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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a worksharing type II variation for Simparica and MiPet Easecto (EMEA/V/C/WS2217)

INN: sarolaner

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

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Table of contents

1. Introduction

1.1. Submission of the variation application

In accordance with Article 20 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 type II variation for Simparica and MiPet Easecto, following a worksharing procedure.

1.2. Scope of the variation

Variation 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

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. The MAH also takes the opportunity to update the product information for MiPet Easecto following a PSUR recommendation.

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 products Simparica chewable tablets for dogs and MiPet Easecto chewable tablets for dogs contain the active substance sarolaner.

Simparica chewable tablets and MiPet Easecto chewable tablets are currently indicated for dogs for the treatment of tick infestations (*Dermacentor reticulatus*, *Ixodes hexagonus*, *Ixodes ricinus*, and *Rhipicephalus sanguineus*) and flea infestations (*Ctenocephalides felis* and *Ctenocephalides canis*). The products can be used as part of a treatment strategy for the control of flea allergy dermatitis. The products are also indicated for the treatment of sarcoptic mange (*Sarcoptes scabiei*), ear mite infestations (*Otodectes cynotis*) and demodicosis (*Demodex canis*).

The proposed variation is to add a new indication for Simparica chewable tablets and MiPet Easecto chewable tablets for the reduction of the risk of infection with *Babesia canis* via transmission by

Dermacentor reticulatus for up to 28 days after treatment. The effect is indirect due to the product's activity against the vector. In addition, the applicant has proposed amendment of section 4.6 of the SPC for MiPet Easecto, to reflect changes agreed during a recent PSUR assessment.

Simparica chewable tablets and MiPet Easecto chewable tablets are presented in 6 different strengths with sarolaner administered at a dose rate of 2 - 4 mg/kg bodyweight (bw). The currently authorised dose rate is also proposed for the new indication.

2.1. 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 products 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 products. 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.

2.2. 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 5 weeks has already been accepted by CVMP for Simparica and MiPet Easecto.

In support of the proposed indication for the reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus*, the applicant has provided the results of 3 studies:

- A laboratory study to compare efficacy of oral sarolaner against induced infestations of *D. reticulatus* in dogs (A);
- A laboratory study to evaluate the efficacy of sarolaner for the prevention of *B. canis* transmission by infected *D. reticulatus* in dogs (B);
- A laboratory efficacy study to evaluate the efficacy of Simparica Trio for the prevention of transmission of *B. canis* by *D. reticulatus* (C).

The first study (A) was a GCP-compliant speed of kill laboratory efficacy study. In accordance with 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), the speed of kill of the VMP against the ectoparasite in relation to the transmission time of a vector borne pathogen (VBP) to the host is considered supportive information. The study was conducted outside of the EU; however,

the tick strain originated from a laboratory within the EU. A parallel study design was used, with both a negative (placebo) and a positive control (imidacloprid+permethrin).

Twenty-four beagle and mixed-breed dogs (8 males and 16 females) were included, encompassing a range of weights (10.8 – 24.8 kg) and ages (9 – 81 months). Whilst information on hair length was not provided, the method of tick application can be considered adequate to ensure tick penetration and retention on the study animals and 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 treatment group, which is considered acceptable, and the study sample was considered suitably representative of the intended target population.

On study day 0, animals in groups T01 and T02 were orally administered the control (placebo) and test articles (Simparica) respectively, whilst animals in group T03 were topically administered the positive control (imidacloprid+permethrin). Although it is expected that the sarolaner dose administered should be as close as possible to the minimum recommended dose, study animals were administered a dose rate ranging from 2 – 3.92 mg sarolaner per kg bw, which, although not fully representative of the minimum recommended dose, was within the clinical dose range likely to be administered when following the SPC.

Approximately 50 unfed adult *D. reticulatus* ticks were applied to each study animal with a 1:1 male to female sex distribution. The infestation method was well characterised. Speed of kill was investigated at 8, 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. Live attached tick counts in the control group at 8 hours ranged between 12-43 ticks, at 12 hours ranged between 6-43 ticks and at 24 hours ranged between 7-41 ticks, with 6 control animals demonstrating counts falling within the range of 14 to 43 at each time point, thus confirming the existence of an adequate infestation.

