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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped type II variation for Simparica Trio (EMEA/V/C/004846/II/0007/G)

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 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) on 22 December 2021 an application for a grouped type II variation for Simparica Trio.

1.2. Scope of the variation

Variations requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

To add a new therapeutic indication for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for up to 28 days after treatment and to update SPC section 5.1 regarding the onset of efficacy for *Ixodes ricinus* ticks.

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 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

The product Simparica Trio chewable tablets for dogs contains the active substances sarolaner, moxidectin and pyrantel.

Simparica Trio chewable tablets are currently indicated for dogs with or at risk from mixed external and internal parasitic infestations; the product is exclusively indicated when use against ticks or fleas and gastrointestinal nematodes is indicated at the same time. The ectoparasite species for which the product is indicated include ticks (*Ixodes hexagonus, Ixodes ricinus*, *Rhipicephalus sanguineus* and *Dermacentor reticulatus)* and fleas *(Ctenocephalides felis* and *Ctenocephalides canis).* The product can also be used as part of a treatment strategy for the control of flea allergy dermatitis. The product is also indicated for the treatment of endoparasites, including *Toxocara canis, Ancylostoma caninum*, *Toxascaris leonina* and

Uncinaria stenocephala. The product also provides concurrent efficacy for the prevention of heartworm disease (*Dirofilaria immitis*) and angiostrongylosis (*Angiostrongylus vasorum*).

The proposed variation is to add a new indication for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for up to 28 days after treatment and to update SPC section 5.1 regarding the onset of efficacy for *Ixodes ricinus* ticks.

Simparica Trio chewable tablets are presented in 6 different strengths with sarolaner administered at a dose rate of 1.2 – 2.4 mg/kg body weight, moxidectin administered at a dose rate of 0.024 – 0.048 mg/kg body weight and pyrantel administered at a dose rate of 5-10 mg/kg body weight. The currently authorised dose rates are also proposed for the new indication.

2.1. New indication: Reduction of the risk of infection with Babesia canis via transmission by Dermacentor reticulatus

2.1.1. Safety (tolerance, user, environment)

No new preclinical or specific target animal safety studies have been conducted by the applicant in the context of this variation application. Given that the dose rate and re-treatment interval for the newly proposed indication do not differ from those which have already been accepted for the existing target parasites, it can be accepted that no concerns in terms of target animal tolerance/safety are considered to arise.

Further, as the product will be administered to the same target species, using the same route of administration and at the same posology that has already been accepted by the CVMP, no concerns in terms of user safety are considered to arise; that is, the user will not be exposed to a greater amount of the active substances or for a greater frequency than that which has been assessed for the existing indications approved for the product. No change to the impact on the environment is envisaged.

Therefore, no further assessment is deemed necessary in respect of target animal tolerance, user safety or safety for the environment and it can be concluded that the introduction of the proposed indication will not present an unacceptable risk for the animal, user or the environment.

2.1.2. Efficacy

In support of the proposed new indication for the reduction of the risk of infection with *B. canis* via transmission by *D. reticulatus*, the applicant has presented bibliographic data on the pathogenesis of canine babesiosis and it can be accepted that *B. canis canis* is transmitted exclusively by *D. reticulatus*, with dogs becoming infected when infected ticks take a blood meal. Transmission time for *B. canis* in previously unfed ticks is reported to be between 36-48 hours, however transmission time may be reduced in male ticks due to their tendency for shorter more frequent feeds and co-feeding with females. Immediate and persistent acaricidal efficacy against *D. reticulatus* for at least 4 weeks has already been accepted by CVMP for Simparica Trio.

The applicant has presented the results of a well-designed GCP compliant laboratory efficacy study, which evaluated the efficacy of the product in the prevention of the transmission of *Babesia canis* by infected *Dermacentor reticulatus* to dogs. The study was conducted outside of the EU, however the parasite (*D. reticulatus*) and the vector-borne pathogen (*B. canis*) originated from within the EU. A parallel study design was used, with the inclusion of a negative control; a rescue protocol was described for all animals subsequently infected with *B. canis.*

Twenty-four beagle and mongrel dogs (13 males and 11 females) were included, encompassing a broad range of weights (11.8 – 26.4 kg) and ages (28 – 90 months). Whilst information on hair length was not provided, the method of tick application can be considered adequate to ensure tick penetration and adequate numbers of ticks were retained on the control animals (arithmetic mean ranging from 27.1 – 34.4 ticks). Study animals were confirmed healthy and free of both tick infestation and *B. canis* infection prior to inclusion. Eight animals were included in each treatment group.

