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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP type II variation assessment report for Simparica (EMEA/V/C/003991/II/0006)

International non-proprietary name: sarolaner

To add new indications for the treatment of ear mites and demodicosis in dogs

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

Rapporteur: J. G. Beechinor

Co-rapporteur: P. Hekman

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1. Background information on the variation

Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Zoetis Belgium SA (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for Simparica.

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 new indications for the treatment of ear mites and demodicosis in dogs.

Current	**Proposed**
ANNEX I **SUMMARY OF PRODUCT CHARACTERISITISC** 4.2 Indications for use, specifying the target species For the treatment of tick infestations (*Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus* and *Rhipicephalus sanguineus*). The veterinary medicinal product has immediate and persistent tick killing activity for at least 5 weeks. For the treatment of flea infestations (*Ctenocephalides felis* and *Ctenocephalides canis*). The veterinary medicinal product has immediate and persistent flea killing activity against new infestations for at least 5 weeks. The veterinary medicinal product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). For the treatment of sarcoptic mange (*Sarcoptes scabiei*).	**ANNEX I** **SUMMARY OF PRODUCT CHARACTERISITISC** 4.2 Indications for use, specifying the target species For the treatment of tick infestations (*Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus* and *Rhipicephalus sanguineus*). The veterinary medicinal product has immediate and persistent tick killing activity for at least 5 weeks. For the treatment of flea infestations (*Ctenocephalides felis* and *Ctenocephalides canis*). The veterinary medicinal product has immediate and persistent flea killing activity against new infestations for at least 5 weeks. The veterinary medicinal product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). For the treatment of sarcoptic mange (*Sarcoptes scabiei*). **For the treatment of ear mite infestations (*Otodectes cynotis*).** **For the treatment of demodicosis (*Demodex* spp.).**
4.9 Amounts to be administered and administration route n/a	4.9 Amounts to be administered and administration route **For the treatment of ear mite infestations (*Otodectes cynotis*) a single dose should be administered.** (...)

	For the treatment of demodicosis (caused by *Demodex* spp.) the administration of a single dose for three consecutive months is efficacious and leads to a marked improvement of clinical signs. As demodicosis is a multi-factorial disease, it is advisable to also treat any underlying disease appropriately.
5.1 Pharmacodynamic properties (...) Sarolaner is active against adult fleas (*Ctenocephalides felis* and *Ctenocephalides canis*) as well as several tick species such as *Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus, Rhipicephalus sanguineus* and the mite *Sarcoptes scabiei*. In addition, in laboratory studies, sarolaner was shown to be active against other tick species such as *Dermacentor variabilis, Ixodes scapularis, Amblyomma americanum, Amblyomma maculatum* as well as the mite species *Demodex canis* and *Otodectes cynotis*.	5.1 Pharmacodynamic properties (...) Sarolaner is active against adult fleas (*Ctenocephalides felis* and *Ctenocephalides canis*) as well as several tick species such as *Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus, Rhipicephalus sanguineus* and the mites ***Demodex canis, Otodectes cynotis*** and *Sarcoptes scabiei*. In addition, in laboratory studies, sarolaner was shown to be active against other tick species such as *Dermacentor variabilis, Ixodes scapularis, Amblyomma americanum* and *Amblyomma maculatum* ~~as well as the mite species *Demodex Canis* and *Otodectes cynotis*.~~
Annex IIIB **PACKAGE LEAFLET** 4 Indications For the treatment of tick infestations (*Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus* and *Rhipicephalus sanguineus*). The veterinary medicinal product has immediate and persistent tick killing activity for at least 5 weeks. For the treatment of flea infestations (*Ctenocephalides felis* and *Ctenocephalides canis*). The veterinary medicinal product has immediate and persistent flea killing activity against new infestations for at least 5 weeks. The veterinary medicinal product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). For the treatment of sarcoptic mange (*Sarcoptes scabiei*).	**Annex IIIB** **PACKAGE LEAFLET** 4 Indications For the treatment of tick infestations (*Dermacentor reticulatus, Ixodes hexagonus, Ixodes ricinus* and *Rhipicephalus sanguineus*). The veterinary medicinal product has immediate and persistent tick killing activity for at least 5 weeks. For the treatment of flea infestations (*Ctenocephalides felis* and *Ctenocephalides canis*). The veterinary medicinal product has immediate and persistent flea killing activity against new infestations for at least 5 weeks. The veterinary medicinal product can be used as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD). For the treatment of sarcoptic mange (*Sarcoptes scabiei*). **For the treatment of ear mite infestations (*Otodectes cynotis*).** **For the treatment of demodicosis (*Demodex* spp.).**
8 Dosage for each species, route(s) and method of administration n/a	8 Dosage for each species, route(s) and method of administration **For the treatment of ear mite infestations (*Otodectes cynotis*) a single dose should be administered.**

