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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Simparica Trio (EMEA/V/C/004846/VRA/0009/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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Table of contents

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 SA (the applicant), submitted to the European Medicines Agency (the Agency) on 26 July 2022 an application for a group of variations requiring assessment for Simparica Trio.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
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The grouped variation is to add three new therapeutic indications: for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), for the treatment of demodicosis (caused by *Demodex canis*), and for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection).

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. Limited market status

Not applicable.

2. Scientific Overview

Simparica Trio is authorised for use in 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 product also provides concurrent efficacy for the prevention of heartworm disease and angiostrongylosis. The product can be used as part of a treatment strategy for the control of flea allergy dermatitis.

The product contains a fixed combination of three active substances: sarolaner, moxidectin and pyrantel (as embonate). Sarolaner is a systemically acting acaricide and insecticide belonging to the isoxazoline family, whilst moxidectin, a second-generation macrocyclic lactone of the milbemycin family, and

pyrantel, a nicotinic acetylcholine channel receptor agonist, act against endoparasites (gastrointestinal and vascular).

The product 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 is to add three new therapeutic indications: for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), for the treatment of demodicosis (caused by *Demodex canis*), and for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection).

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 indications do not differ from that which has already been accepted for the existing target parasites, 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.

2.2. Efficacy

2.2.1. Treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*)

In support of the proposed indication for the treatment of sarcoptic mange, the applicant has presented one dose confirmation study and the results of a clinical field trial.

The dose confirmation study presented was conducted to evaluate the efficacy and safety of Simparica Trio when used in the treatment of natural *S. scabiei* infestations in dogs. The study was GCP compliant, randomised and blinded and a study protocol was provided. The study was conducted outside of the EU (South Africa).

This was a negatively controlled study using the commercial presentations of Simparica Trio chewable tablets for dogs as the IVP investigational product and placebo as comparator product. The IVP was administered to achieve doses close to the minimum recommended treatment dose using a combination of different tablet strengths. The IVP was administered on two occasions with a between treatment interval of one month. The dose ranges administered for sarolaner ranged from 1.23 – 2.35 mg/kg bw and therefore it can be accepted that the minimum recommended dose rate of sarolaner (range of 1.2 – 2.4 mg sarolaner/kg bw specified in the SPC) was evaluated.

31 privately owned crossbreed dogs were included in the study (17 male, 14 female), encompassing a range of weights (5.9 – 26.2 kg) and ages (0.8-9 years of age). Both medium and short-haired dogs were included in the study population. All animals included in the study were determined to have natural infestation with *S. scabiei* mites, as determined by the identification of at least 5 live *S. scabiei* mites on

deep skin scrapings and clinical signs consistent with sarcoptic mange. The inclusion criteria and approach for the diagnosis of sarcoptic mange was considered acceptable. Each animal underwent physical examination at enrolment and at all subsequent visits to the veterinary clinic. Clinical assessments for sarcoptic mange were conducted on Study days 0, 14, 30 and 60, with scoring of skin lesions characteristic of sarcoptic mange.

The primary efficacy parameter was the percentage reduction in live mite counts compared to placebo, with percentage efficacy calculated in accordance with arithmetic means and using Abbott's formula, in accordance with guideline recommendations (*Demonstration of efficacy of ectoparasiticides*, 7AE17a). In line with the aforementioned guideline, in order for a claim to be accepted for *S. scabiei*, approximately 100% efficacy should be demonstrated. Based upon the calculations conducted, >99% efficacy was observed at Day 60, which is adequate to support the claim. Mite counts were also statistically significantly lower ($p<0.0001$) compared to placebo on Days 14, 44 and 60.

Parasitological cure rate was evaluated as a secondary efficacy parameter (that is, the percentage of dogs in the treatment group having no live mites in the skin scrapings on respective study days). For parasitological cure rate, 16.7%, 16.7%, 58.3% and 81.8% of animals in the IVP group were considered cured by Days 14, 30, 44 and 60 respectively.

The severity of clinical signs and the extent of skin lesions were also evaluated as secondary efficacy parameters and it is noted that by Day 60, all clinical signs evaluated had improved: at Day 0, in the IVP group 100% of animals exhibited moderate to severe pruritis, erythema, scaling, 83.3% exhibited moderate to severe crusting and papules and 91.7% exhibited moderate to severe alopecia. By Day 60, no animals in the IVP group were exhibiting moderate to severe pruritis, crusting or papules and whilst moderate hair loss, erythema and scaling was still observed for 9.1% of animals, none of the animals in the IVP group exhibited severe manifestations of these clinical signs at Day 60. With regards the extent of skin lesions, a 76% reduction from baseline was observed for the IVP group at Day 60.