The control and test articles (placebo and Simparica Trio respectively) were administered orally on study days 0 and 7. Animals in group T01 received placebo on days 0 and 7. Animals in group T02 received Simparica Trio on day 0 and placebo on day 7 to evaluate efficacy after 28 days. Dogs in group T03 received placebo on day 0 and Simparica Trio on day 7 to evaluate efficacy after 21 days.

On study day 28, approximately 50 unfed adult *D. reticulatus* ticks were applied to each study animal with a male:female ratio of 1:1. The infestation method was well characterised. It is noted that in line with the draft guideline EMA/CVMP/EWP/278031/2015, for a product with short term-effect (up to 4 weeks), it is recommended to perform two challenges, one at the start and one close to the end of the claimed protection period. Whilst each study animal was only exposed to a single challenge, two IVP study groups were included and challenges were conducted at two time points - either 21 days (group T03) or 28 days (group T02) post-treatment (albeit in the latter half of the proposed protection period). Given the severity of the challenge (the application of 50 ticks; >50% attachment rate; >22% of ticks positive for *B. canis*) and noting the fact that the CVMP has already accepted the product as having an immediate acaricidal effect against *D. reticulatus,* the approach to timing of challenge is acceptable in this instance. The ticks were not removed from the animals until study day 33. Given the bibliographic data provided which indicates that transmission of *B. canis* in previously unfed ticks occurs between 36-48 hours, this period of exposure is considered adequate to enable transmission of *B. canis.*

The primary efficacy parameter was the blocking efficacy of Simparica Trio on *B. canis* transmission. Animals were defined as 'ever positive' for *B. canis* when confirmed positive by indirect immunofluorescence assay (IFA) and PCR post-infestation, with efficacy to prevent transmission calculated in accordance with the draft guideline EMA/CVMP/EWP/278031/2015 and based upon the proportion of ever positive dogs in the treated group compared to the control group. Blood samples were collected on days 28 (prior to tick infestation), 35, 42, 49 and 56 and tested by IFA for *B. canis* antibodies and by PCR for *B. canis* DNA.

None of the animals administered Simparica Trio were 'ever positive' for *B. canis* infection (neither IFA positive nor PCR positive), however all animals administered the placebo were confirmed 'ever positive' (by PCR and IFA) by 28 days post-infestation (study day 56). In addition, clinical signs of babesiosis were observed in all of the control animals (including lethargy, haematuria, anaemia, inappetence and fever).

Although two animals administered Simparica Trio exhibited an elevated body temperature on a number of days, this was considered to be induced by excitement with neither animal exhibiting any other clinical signs of babesiosis nor testing positive upon blood smear, PCR or IFA. Based upon the percentage calculations for the blocking efficacy of Simparica Trio on *B. canis* transmission, it can be accepted that the product was demonstrated to be 100% effective by study day 56 with the difference between the treated and control groups statistically significant ($P<0.0001$). The duration of the follow-up period (4 weeks) can be accepted as being adequate with regard to the pre-patent or incubation period of *B. canis* (1 to 3 weeks) reported in the published literature and is considered sufficient in terms of allowing adequate time for response to antibody testing (IFA) given that a serological response may take 2-4 weeks to be detectable.

Acaricidal efficacy against ticks was also evaluated with Abbott's formula used to calculate the percentage reduction between the treated and control animals by arithmetic means, consistent with guideline for the

testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3). Tick counts were performed 24 hours post-challenge (day 29), 48 hours post-challenge (day 30) and again on day 33, at which time point ticks were removed. The control animals were observed to maintain adequate tick infestations up until Study Day 33. For the group administered Simparica Trio on day 0 (T02), with subsequent infestation 28 days later, percentage reduction compared to control was 73.3% on day 29 (24 hours post-challenge) and 100% on days 30 (48 hours post-challenge) and 33. For the group administered Simparica Trio on day 7 (T03), with subsequent infestation 21 days later, percentage reduction compared to control was 81% on day 29 (24 hours post-challenge), 99.5% on day 30 (48 hours post-challenge) and 100% on day 33. Based upon these results it can be accepted that an acceptable level (>90%) of acaricidal efficacy against *D. reticulatus* was demonstrated by 48 hours post-challenge. Whilst the acaricidal efficacy calculations conducted included both free and attached live ticks whereas in accordance with the guideline EMEA/CVMP/EWP/005/2000-Rev.3 '*for the systemically acting product, live free ticks may not be considered for efficacy evaluation'*, the inclusion of live free ticks in efficacy calculations can be accepted as representing a 'worst case' approach.