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2. Scientific overview

Simparica is currently indicated for use in dogs for the treatment of flea and tick infestations, as well as part of a treatment strategy for the control of Flea Allergy Dermatitis (FAD), and for the treatment of sarcoptic mange (*Sarcoptes scabiei).* The product is authorised with a treatment schedule of administration at monthly intervals, based on the local epidemiological situation, at a dose of 2-4 mg/kg. This variation application is to include new indications for the treatment of ear mites (*Otodectes cynotis*) and demodicosis (*Demodex canis*).

In support of the new indications (treatment of ear mites, treatment of demodicosis), the applicant has presented the results of four efficacy studies. The dose used in the studies is the same as that currently approved; namely 2-4 mg/kg. For the treatment of ear mite infestations it is proposed that a single dose should be administered. For the treatment of demodicosis it is proposed that a single dose once monthly for three consecutive months is efficacious.

No new preclinical or specific target animal safety studies have been conducted by the applicant in the context of this variation application. Given that no change to the posology is proposed, no new user safety assessment or environmental safety assessment has been provided. The CVMP accepts that the proposed change to the marketing authorisation does not impact on target animal tolerance, user safety, or safety for the environment.

Ear mites (*O. cynotis*)

Efficacy of sarolaner against *Otodectes cynotis* was evaluated in a laboratory dose confirmation study conducted in South Africa and a multicentre clinical field study conducted in Europe with client owned dogs presenting with ear mite infestation.

A GCP laboratory study was conducted for the purpose of evaluating the efficacy of the test product at a dosage of 2 mg/kg given as a single dose or as two doses at a one-month interval, against induced *O. cynotis* infestations in dogs. 32 mixed breed and beagle adult dogs were used in the study.

O. cynotis mites were harvested from donor dogs and approximately 100 mites were transferred into each of the ears of recipient dogs before study start. The test animals were randomly allocated to four treatment groups (eight dogs/group) and were administered either placebo (groups 1 and 2) or the test item (groups 3 and 4) on Day 0. Treatments were repeated on Day 30 for dogs in group 2 (placebo) and group 4 (test item). Total, quantitative mite counts were performed using a lavage technique on Day 30 (groups 1 and 3) or Day 60 (groups 2 and 4). The percent reductions in live mite counts relative to placebo based on the arithmetic means were calculated. Under the conditions tested, the test item administered orally as a single dose resulted in a 98.7% reduction in ear mites and two doses administered at an interval of one month resulting in a 99.9% reduction in ear mites. In this study, the test product was well tolerated. Based on the findings of this study, the applicant recommends a single oral dose of 2 mg PF-06450567/kg for the treatment of aural *O. cynotis* infestations in dogs.

A GCP clinical field study, designed as a randomised, single-blinded, multi-centre clinical field study with a positive control, was conducted at multiple sites in France, Hungary, Italy and Portugal. A total of 414 dogs (≥8 weeks of age and weighing ≥1.3 kg) from single- or multi-dog households were enrolled. The dog in each household with the most severe signs of ear mite infestation and with visible live ear mites present in at least one ear was selected as a primary patient at enrolment. All other dogs in the same household were enrolled in the study as supplementary dogs. Primary dogs were allocated in a ratio of 2:1 to one of two treatment groups: the test (Simparica) and positive control (Advocate Spot-On), in a randomised block design. In the test product group, there were 163 primary (120 supplemental) dogs and in the control group there were 78 primary (53 supplemental) dogs. The test and positive control products were administered on Day 0. Mite assessments by otoscopic examination and/or microscopic examination of an ear swab and clinical assessments of ear lesions were conducted on Days 0, 14 and 30. Dogs with viable mites on Day 30 received a second treatment and were re-evaluated on Day 60. Dogs that did not have viable mites on Day 30 completed the study on Day 30 and did not received further treatment. The primary efficacy end point was parasitological cure rate on Day 30, defined as animals having no live mites present during *O. cynotis* assessment (otoscopic examination and/or microscopic examination of an ear swab and clinical assessments of ear lesions).

The test product and positive control populations were similar in terms of age, breed, gender, weight and time spent indoors and/or outdoors. The parasitological cure rate for sarolaner was non-inferior to moxidectin/imidacloprid at Day 30 (for sarolaner, the parasitological cure rate on Day 30 was 90.5%, increasing to 99.4% on Day 60 (following two treatments)). Over the course of the study, there was a reduction in the numbers of animals with clinical signs of *O. cynotis* infection in both study groups.