The clinical field trial presented was conducted to evaluate the efficacy and safety of Simparica Trio when used in the treatment of natural *S. scabiei* infestations in dogs presented as veterinary patients in Europe. The study was GCP compliant, randomised and blinded and a study protocol was provided. The study was conducted in veterinary practices across three EU member states, France, Italy and Portugal.

This was a positively controlled study using the authorised presentations of Simparica Trio chewable tablets for dogs as the investigational product (IVP) and NexGard Spectra chewable tablets for dogs as comparator product (CP). The use of NexGard Spectra as control product was considered appropriate given that it is approved for the treatment of sarcoptic mange. Allocation to treatment was randomised and used a 2:1 allocation ratio (Simparica Trio:NexGard Spectra). The IVP and CP were used at the recommended treatment doses as specified in the product SPCs and administered at monthly intervals for up to 2 treatments.

193 privately owned dogs (88 male, 105 female) of various breeds, ranging from 0.2–14 years of age and 2.1 – 50.4 kg in bodyweight were included in the study population with short, medium and long-haired dogs represented. All animals included in the study were determined to have natural infection with *S. scabiei* mites, as determined by deep skin scrapings and clinical signs consistent with sarcoptic mange. Dogs were kept in normal domestic arrangements and households with up to five dogs were selected for the study; if more than one dog in a household met the inclusion criteria, the dog with the most severe clinical signs of sarcoptic mange was selected as the primary patient and used for efficacy and safety evaluations. All other dogs in the same household exhibiting clinical signs of sarcoptic mange were considered as supplementary patients and received the same treatment as the primary patient in the household but were only included in safety evaluations.

Each animal underwent physical examination at enrolment and at all subsequent visits to the veterinary clinic. Clinical assessments for sarcoptic mange were conducted on Study days 0, 14, 30 and 60, with scoring of skin lesions, characteristic of sarcoptic mange. Skin scraping for the detection of live *S. scabiei* mites on primary dogs were conducted on Study days 0, 30 and 60.

The primary efficacy parameter was parasitological cure, which was defined as the percentage of dogs in the given treatment group having no live mites in the skin scrapings on the respective study days. Based upon the counts conducted, 97.3% efficacy was observed for the IVP on Day 30, with 100% efficacy observed at Day 60, which would appear to demonstrate adequate efficacy given that guideline 7AE17a specifies that approximately 100% efficacy should be demonstrated for a claim for *Sarcoptes scabiei* mites.

The secondary efficacy parameter was the frequency distribution of the clinical signs related to sarcoptic mange presented by severity grade. By Day 60, all clinical signs evaluated had improved, with none of the animals exhibiting severe or moderate clinical signs at that timepoint despite >70% of animals in the IVP group demonstrating these severities for pruritus, erythema, scaling, crusting and hair loss at Day 0.

It is acknowledged that the *Guideline on the demonstration of efficacy of ectoparasiticides (7AE17a)* suggests that efficacy data from at least two dose confirmation studies and clinical field trial data are required and, therefore, the adequacy of the efficacy data package for this specific indication could be questioned on the basis that a single confirmatory study only was presented and that this study was conducted outside the EU. However, it is noted that the dose confirmation study presented was conducted in naturally infested (privately owned) dogs, thus involving a variety of strains and demographic characteristics, while being negatively controlled and using the most appropriate (parasitological and clinical) endpoints and examination frequency. Further, the clinical field trial, which included a substantial number of client-owned dogs, was conducted in a number of different EU countries (3) and thus can be considered representative of the EU situation and involved a large number of veterinary practices (27), with determination of efficacy based on parasitological cure (absence of live mites) and, therefore, this study can be regarded as a confirmatory study. In light of the above, the CVMP is of the opinion that further confirmatory data to support efficacy of the product is unnecessary.

Therefore, given the overall data package presented and the conclusions drawn from the dose confirmation study A166C-ZA-19-A65 and the clinical field trial A161C-XC-19-A68, the indication proposed for inclusion in SPC section 4.2 ("For the treatment of sarcoptic mange (caused by *Sarcoptes scabiei var. canis*)") is considered to have been suitably supported and can be accepted.

2.2.2. Treatment of demodicosis (caused by *Demodex canis*)

In support of the proposed indication for the treatment of demodicosis, the applicant has presented one dose confirmation study and the results of a clinical field trial.