It can be accepted that the results of this study demonstrate protection of dogs against infection with *B. canis*, with all animals administered Simparica Trio testing negative for antibodies (IFA), negative for *B. canis* DNA (PCR) and none developed clinical signs of babesiosis, by day 56 post-treatment administration, when challenged at 21 and 28 days post-treatment administration. Consequently, the results from this study are considered to support the proposed indication for Simparica Trio for the reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for up to 28 days after treatment.

However, the draft CVMP guideline on data requirements for veterinary medicinal products for the prevention of transmission of vector borne diseases in dogs and cats (EMA/CVMP/EWP/278031/2015) states: "*Unless otherwise justified, the efficacy of a VMP for the reduction of the risk of transmission of VBPs has to be proven by appropriate clinical studies under laboratory and field conditions*."

For this variation, the applicant has only presented the results of one laboratory efficacy study and provided justification for not providing field study data as follows:

- The laboratory study data provided is based upon laboratory transmission models validated by the scientific community, study animals were exposed to ticks with an infection rate of >20%, which is considered adequate based upon scientific literature and 100% of the untreated control animals became infected and the laboratory study reflects field conditions and the parameters outlined in draft guideline EMA/CVMP/EWP/278031/2015.
- Further, whilst the provision of a field study may enable evaluation of the effect of partially fed male *D. reticulatus* ticks on transmission (potentially shorter transmission times), transmission times or confirmation that transmission occurred via partially fed male ticks would be difficult to confirm under field conditions.
- The applicant also highlighted animal welfare implications given the pathogenesis of the disease, the frequency at which observations for clinical signs of babesiosis must be conducted and the necessity for rapid rescue treatment and considered the inclusion of a negative control in a clinical field trial in client-owned dogs to be questionable from an ethical perspective. Whilst the inclusion of a positive control may be considered, at time of study conduct no other product was approved for the reduction of the risk of *B. canis* via transmission by *Dermacentor reticulatus. A*lthough at least one other product is authorised in the EU for a somewhat similar indication (reducing the risk of canine babesiosis), the CVMP acknowledges that the indication for that product relates to transmission of *B. canis* by a different tick (*R. sanguineus*) and that product

exerts both an acaricidal and a repellent effect against ticks. The applicant also highlighted the fact that even if a field study were to be conducted, no product can provide total protection against *B. canis* transmission.

However, during initial assessment, the CVMP did not accept that the absence of field efficacy data in support of the variation to include an indication for the 'reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus*' had been adequately justified. The CVMP highlighted the need for field data as a general requirement in order to take into account the numerous factors which may influence efficacy under natural conditions of infection and practical conditions of use. In the present case, there is a known factor that could decrease efficacy under field conditions, i.e. the potentially shorter transmission time in partially fed male ticks. Therefore, the applicant was requested to provide further justification for the absence of a field efficacy study, that is, that the findings of the laboratory study provide adequate assurances in relation to expected efficacy in the field.

Following the CVMP comments/list of questions regarding the indication 'reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus'*, the applicant decided to no longer pursue this indication in the context of this procedure and withdrew the C.I.6.a variation.

2.2. SPC update: onset of efficacy for Ixodes ricinus ticks

A GCP-compliant laboratory efficacy study was provided in support of the proposed amendment to section 5.1 of the SPC to specify that the onset of efficacy for *Ixodes ricinus* is within 24 hours of attachment. The IVP was confirmed as the commercial formulation. The study was conducted within the EU with the tick strain originating from field collections in Europe. A parallel study designed was used with the inclusion of a negative control.

Sixteen beagle dogs (10 males and 6 females) were included, encompassing range of weights (8.8 – 16 kg) and ages (8-29 months). Whilst Beagle hair is not typically considered of moderate length (a criteria specified as desirable in guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats EMEA/CVMP/EWP/005/2000-Rev.3), it can be accepted that the method of tick application was adequate to ensure tick penetration and retention on the study animals and study animals were tested prior to inclusion for their ability to carry adequate numbers of ticks. A washout period was applied to ensure no residual ectoparasiticide effect from previous treatments. Eight animals were included in each group, which is considered acceptable.