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 8, 12 and 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 75.6% at the 8-hour count, 95.9% at the 12-hour count and 100% at the 24-hour count. Against new infestations, percentage reductions at 8 hours were 44.1%, 65%, 30%, 31.7% and 40.3% on days 7, 14, 21, 28 and 35 respectively, at 12 hours were 57.9%, 72.4%, 59.3%, 45.2% and 49.2% on days 7, 14, 21, 28 and 35 respectively, and at 24 hours were 99%, 100%, 99.6%, 96.9% and 95.8% on days 7, 14, 21, 28 and 35 respectively.

The results demonstrate an acceptable level of acaricidal efficacy (>90%) against existing infestations of *D. reticulatus* at 12 hours and new infestations of *D. reticulatus* 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 2-4 mg sarolaner per kg bodyweight.

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*". In this regard, the applicant has provided the results of two GCP-compliant laboratory efficacy studies.

One study (B) evaluated the efficacy of Simparica in the prevention of the transmission of *Babesia canis* by infected *Dermacentor reticulatus* ticks in dogs. The study was conducted outside of the EU, however the strain of the vector, *D. reticulatus*, originated from Europe. The vectors were infected with *B. canis* by feeding on a dog with confirmed *B. canis* infection. A parallel study design was used with the inclusion of

a negative control and a rescue protocol was described for all animals subsequently infected with *B. canis*.

Twenty-four beagle and mongrel dogs (14 male and 10 female) were included, encompassing a broad range of weights (10.2 – 24.8 kg) and ages (1 – 8 years). Whilst information on hair length was not provided, it can be accepted that the method of tick application was adequate to ensure tick penetration and adequate numbers of ticks were retained on the control animals (arithmetic mean for attached live ticks ranged from 33.1 – 30.9 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 sarolaner respectively) were administered orally on study days 0 and 7. Animals in group T01 received placebo tablets on days 0 and 7. Animals in group T02 received sarolaner on day 0 and placebo on day 7 to evaluate efficacy 28 days post-treatment. Animals in group T03 received placebo on day 0 and sarolaner on day 7 to evaluate efficacy 21 days post-treatment. Simparica was administered at a dose rate ranging from 2.03 mg to 2.30 mg of sarolaner per kg bw, which can be accepted as being generally consistent with the lowest dose achievable.

The challenge vector was adult *D. reticulatus* ticks originating from a laboratory within Europe. The vectors were infected with *B. canis* by feeding off an infected dog, with PCR confirmation that 25% of ticks were infected. 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; approximately 25% 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 considered 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 typically 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 the IVP 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, 56, 63 and 70 and tested by IFA for *B. canis* antibodies and by PCR for *B. canis* DNA.

All of the animals administered the placebo (T01) were confirmed 'ever positive' (by PCR and IFA) by 28 days post-infestation (study day 56), with positive results for PCR and IFA having been recorded in all animals and clinical signs of babesiosis also observed in all of these animals (anaemia, haematuria, lethargy, lymph node enlargement and febrile).

None of the Simparica-treated animals (groups T02 and T03) was confirmed 'ever positive' (i.e. positive by both IFA and PCR), indicating 100% efficacy in the prevention of the *B. canis* transmission. However, 9 animals in the groups administered the test article were PCR positive on study day 49 (group T02 = 6 animals; group T03 = 3 animals); however, none were reported to be PCR positive on any other study day. Furthermore, none of these animals ever tested IFA positive nor demonstrated clinical signs of

babesiosis throughout the duration of the study period. Although the applicant hypothesized that the positive PCR test results observed may have been due to sample contamination, with similar positive results observed in the control group on day 49, this theory cannot be confirmed and consequently it cannot be excluded that transmission of *B. canis* may have occurred.

Acaricidal efficacy against ticks was also evaluated, with Abbott's formula used to calculate the percentage reduction between the treated and control animals based on arithmetic means. 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 tick infestations up until study day 33. For the group administered Simparica on day 0 (T02), with subsequent infestation 28 days later, percentage reduction compared to control was 87.9% on Day 29 (24 hours post-challenge) and 100% on days 30 (48 hours post-challenge) and 33. For the group administered Simparica on day 7 (T03), with subsequent infestation 21 days later, percentage reduction compared to control was 93.6% on day 29 (24 hours post-challenge) and 100% on days 30 (48 hours post-challenge) and 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.

This study was previously submitted with the initial application for marketing authorisation for the product; however, the CVMP considered the study to be inadequate on its own to support the indication proposed at that time.