The dose confirmation study presented was conducted to evaluate the efficacy and safety of Simparica Trio when used in the treatment of natural infestations of *Demodex* spp. in dogs. The study was GCP compliant, randomised and blinded and a study protocol was provided. The study was conducted outside of the EU (South Africa).

This was a positively controlled study using the authorised presentations of Simparica Trio chewable tablets for dogs as the investigational product (IVP) and NexGard Spectra chewable tablets for dogs as comparator product (CP). Due to the potentially debilitating nature of the disease, the use of a positive control for this laboratory study is accepted as justified. The use of NexGard Spectra as control product is considered appropriate given that it is approved for the treatment of demodicosis caused by *Demodex canis*. Allocation to treatment was randomised and used a 1:1 allocation ratio (Simparica Trio:NexGard

Spectra). The IVP was administered to achieve doses close to the minimum recommended treatment dose using a combination of different tablet strengths and the CP were used at the recommended treatment doses as specified in the product SPC. Both IVP and CP were administered at monthly intervals for up to 4 treatments.

18 privately owned cross-breed dogs (8 male, 10 female), ranging from 6.1 – 15.2 kg and 8 months-15 years of age were included in the study population with both long and short-haired dogs represented. All animals included in the study were determined to have natural infection with *Demodex* mites (as determined by deep skin scrapings) and clinical signs consistent with generalised demodicosis involving either: an entire body region, five or more separate areas each with a diameter >2.5 cm, or pododemodicosis involving 2 of more feet.

Each animal underwent physical examination at enrolment and at subsequent visits to the veterinary clinic. On Study days -3, 14, 29, 44, 59, 74 and 90, clinical assessments for the scoring of skin lesions associated with demodectic mange and mite counts were conducted. The percentage body surface area affected was also determined.

The primary efficacy parameter was the percentage reduction in live mite counts compared to baseline, with percentage efficacy calculated in accordance with arithmetic means and using Abbott's formula, in accordance with guideline recommendations (7AE17a). Based upon the calculations conducted, >99% efficacy was observed at Day 29 and at all subsequent timepoints and mite counts were statistically significantly lower ($p<0.0001$) compared to baseline counts using ANOVA at all timepoints (Day -14 – Day 90). Adequate efficacy in support of the claim was demonstrated (guideline 7AE17a specifies that in order for a claim for *Demodex* mites to be accepted greater than 90% efficacy should be demonstrated).

Secondary efficacy parameters evaluated included the parasitological cure rate, with study results indicative of a 67% cure-rate in the IVP group by Study Day 14 and 100% cure rate in the IVP group by Day 44. Additional secondary efficacy parameters were improvements, relative to baseline, in the clinical signs of demodicosis and the extent of skin lesions. With regards the improvement of the clinical signs of demodicosis, it is noted that by Day 90, all clinical signs evaluated had improved, with none of the animals in the IVP group demonstrating casts, comedones, crusts, erythema, papules or pustules. Although some of the animals in the IVP continued to exhibit alopecia, this had markedly improved: At Day -3, 55.6% of the IVP animals exhibited moderate alopecia and 44.4% severe alopecia, however by Day 90, alopecia was not evident in 62.5% of animals in the IVP group and was considered mild in 37.5% of animals. With regards the extent of skin lesions, a 95% reduction from baseline was observed for the IVP group at Day 90.

The clinical field trial presented was conducted to evaluate the efficacy and safety of Simparica Trio when used in the treatment of natural *D. canis* infestations in dogs presented as veterinary patients in Europe. The study was GCP compliant, randomised and blinded and a study protocol was provided. The study was conducted in veterinary practices across three EU member states, France, Italy and Portugal.

This was a positively controlled study using the authorised presentations of Simparica Trio chewable tablets for dogs as the investigational product (IVP) and NexGard Spectra chewable tablets for dogs as comparator product (CP). The use of NexGard Spectra as control product is considered appropriate given that it is approved for the treatment of demodicosis caused by *Demodex canis*. Allocation to treatment was randomised and used a 2:1 allocation ratio (Simparica Trio:NexGard Spectra). The IVP and CP were used at the recommended treatment doses as specified in the product SPCs and administered at monthly intervals for up to 4 treatments.

111 privately owned dogs (55 male, 56 female) of various breeds ranging from 0.2 – 12 years of age and 2.3 – 59.0 kg in bodyweight were included in the study population, with short and long-haired dogs represented. All animals included in the study were determined to have natural infection with *Demodex*

mites (as determined by deep skin scrapings) and clinical signs consistent with generalised demodicosis involving either: an entire body region; five or more separate areas each with a diameter >2.5 cm; or, pododemodicosis involving 2 of more feet. Dogs were kept in normal domestic arrangements and households with up to three dogs were selected for the study and if more than one dog in a household met the inclusion criteria, the dog with the most severe clinical signs of demodicosis was selected as the primary patient and used for efficacy and safety evaluations. All other dogs in the same household exhibiting clinical signs of demodicosis were considered as supplementary patients and received the same treatment as the primary patient in the household but were only included in safety evaluations.