In terms of efficacy, the overall conclusions of the study are accepted: the product when administered once to dogs under field conditions of use was effective against ear mites (elimination of live *O. cynotis* and improvement of clinical signs associated with infection). Regarding safety, the test product was well tolerated.

CVMP overall conclusions on acceptability of the proposed indication for *O. cynotis*

Based on the results of this clinical field study conducted in the EU, supported by the results of the laboratory, the CVMP accepts that a single dose with sarolaner (2-4 mg/kg in a chewable tablet) was safe and effective in the treatment of ear mites, with elimination of live mite infestation and reduction in clinical signs by Day 30 after treatment. Therefore, the proposed treatment recommendation ("For the treatment of ear mite infestations (*Otodectes cynotis*) a single dose should be administered") is accepted. However, noting the findings of the field study that live mites were detected in approximately 10% of dogs 30 days post-treatment, the following statement is proposed for inclusion

in section 4.9: "A further veterinary examination 30 days after treatment is recommended as some animals may require a second treatment."

While 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, the CVMP is of the opinion that further confirmatory data to support efficacy of the product is unnecessary on the basis that:

- In the field study, determination of efficacy was based on parasitological cure (absence of live mites at the site of infestation, ear) and, therefore, this study can be regarded as a confirmatory study. Further, the study included a substantial number of client-owned dogs and was conducted at multiple sites in the EU and can be considered representative of the EU situation.
- The CVMP, during the assessment of the initial MAA, suggested/implied that the indication for *Otodectes cynotis* could not be approved in the absence of additional field data generated in the EU. This deficiency has now been addressed.

Demodicosis (*D. canis*)

Efficacy of sarolaner against *Demodex canis* was evaluated in a laboratory dose confirmation study conducted in South Africa and a multicentre clinical field study conducted in Europe with client owned dogs presenting with generalised demodicosis.

A GCP laboratory study was conducted for the purpose of evaluating the efficacy of the test product at a dosage of 2 mg/kg given as three doses at a one-month interval, against natural infestations of *D. canis* in dogs. Sixteen mixed breed adult dogs were used in the study. The test animals were randomly allocated to two treatment groups (eight dogs/group) and were administered either the test product (group 1) or a positive control product (group 2, Advocate Spot-on for Dogs) on Day 0. Due to the potentially debilitating nature of the disease, the use of a positive control is accepted as justified. Treatments were repeated on Day 30 and 60 for dogs in group 1 and weekly (in accordance with the approved treatment schedule) for dogs in group 2. Mite counts were performed on samples collected by deep skin scrapings from five different body areas on study days -4, 14, 29, 44, 59, 74 and 91. In addition, at each time point, skin lesions, characteristic for demodicosis including comedones/papules/pustules, casts/scales/crusts, alopecia and erythema were graded in four categories as absent, mild, moderate or severe. The primary efficacy endpoint was the percent reductions in live mite counts relative to the pre-treatment counts. The secondary efficacy end points were the frequency of dogs in each group with no live mites following treatment on each assessment day and frequency distribution of skin lesion severity grades for each lesion type in each group.

Under the conditions tested, the test item resulted in a 99.8% and 100.0% reduction in live mites, compared to pre-treatment counts, on Days 29 and 59, respectively. In this study, the test product was well tolerated. Clinical signs of demodicosis improved throughout the treatment period for dogs in both treatment groups. There were no treatment-related adverse reactions during the study.

Based on these data, and in the study population tested, it is accepted that three treatments at monthly intervals with sarolaner was effective at eliminating *D. canis* infestation.

A GCP clinical field study, designed as a randomised, single-blinded, multi-centre clinical field study with a positive control, was conducted at multiple sites in France, Hungary, Italy and Portugal. A total of 98 dogs with natural infestations of *D. canis* (≥8 weeks of age and weighing ≥1.3 kg) from single- or multi-dog households were enrolled. One dog in each household that showed clinical signs of generalised demodicosis (presence of clinical signs consistent with demodicosis) and had at least four live *D. canis* mites in five deep skin scrapings at enrolment was selected as primary patient. All other dogs in the same household were enrolled in the study as supplementary dogs if they showed signs of

demodicosis and needed miticide treatment. Primary dogs were allocated in a ratio of 2:1 to one of two treatment groups: the test (Simparica) and positive control (Advocate Spot-On), in a randomised block design. In the test product group, there were 53 primary (10 supplemental) dogs and in the control group there were 28 primary (7 supplemental) dogs. The test and positive control products were administered on Day 0 and treatment was repeated monthly for the test product and either monthly (for mild and moderate cases, 60.7%) or weekly (for severe cases, 39.3%) for the reference product (imidacloprid/moxidectin) for up to six months. Efficacy assessment was conducted monthly and included mite assessments (skin scrapings) and clinical assessment (skin lesions). Dogs remained in the study at least until Day 60 and completed the study when no live mites were found on two consecutive monthly skin scrapings or on Day 180. The primary efficacy end point was parasitological cure rate on Day 30 and 60, defined as no live mites present in the skin scrapings.

