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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/0000240712)

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 28 November 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

The variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment.

In addition, the applicant has updated the contact details to report suspected adverse reactions for Iceland 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 product provides concurrent efficacy for the prevention and treatment of angiostrongylosis, and the prevention of heartworm disease and thelaziosis. The proposed variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment. Additionally, the applicant has proposed an amendment to the contact details to report suspected adverse reactions for Iceland 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 of tablet 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 reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis*.

Dipylidiasis is caused by the heteroxenous cestode *Dipylidium caninum* through ingestion of the intermediate host (fleas) by the definitive host (carnivores). *D. caninum* is also a zoonotic pathogen, although human infections are rare. Children seem the most vulnerable due to their playing habits and close proximity to pets.

To support the proposed change, two laboratory dose confirmation studies were conducted. These studies were conducted outside the European Union (USA and South Africa respectively) using the commercial formulation of Simparica Trio, in accordance with VICH GCP standards. While not performed within the EU, the studies were largely designed taking into account the relevant CVMP and VICH guidelines for efficacy of ectoparasiticides, anthelmintics, and data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats. Regarding compliance of these laboratory studies with Directive 2010/63/EU, the use of individual housing was accepted based on the need to prevent cross-infection between dogs. In both studies, each dog was provided with appropriate enrichment items and, while physical contact was not possible, there was visual and auditory stimuli from other dogs. However, no information on cage dimensions was available in the study reports.

The first laboratory dose confirmation study was conducted in the US, using US strains of *C. felis* and *D. caninum*. The study was performed in accordance with the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015) and the requirements provided in the VICH GL19: Efficacy of anthelmintics: specific recommendations for canines (EMA/CVMP/VICH/835/1999).

Twenty laboratory Beagles were included in this study, with a range of ages and bodyweights included in the population. Prior to treatment, test animals were confirmed to be *D. caninum* negative based on PCR analysis of faecal samples collected at Day -9. All dogs included in the study were also assessed for the ability to carry an adequate burden of *C. felis*, with a trial infestation with 100 uninfected, viable adult fleas being carried out on Day -8 followed by counting and removal on Day -7. The primary efficacy variable was *D. caninum* scolex counts at necropsy (performed on Day 58). The secondary efficacy variable was the flea count conducted on each animal on study day 33 (72 ±2 hours post-infestation on Day 30).

Dogs were allocated, based on pre-treatment flea counts, to either the placebo control group (T01, n=10) which received chewable tablets containing palatable vitamin-mineral supplements for dogs or the Simparica Trio treated group (T02, n=10) which received the minimum dosage 1.2 mg/kg sarolaner, 24 µg/kg moxidectin, and 5 mg/kg pyrantel (as embonate salt). Treatments for both groups were administered orally once on Day 0. Dogs were assessed for general health at least once daily and clinical observations were conducted prior to treatment and at 1, 3, 6, and 24 hours after treatment.

All dogs were infested with 200 (±5) adult *C. felis* (infected with *D. caninum*) after treatment on Day 0 and on Days 7, 14, 21, and 30. Flea counts (with removal) were conducted 72 hours after the last infestation, on Day 33. Flea efficacy was calculated based on the reduction of arithmetic means between the Simparica Trio-treated group and the control group. Dogs were allowed to engage in normal grooming behaviour throughout the course of study to mimic the natural infection method of *D. caninum*.

The second dose confirmation study followed an identical study design, with the following exceptions:

- The twenty dogs used in the study included 14 mixed-breed "mongrels", with the remaining 6 animals being purebred Beagles.
- The initial "trial" C. felis infestation on Day -8 used 200 viable, unfed adult fleas.

- The strain of D. caninum used was of EU origin (collected from cats in Thessaloniki, Greece in 2019).

While it is noted that the strains of both C. felis and D. caninum used in the first dose confirmation study were of US origin, the applicant's justification that the results obtained are also applicable to the EU can be accepted. Uniform susceptibility of C. felis to sarolaner between the EU and US was demonstrated in the original marketing authorisation application (MAA) of Simparica Trio (EPAR EMA/413747/2019), where the results of both the EU and US dose confirmation studies (using local strains in each case) showed very high immediate and persistent efficacy (≥99% efficacy). The high efficacy of Simparica Trio against fleas was further confirmed in an EU clinical trial. Although a US strain of D. caninum was used in this first dose confirmation study, no differences for EU strains are anticipated as it has been shown that the distinct genotypes of the D. caninum population are related to host origin (dogs or cats), irrespective of their geographical origin (Labuschagne et al. 2018). Moreover, the effect of Simparica Trio (sarolaner) is against the flea and not the tapeworm, which renders the specific strain of D. caninum of lesser importance for the "reduction" claim sought for the VMP. The strain of D. caninum used in the second dose confirmation study was of EU (Greek) origin. This lends support to the anticipated efficacy for reduction of infection risk when Simparica Trio is administered to dogs in European field conditions. However, as mentioned previously, the specific strain of D. caninum is of lesser importance for the "reduction" claim sought for the VMP.