Each animal underwent physical examination at enrolment and at subsequent visits to the veterinary clinic. On study days 1, 30, 60, and if necessary 90 and 120, mite counts were conducted. On Study days 0, 14, 30, 60, 90 and 120, clinical assessments for the scoring of skin lesions associated with demodectic mange were conducted and the percentage body surface area affected was also determined.

The primary efficacy parameter was the percentage reduction in live mite counts compared to baseline on Days 30 and 60, with percentage efficacy calculated via Abbott's formula and using arithmetic means, which is acceptable in accordance with guideline recommendations (7AE17a). Based upon the calculations conducted, >92% efficacy was observed at Day 30 and at all timepoints thereafter, which meets guideline 7AE17a requirements in support of efficacy (the guideline specifies that ≥90% efficacy should be demonstrated for a claim for mites).

Secondary efficacy parameters included the parasitological cure rate, with results demonstrating a 76.2% cure rate in dogs in the IVP group by Study Day 30, a 98.4% cure rate in the IVP group by Study Day 60 and 100% at all timepoints thereafter. Additional secondary efficacy parameters were improvements in the clinical signs of demodicosis and the extent of skin lesions from baseline. It is noted that by Day 90, all clinical signs evaluated had improved, with none of the animals in the IVP group demonstrating casts, comedones, crusts or papules and only 1.6% demonstrating crusts, erythema and pustules. Further, alopecia had markedly improved with a reduction from 100% of animals with this clinical sign at baseline to 27.4% at study completion. With regards the extent of skin lesions, a 93% reduction from baseline was observed for the IVP group at Day 90.

It is acknowledged that the *Guideline on the demonstration of efficacy of ectoparasiticides (7AE17a)* suggests that efficacy data from at least two dose confirmation studies and clinical field trial data are required, and, therefore, the adequacy of the efficacy data package for this specific indication could be questioned on the basis that a single confirmatory study only was presented and that this study was conducted outside the EU. However, it is noted that the dose confirmation study presented was conducted in naturally infested (privately owned) dogs, thus involving a variety of strains and demographic characteristics, while using the most appropriate (parasitological and clinical) endpoints and examination frequency. Further, the clinical field trial, which included a substantial number of client-owned dogs, was conducted in a number of different EU countries (3) and involved a large number of veterinary practices (19). Therefore, given the overall data package provided and the conclusions drawn from the dose confirmation study and the clinical field trial presented, the indication proposed for inclusion in SPC section 4.2 ("For the treatment of demodicosis (caused by *Demodex canis*)") is considered to have been suitably supported and can be accepted.

It is noted that the following text is proposed for inclusion in section 4.9 of the SPC:

"Treatment of demodicosis (caused by *Demodex canis*):

Administration of a single dose once monthly for two consecutive months is efficacious and leads to a marked improvement of clinical signs. Treatment should be continued until skin scrapings are negative on at least two consecutive occasions one month apart. As demodicosis is a multifactorial disease, it is advisable to also treat any contributing, underlying conditions appropriately."

The text proposed for inclusion in the Simparica Trio SPC is supported by the data package presented (efficacy in line with guideline requirements was achieved after two consecutive monthly administrations). Further, it is noted that the text includes clear instruction that treatment should be continued until skin scrapings are negative on at least two consecutive occasions one month apart. This is considered appropriate.

2.2.3. Prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection)

To support the proposed indication for the prevention of the eye worm *Thelazia callipaeda* in dogs, the applicant has presented results of one clinical field trial.

The GCP compliant, negatively controlled, clinical field trial investigated the efficacy of Simparica Trio (IVP) administered orally at monthly intervals for the prevention of establishment of infection with *Thelazia callipaeda* (thelaziosis) in dogs presented as veterinary patients in two EU member states, France and Italy. The study sites were either regions endemic for *T. callipaeda* or regions in which autochthonous cases had been reported for several years. The study was conducted during a period in which transmission of *T. callipaeda* is known to occur.

The negative control used was Simparica (CP), which contains sarolaner as active substance and whilst this active substance is also included in the formulation of the IVP, it is noted that sarolaner acts as an ectoparasiticide and is not expected to demonstrate efficacy against helminths such as *T. callipaeda*. This is further supported by the overall incidence rate of *T. callipaeda* infection (27.6%) observed in control animals during the study period. It is considered that an acceptable level of exposure to *T. callipaeda* was present during the conduct of the study.