The control and test articles were administered orally on study day 0 to groups T01 and T02 respectively. With regards dose rate of the test article (Simparica Trio), rates administered ranged from 1.24 to 1.39 mg sarolaner per kg bw.

Approximately 50 unfed adult *I. ricinus* ticks were applied to each study animal on days -2, 7, 14, 21, 28 and 35, with a 30 female: 20 male sex distribution. The infestation method was well characterised. Speed of kill was investigated at 12 and 24 hours after treatment on day 0 and post-challenge on study days 7, 14, 21, 28 and 35, with speed of kill for both existing and new infestations investigated. Following infestation, arithmetic mean for live attached tick counts in the control group ranged from 17.1 to 21.8 ticks at 12 hours and from 17.3 to 20.8 at 24 hours.

The primary endpoint was the percentage reduction in arithmetic mean tick count compared to the control, with Abbott's formula used to calculate the percentage reduction between the treated and control animals. Against existing infestations (evaluated at 12 & 24 hours after treatment on study day 0), percentage reduction (compared to control) including live free ticks (representing a 'worst case' approach for a systemically-acting acaricide) was 26.2% at the 12-hour count and 96.2% at the 24-hour count. Against new infestations, percentage reductions at 12 hours were 26.4%, 34.2%, 28.2%, 10.1% and

10.3%, on days 7, 14, 21, 28 and 35, respectively, and at 24 hours were 92.2%, 99.4%, 98.4%, 97.3% and 92.0% on days 7, 14, 21, 28 and 35, respectively.

In conclusion, the results demonstrate an acceptable level of acaricidal efficacy (>90%) against *I. ricinus* at 24 hours for the entire duration of the approved persistent efficacy claim (35 days), when the product is administered at the recommended treatment dose of 1.2-2.4 mg sarolaner per kg bodyweight.

Therefore, the CVMP agrees that section 5.1 of the SPC be updated with the relevant information, as follows: "*For the species I. ricinus, this onset of efficacy is within 24 hours, during the 35-day period after product administration*".

3. Benefit-risk assessment of the proposed change

Simparica Trio is authorised in dogs 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 gastrointestinal roundworm and hookworm infections (*Toxocara canis, Ancylostoma caninum, Toxascaris leonina* and *Uncinaria stenocephala*) and for the prevention of heartworm disease (*Dirofilaria immitis*) and angiostrongylosis (*Angiostrongylus vasorum*). 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.

At the time of submission, the proposed grouped variation was to add a new indication for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for up to 28 days after treatment and to update SPC section 5.1 regarding the onset of efficacy for *Ixodes ricinus* ticks. However, the proposed indication for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* was withdrawn by the applicant during the procedure in response to concerns having been raised by the CVMP in respect of the adequacy of the data provided.

3.1. Benefit assessment

Direct therapeutic benefit

The benefits of the product remain unaffected by this variation.

Additional benefits

No additional benefits foreseen.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

The dose rate and frequency of treatment administration does not differ on account of this variation and consequently, no additional risk for the target species is foreseen.

Administration of Simparica Trio in accordance with SPC recommendations is generally well-tolerated. The main reported adverse reactions are appropriately included in the SPC and no new adverse reactions arise from the studies performed in support of the current variation application.

Risk for the user:

The dose rate and frequency of treatment does not change on account of this variation. Therefore, no additional risk for the user arises.

The CVMP previously concluded that user safety for this product is acceptable when used according to the SPC recommendations.

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

Appropriate information has previously been included in the SPC and other product information to inform on the potential risks of this product as currently approved, relevant to the target animal, user and 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 benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary 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 (Commission Regulation (EC) No. 1234/2008), as follows: an update of SPC section 5.1 regarding the onset of efficacy for *Ixodes ricinus* ticks (C.I.4).

Following the CVMP comments/list of questions regarding the indication "reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus*", the applicant decided to no longer pursue this indication in the context of this procedure and withdrew the C.I.6.a variation.

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, section 5.1 of the SPC is updated. The corresponding section of the package leaflet is updated accordingly.