The test product and positive control populations were similar in terms of age, breed, gender, weight and time spent indoors and/or outdoors. Based on the primary efficacy parameter the test item was confirmed to be non-inferior to the control product, Advocate, at Day 60. For sarolaner, the parasitological cure rate was 15.1, 69.2, 92.9, 93.8, 100 and 100% on Days 30, 60, 90, 120, 150 and 180, respectively (at most six monthly treatments were required for cure, 69.4% of dogs only needed three treatments and 95.9% were cured after up to four treatments). Over the course of the study, there was a reduction in the numbers of animals with clinical signs of *D. canis* infection in both study groups.

In terms of efficacy, the overall conclusions of the study are accepted: the product when administered once every three months to dogs under field conditions of use was effective against *D. canis* (elimination of *D. canis* and improvement of clinical signs associated with infection). Regarding safety, the test product was well tolerated.

CVMP overall conclusions on acceptability of the proposed indication for *D. canis*

Based on the results of the clinical field study conducted in the EU, supported by the results of the laboratory study, the CVMP accepts that the administration of a single dose once monthly for three consecutive months with sarolaner (2-4 mg/kg in a chewable tablet) was safe and effective in the treatment of *D. canis*. However, noting that parasitological cure for all primary animals was only achieved by Day 180 and allowing for variability in individual response, the following sentence is proposed for inclusion in section 4.9 of the SPC: "In all cases it is essential that the treatment should be continued until skin scrapings are negative on at least 2 consecutive occasions one month apart". In addition, in order to provide clarity to the user, the frequency of dosing for treatment of *D. canis* is highlighted as once monthly in section 4.9 of the SPC: "For the treatment of demodicosis (caused by *Demodex canis*) the administration of a single dose once monthly for three consecutive months is efficacious and leads to a marked improvement of clinical signs".

While 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, the CVMP is of the opinion that further confirmatory data to support efficacy of the product is unnecessary on the basis that:

- In the field study, determination of efficacy was based on parasitological cure (absence of live mites) and, therefore, this study can be regarded as a confirmatory study. Further, the study included a substantial number of client-owned dogs and was conducted at multiple sites in the EU and can be considered representative of the EU situation.
- The CVMP, during the assessment of the initial MAA, suggested/implied that the indication for *D. canis* could not be approved in the absence of additional field data generated in the EU. This deficiency has now been addressed.

CVMP overall conclusion on acceptability of section 5.1 of the SPC

As part of this variation application, the applicant proposed minor amendments to the text included in section 5.1 (Pharmacodynamic properties) of the SPC. Given that the proposed indications for *Otodectes cynotis* and *Demodex canis* are accepted, the original amendments to section 5.1 proposed by the applicant can be accepted. However, noting the advice included in the "Question and answer on the information contained within section 5.1 of the SPC on pharmacodynamic properties for pharmaceutical products (EMA/CVMP/757903/2016)" recently adopted by the CVMP, the CVMP agreed that the following text should be deleted from section 5.1: "In addition, in laboratory studies, sarolaner was shown to be active against other tick species such as *Dermacentor variabilis*, *Ixodes scapularis*, *Amblyomma americanum* and *Amblyomma maculatum*."

3. Benefit-risk assessment of the proposed change

Benefit assessment

Direct benefits arise from the treatment of ear mite infestations and demodicosis.

Risk assessment

The proposed indications for the treatment of ear mite infestations and demodicosis relate to the administration of the product at the same posology as that which is currently approved (i.e. up to once monthly). It can therefore be concluded that no new risk should arise from the introduction of a claim in respect of these mite species.

Evaluation of the benefit-risk balance

Given that it is not expected that any new risk will result from the inclusion of the proposed additional indication, it can be accepted that there should be an increased benefit from the use of the product for the treatment of ear mite infestations and demodicosis in dogs.

No change to the impact on the environment is envisaged.

4. Overall conclusions of the evaluation and recommendations

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

Changes to the Community marketing authorisation

Changes are required in Annexes I, IIIA and IIIB to the Community marketing authorisation. Please refer to the separate product information with tracked changes.