The commercial formulations of the IVP and CP were used at the recommended treatment doses as specified in the product SPCs and administered at monthly intervals for up to 6 treatments.

The study population included 125 privately-owned dogs (72 males and 53 females) ranging from 4.5-56.2 kg in bodyweight and 0.3-15 years of age. For the purpose of confirming that none had pre-existing adult *T. callipaeda* infections at Day 0, all animals were examined by a veterinarian for the presence of *T. callipaeda* and were administered a milbemycin oxime-containing product administered per label for the treatment of *T. callipaeda* prior to Day 0.

The primary efficacy parameter was the observation of eyeworms at any time during the study period. In the IVP-treated group, 100% of animals remained worm-free compared to 72.4% in the control-treated group; a statistically significant difference was observed.

Secondary efficacy parameters included nematode counts in eyeworm positive animals, with sixteen animals in the negative control group confirmed to be infected with *T. callipaeda* during the course of the study and both adult and L4 *T. callipaeda* identified. The individual adult worm counts ranged from 1-7, whilst the individual L4 worm counts ranged from 2-3.

Another secondary efficacy parameter was the clinical signs of thelaziosis: ten of the 16 animals confirmed eyeworm-positive showed ocular clinical signs. Whilst some of the animals in the IVP group were observed to exhibit ocular signs (such as ocular discharge, conjunctivitis and blepharospasm), *T. callipaeda* were not identified in any of the animals in the IVP group.

According to VICH GL7 (Efficacy of anthelmintics: general requirements, CVMP/VICH/832/99-corr) and VICH GL19 (Efficacy of anthelmintics: specific recommendations for canines, CVMP/VICH/835/99-FINAL), it is normally expected that two dose confirmation studies supported by field data should be provided to be granted a claim. However, for the current application no specific dose confirmation studies have been

conducted and instead the data derived from a single clinical field trial has been presented. The applicant has justified such an approach highlighting that no experimental model for eyeworm exists and therefore a comprehensive clinical field efficacy trial is the only viable means of data generation; this is considered acceptable justification for the omission of a specific dose confirmation study.

Therefore, given the results from the GCP clinical field trial presented, which was conducted in two different European locations, indicate 100% efficacy in preventing the establishment of infection with *Thelazia callipaeda* adults, as per the proposed indication, and in consideration of the 'three Rs', the indication proposed for inclusion in SPC section 4.2 ("For the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection)") is considered to have been suitably supported and can be accepted.

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 product is exclusively indicated when use against ticks or fleas and gastrointestinal nematodes is indicated at the same time; the product also provides concurrent efficacy for the prevention of heartworm disease and angiostrongylosis. The product can be used as part of a treatment strategy for the control of flea allergy dermatitis.

The product contains a fixed combination of three active substances: sarolaner, moxidectin and pyrantel (as embonate). Sarolaner is a systemically acting acaricide and insecticide belonging to the isoxazoline family, whilst moxidectin, a second-generation macrocyclic lactone of the milbemycin family, and pyrantel, a nicotinic acetylcholine channel receptor agonist, act against endoparasites (gastrointestinal and vascular).

The product 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 grouped variation is to add three new therapeutic indications: for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), for the treatment of demodicosis (caused by *Demodex canis*), and for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection).

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce additional indications to existing presentations of Simparica Trio chewable tablets for dogs, the benefit will arise from the inclusion of the new indications. The indications for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), for the treatment of demodicosis (caused by *Demodex canis*), and for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection) are considered as being of benefit for the patient.

Additional benefits

The variation increases the range of available treatment possibilities for sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*) and for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection), both of which are of zoonotic potential.

3.2. Risk assessment

As this is a variation to introduce additional indications to existing presentations of Simparica Trio chewable tablets for dogs, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indications. As the product 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 new indications 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 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 proposed new indications.

Risk for the user:

The dose rate and frequency of treatment does not change due to the addition of the new indications for the treatment of sarcoptic mange, for the treatment of demodicosis and for the prevention of establishment of thelaziosis. 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 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 product has been shown to be efficacious for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), for the treatment of demodicosis (caused by *Demodex canis*), and for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection).

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 (Regulation (EU) 2019/6), as follows: to add three new therapeutic indications for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), for the treatment of demodicosis (caused by *Demodex canis*), and for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection).

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 these variations, sections 4.2, 4.9 and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.