Notwithstanding the above, the results from this study are considered supportive of the proposed indication for the reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for up to 28 days after treatment.

Another GCP-complaint laboratory efficacy study (C) evaluated the efficacy of a different formulation (Simparica Trio) authorised to the applicant, in the prevention of the transmission of *Babesia canis* by infected *Dermacentor reticulatus* ticks to dogs. Whilst the test article (Simparica Trio) used for this study was not the product under assessment (Simparica/MiPet Easecto), the active substance sarolaner responsible for acaricidal efficacy against *D. reticulatus* is included in both formulations and, most significantly, the recommended dose rate of sarolaner in Simparica Trio (1.2-2.4 mg/kg bw) is lower than that approved for Simparica/MiPet Easecto (2-4 mg/kg bw). Consequently, it was accepted that if efficacy is demonstrated at a lower dose rate of sarolaner (for Simparica Trio), it is reasonable to conclude that at least the same efficacy would also be attained when administering saraloner at a higher dose rate in Simparica/MiPet Easecto.

The study was conducted outside of the EU, however the vector (*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 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 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 and neither animal exhibited any other clinical signs of babesiosis nor tested 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/MiPet Easecto 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 laboratory efficacy studies, whilst field study data have not been provided.

The transmission time of *B. canis* in previously unfed ticks is generally accepted to be between 36-48 hours due to the duration of time required for sporogony; however, the laboratory study data presented with this variation application for Simparica/MiPet Easecto (A), demonstrated ≥95.8% efficacy against *D. reticulatus* at 24 hours for 35 days.

The transmission time in male ticks may be more rapid due to their tendency for shorter more frequent feeds, co-feeding with females and feeding from several different hosts and one study (Varloud *et al*., 2018) demonstrated transmission within 8 hours. However, in the laboratory study data presented with this variation application, at 8 hours on study days 0, 7, 14, 21, 28 and 35, acaricidal efficacy against *D. reticulatus* ranged from 30 – 75.6% and, at 12 hours, acaricidal efficacy ranged from 45.2 – 95.9%.

The incidence of infection and clinical signs associated with transmission of infection by partially fed male ticks after an exposure time of 8 hours is lower and less pronounced than those observed after an exposure time of 24 hours: in a bibliographic study presented (Varloud *et al.*), after an exposure time of 24 hours, all 6 dogs were infected by *B. canis* and within 5 to 6 days after being exposed to infected ticks, all dogs exhibited clinical signs typical of babesiosis: enlarged lymph nodes, pale mucous membranes, splenomegaly, panting. However, after an exposure time of 8 hours, 3 of 6 dogs were diagnosed as infected with *B. canis*. Within 7 days after being exposed to infected ticks, these 3 dogs started to exhibit clinical signs such as vomiting, tense abdomen, listless, panting.

As per the studies conducted by the applicant, 100% efficacy against the transmission of *B. canis* was observed in the laboratory at the dose of sarolaner (2-4 mg/kg bw) approved for Simparica/MiPet Easecto and also at the dose of sarolaner (1.25 mg/kg bw) accepted for Simparica Trio, despite there being a 40% reduction in the dose of sarolaner administered for the latter compared to the former.

The laboratory studies conducted can be considered worst-case scenarios with regards the risk of transmission by unfed *D. reticulatus* ticks, for the following reasons:

- Each dog included in the laboratory studies presented was exposed to 50 *D. reticulatus* ticks with >50% retention rates in the control groups.
- The percentage of ticks infected with *B. canis* exceeded the prevalence of *B. canis* in *D. reticulatus* ticks reported in the literature (range 0 – 21%).

- Following infestation, the ticks were allowed to remain in-situ and feed for 5 days, greatly exceeding the time considered necessary for sporogony and subsequent transmission of *B. canis*.
- Subsequent to infestation, all animals included in the control groups tested positive for *B. canis* by PCR and IFA and developed clinical signs of babesiosis warranting rescue treatment.
- In one study (C), efficacy was evaluated following administration of Simparica Trio, with actual dose rates ranging from 1.21 mg to 1.43 mg sarolaner per kg bw, which is considerably less than that approved for Simparica/Mipet Easecto: 2-4 mg sarolaner/kg bw.
- Efficacy was evaluated after a single treatment: it is expected that dogs would be administered the product on a monthly basis and, as noted previously by CVMP, the product has the potential for accumulation with repeat dosing.

