stenocephala*) and for the prevention of heartworm disease (*Dirofilaria immitis),* angiostrongylosis (*Angiostrongylus vasorum*) and thelaziosis (*Thelazia callipaeda*). The product can also be used as part of a treatment strategy for the control of flea allergy dermatitis in dogs.

The active substances are sarolaner (an acaricide and insecticide belonging to the isoxazoline family), moxidectin (a second-generation macrocyclic lactone of the milbemycin family) and pyrantel (a nicotinic acetylcholine channel receptor agonist). Simparica Trio is presented as chewable tablets of different strengths, which are administered to dogs at a dose of 1.2–2.4 mg/kg of sarolaner, 0.024–0.048 mg/kg of moxidectin and 5–10 mg/kg of pyrantel.

The proposed variation is to add a new therapeutic indication for the treatment of the lungworm *Angiostrongylus vasorum* and to amend the contact details to report suspected adverse events provided in the package leaflet.

3.1. Benefit assessment

Direct therapeutic benefit

The proposed benefit of Simparica Trio is its efficacy in the treatment of angiostrongylosis (*Angiostrongylus vasorum*) in dogs, which was established in a laboratory dose confirmation study and a clinical trial conducted in Europe to GCP standard.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety for the user, environment and target animal remains unaffected by this variation.

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Administration of Simparica Trio in accordance with SPC recommendations is generally well tolerated.

Risk for the user:

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment:

Simparica Trio is not expected to pose a risk for the environment when used according to the SPC recommendations. The veterinary medicinal product should not enter water courses as this may be dangerous for fish and other aquatic organisms.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, the user, and the environment and to provide advice on how to prevent or reduce these risks.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, target animal safety, efficacy.

The product has been shown to be efficacious for the treatment of angiostrongylosis in dogs.

The product is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended.

Appropriate precautionary measures have been included in the SPC and other product information.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Simparica Trio can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: to add a new therapeutic indication for the treatment of angiostrongylosis (*Angiostrongylus vasorum*) and to amend the contact details to report suspected adverse events provided in the package leaflet.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above-mentioned medicinal product.

Changes are required in the following Annexes to the Community marketing authorisation:

I and IIIB.

As a consequence of this variation, sections 3.2, 3.9 and 4.2 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly. Additionally, section 16 of the package leaflet has been updated to amend the contact details to report suspected adverse events.