Primary efficacy results, based on D. caninum scolex counts, showed a reduction in geometric mean counts for Simparica Trio compared to placebo-treated animals in both dose confirmation studies. Reductions of 92.1 and 100% in D. caninum scolex counts were reported in the South African and US studies respectively, that is, above the efficacy threshold of ≥90% recommended by the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015). Adequacy of D. caninum infection in accordance with VICH GL19 Efficacy of anthelmintics: specific recommendations for canines (EMA/CVMP/VICH/835/1999) was also demonstrated in both studies. 90.0% and 88.9% of control group dogs in the US and South African studies, respectively, had ≥2 adult D. caninum scoleces at the time of necropsy, compared with 0.0% and 20% in the corresponding Simparica Trio-treated groups in each case.

With regards to the secondary efficacy variable, the reduction in flea counts at Day 33 compared to the placebo-treated group was 100% for Simparica Trio-treated groups in both studies, following multiple infestations. The non-treated control groups maintained high mean flea counts following multiple infestations, with least squares means of 67.0 and 94.7 in the US and South African studies, respectively. Adequacy of flea infestation was demonstrated on the basis that >70.0% of control animals in each study maintained ≥50 fleas following the final flea infestation on Day 30.

In relation to target animal safety, the IVP appears to have been generally well-tolerated by dogs across both studies. The only adverse clinical signs observed following administration of Simparica Trio consisted of mild diarrhoea in one dog on Day 0 in the South African study. While the applicant did not consider this episode to be treatment-related, and no concomitant treatments were required, it is noted that "diarrhoea" is already captured as a possible adverse reaction in the approved SPC. The product information literature pertaining to safe use in the target species is therefore considered to be adequate in its current state.

It is noted that the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015) stipulates that at least one laboratory study and one clinical trial is needed for each claimed vector-borne pathogen, unless otherwise justified. However, it is accepted that a high level of efficacy against C. felis (and consequently transmission of D. caninum) was

demonstrated in the presented laboratory dose confirmation studies conducted in two different locations using different flea and tapeworm strains.

Additionally, it is noted that proglottid shedding from D. caninum infected dogs can be variable and inconsistent, and that faecal flotation significantly underestimates prevalence compared to necropsy. Given that terminal procedures are not possible under field conditions, and that results presented using other diagnostic methods often preclude accurate conclusions from being drawn, the CVMP can accept that the approach taken by the applicant is appropriate in the context of D. caninum.

The D. caninum infection rate (6.7 to 36.7%) in the study fleas is also much higher than the 5% infection rate reported in the field according to published literature. All dogs were also repeatedly infested (weekly infestations for one month) and this is considered to mimic a high and prolonged infection pressure.

Furthermore, the efficacy of Simparica Trio against fleas under field conditions in the EU has previously been assessed and accepted by the CVMP during the original MAA of Simparica Trio. Based on the totality of evidence presented with the original and current applications, it is considered that the omission of a clinical trial has been adequately justified by the applicant.

The recommended dose rate for Simparica Trio will remain unchanged as a result of this variation, and appropriate guidance is given in relation to reduction of the risk of infection with Dipylidium caninum via transmission by Ctenocephalides felis in the proposed SPC.

In conclusion, based on the findings of the two dose confirmation studies presented, it is accepted that Simparica Trio, when administered on a single occasion at the recommended therapeutic dose, achieved an adequate level of efficacy for the reduction of the risk of infection with Dipylidium caninum via transmission by Ctenocephalides felis for one month after treatment.

3. Benefit-risk assessment of the proposed change

Simparica Trio is 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 product also provides concurrent efficacy for the treatment and prevention of angiostrongylosis, and the prevention of heartworm disease and thelaziosis. 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 authorised as chewable tablets with six different strengths and is administered at a dose of 1.2–2.4 mg/kg bodyweight of sarolaner, 0.024–0.048 mg/kg bodyweight of moxidectin and 5-10 mg/kg bodyweight of pyrantel.

The proposed variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: reduction of the risk of infection with Dipylidium caninum via transmission by Ctenocephalides felis for one month after treatment.

3.1. Benefit assessment

Direct therapeutic benefit

The proposed benefit of Simparica Trio is its efficacy in the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* in dogs for one month after treatment, which was established in two GCP-compliant laboratory dose confirmation studies.

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 previously 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.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

Appropriate information has previously 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.

The product has been shown to be efficacious for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for one month after treatment.

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.

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original data presented on 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: change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: reduction of the risk of infection with

Dipylidium caninum via transmission by *Ctenocephalides felis* for one month after treatment, and amendment to the contact details to report suspected adverse events for Iceland 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 veterinary 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 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 for Iceland.