In light of the results of the laboratory studies and the justification provided by the applicant for not conducting a field study, the CVMP agreed to accept the omission of field study data for the following reasons:

- The laboratory studies conducted can be considered to reflect a worst-case transmission scenario in the field;
- The fast speed of kill provides confidence that transmission by previously unfed ticks is blocked;
- In the laboratory studies conducted for Simparica Trio, 100% blocking efficacy for *B. canis* was observed, despite sarolaner being administered at a 40% lower dose than that approved for Simparica/MiPet Easecto;
- While transmission of *B. canis* by partially fed male ticks to sarolaner-treated dogs may not be fully prevented, administration of Simparica/MiPet Easecto would be expected to reduce the risk of infection with *B. canis* by *D. reticulatus*. Further, any transmission that may occur under these circumstances is expected to result in a lower incidence of and less severe clinical disease than that recorded in the laboratory studies for untreated dogs. On this point, it is noted that the proposed indication does not claim complete prevention of transmission of infection with *B. canis*, but instead claims a reduction in the risk of infection.

Based upon the data package presented and in light of the above, the CVMP considers the proposed indication to have been adequately supported by the data provided. For accuracy purposes, the protozoan agent has been referred to as *Babesia canis* <u>*canis*</u> in the product information in order to differentiate from other *Babesia canis* subspecies which can be transmitted by other tick species. This aspect is reflected in the indication for use as accepted by the CVMP for inclusion under section 4.2 of the SPC: "*For reduction of the risk of infection with Babesia canis canis via transmission by Dermacentor reticulatus for 28 days after treatment. The effect is indirect due to the product's activity against the vector*".

3. Benefit-risk assessment of the proposed change

The products Simparica and MiPet Easecto are authorised for the treatment of tick (*Dermacentor reticulatus*, *Ixodes hexagonus*, *Ixodes ricinus* and *Rhipicephalus sanguineus*) and flea (*Ctenocephalides felis* and *Ctenocephalides canis*) infestations, and for the treatment of sarcoptic mange (*Sarcoptes scabiei*), ear mite infestations (*Otodectes cynotis*) and demodicosis (*Demodex canis*) in dogs. The products can also be used as part of a treatment strategy for the control of flea allergy dermatitis in dogs. The active substance is sarolaner, an acaricide and insecticide belonging to the isoxazoline family. Both products are presented as chewable tablets of different strengths, which are administered to dogs

at a dose of 2–4 mg sarolaner/kg bodyweight.

The proposed variation is 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. The MAH also takes the opportunity to update the product information for MiPet Easecto following a PSUR recommendation.

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce an additional indication to existing presentations of Simparica chewable tablets for dogs and MiPet Easecto chewable tablets for dogs, the benefit will arise from the inclusion of the new indication. The indication for the reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days after treatment is considered as being of benefit for the patient.

Additional benefits

No additional benefits foreseen.

3.2. Risk assessment

As this is a variation to introduce an additional indication to existing presentations of Simparica chewable tablets for dogs and MiPet Easecto chewable tablets for dogs, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indication. As the products will be administered to the same target species at the same dose rate and at the same frequency as already approved for existing indications, no new risk is considered to arise in terms of user safety, target animal tolerance, potential for resistance development or for the environment.

Quality:

Quality remains unaffected by this variation.

Safety:

Risks for the target animal:

The dose rate and frequency of treatment administration does not differ for the proposed indication in the target species when compared to that already approved for the existing indications. Consequently, no additional risk for the target species is foreseen.

Administration of both Simparica and MiPet Easecto in accordance with SPC recommendations is generally well-tolerated. The main reported adverse reactions are appropriately included in the SPCs and no new adverse reactions arise from the studies performed in support of the proposed new indication.

Risk for the user:

The dose rate and frequency of treatment does not change due to the addition of the new indication for the reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus*. 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 and MiPet Easecto are 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 these products, 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.

The products have been shown to be efficacious for the reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days after treatment.

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 and MiPet Easecto can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add a new therapeutic indication for reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days after treatment. In addition, the product information for MiPet Easecto was updated following a PSUR recommendation.

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 products.

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

I and IIIB.

As a consequence of this variation, sections 4.2 and 4.4 of the SPC for Simparica and sections 4.2, 4.4 and 4.6 of the SPC for MiPet Easecto are updated. The corresponding sections of the package leaflet are updated accordingly.