EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for type II variation for Bravecto Plus (EMEA/V/C/004440/II/0006)

INN: fluralaner / moxidectin

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Intervet International B.V. (the applicant), submitted to the European Medicines Agency (the Agency) on 25 July 2019 an application for a type II variation for Bravecto Plus.

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 modify the approved therapeutic indication for the prevention of heartworm disease caused by *Dirofilaria immitis*, i.e. to extend the duration of prevention from 8 weeks to 12 weeks.

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

The applicant received scientific advice from the CVMP on 21 March 2019 (EMA/CVMP/SAWP/16549/2019). The scientific advice pertained to clinical development of the dossier. The company provided the Agency with the request concerning advice on efficacy issues in relation to proposed changes in the indication, i.e. extension of the duration of prevention of heartworm disease.

The applicant proposed to further support the claim "*For the prevention of heartworm disease caused by Dirofilaria immitis for 12 weeks*" by use of available PK data.

Based on the scientific advice provided, the CVMP was willing to accept the concept of an effect of the active substance on larvae already present in the animal at the time of treatment. However, this effect is usually demonstrated in clinical trials using a challenge with L3 larvae of *D. immitis* performed before treatment, however, such data was not available.

In their scientific advice, the CVMP concluded that if the applicant can

1. Establish a moxidectin threshold plasma concentration for reliable parasiticidal activity against *D. immitis* larvae (minimal effective concentration).
2. Confirm susceptibility of L4 larvae (that would be the stage that is present in the animal 30 days following infection) to moxidectin in cats

a 12-weeks treatment interval for the prevention of heartworm disease may be accepted.

After having taken into account all the data provided, it is considered that the applicant followed the scientific advice.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

The product Bravecto Plus spot-on solution for cats is a fixed combination of two active pharmaceutical ingredients, fluralaner (an insecticide and acaricide of the isoxazoline family) and moxidectin (a semisynthetic derivative of nemadectin, belonging to the milbemycin group of macrocyclic lactones).

Bravecto Plus spot-on solution for cats is currently indicated for use in cats for the treatment of tick (*Ixodes ricinus*) and flea (*Ctenocephalides felis*) infestations, providing immediate and persistent killing activity for a period of 12 weeks and can be used as part of a treatment strategy for flea allergy dermatitis. It is also indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* for a period of 8 weeks, for the treatment of infestations with ear mites (*Otodectes cynotis*) and for the treatment of infections with intestinal roundworm (*Toxocara cati* - 4th stage larvae, immature adults and adults) and hookworm (*Ancylostoma tubaeforme* - 4th stage larvae, immature adults and adults).

Bravecto Plus spot-on solution for cats is available in three different strengths: 112.5 mg fluralaner/5.6 mg moxidectin, 250 mg fluralaner/12.5 mg moxidectin and 500 mg fluralaner/25 mg moxidectin per pipette.

The proposed variation is to change the following indication of Bravecto Plus as stated in the product information:

"For the prevention of heartworm disease caused by Dirofilaria immitis for 8 weeks."

to:

"For the prevention of heartworm disease caused by Dirofilaria immitis for 12 weeks."

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 amended 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 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 have 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 proposed modification of the heartworm indication will not present an additional risk to the one currently accepted for the animal, user of the environment.

2.2. Efficacy for the proposed claim: "For the prevention of heartworm disease caused by Dirofilaria immitis for 12 weeks"

In support of the above indication, the applicant has provided the efficacy results of five dose confirmation studies and data on the pharmacokinetics of moxidectin obtained in four laboratory studies. Also, as supportive information for the targeted claim, the applicant has provided scientific articles and reports from the public domain concerning the efficacy of moxidectin against *D. immitis*.

2.2.1. Dose confirmation studies

The applicant has performed five GCP-compliant dose confirmation studies in order to demonstrate the efficacy of a single topical dose of Bravecto Plus for the prevention of heartworm disease for a period of 12 weeks. All five studies followed the same design: 30 healthy cats/study, the same number of groups (3 groups), the same number of cats per group (n=10), the same number of parasites used at challenge (100 L3 larvae of *D. immitis*), the same type of animals and same experimental conditions.

Three of these dose confirmation studies were submitted with the initial marketing authorisation application, whilst two studies are new and assessed for the first time in the context of the current variation application.

All dose confirmation studies were conducted in the USA, using USA isolates. The main difference between the five studies consists in the *D. immitis* isolate origin; however, use of the same isolate origin is not mandatory. With regard to the non-European origin of the *D. immitis* strains used, the applicant has already substantiated in the context of the initial marketing authorisation application that no variation in susceptibility between USA and EU strains is expected and therefore the relevance for the EU (in terms of representativeness and susceptibility) of an USA isolate is accepted.

In all studies, Bravecto Plus was administered either 60 or 90 days before infection (Day 0 or Day 30); all studies were conducted as negatively controlled studies, using an untreated group. The product was administered to cats at a dose of 2 mg moxidectin/kg bodyweight, i.e. at the minimum dose rate indicated in the SPC. In order to induce infection, the cats in all three groups were inoculated subcutaneously with 100 *D. immitis* L3 larvae at Day 90.

In order to demonstrate the preventive action of the product, animals were necropsied approximately 6 months after infection, which corresponds to the duration of development from L3 larvae to adult *D. immitis* worms. The evaluation of effectiveness was based on parasite counts (the number of adult heartworms recovered at necropsy in the treated groups compared to the control group), as required by VICH GL7 *Efficacy of anthelmintics: general requirements*; effectiveness was defined as 100% prevention of establishment of adult *D. immitis* infections. Efficacy was calculated using arithmetic or geometric mean worm counts. For each treatment group, the infection prevention rate was also calculated, as the percentage of treated animals free of heartworms at necropsy, relative to the control group.

The results obtained in these studies are summarised below:

- 100% efficacy against the establishment of infection with adult *D. immitis* was demonstrated in this study when treatment was administered either 60 or 90 days before artificial infection; heartworm prevention rate for each treated group was 100%. There was adequate infection of cats in the control group. Therefore, this study supported the prevention of heartworm disease caused by *D. immitis* for a period of up to 12 weeks. In this study, the pharmacokinetics of moxidectin was also evaluated (plasma concentrations were determined, including at Day 86).

- Prevention of infection was achieved in 7 out of 10 cats when the product was applied 90 days before artificial infection (one worm was recovered from each of 3 cats). Using geometric mean counts, 92.3% efficacy was determined for animals treated 90 days before infection. There was adequate infection of cats in the control group. As VICH GL20 *Efficacy of anthelmintics: specific recommendations for felines* indicates that higher efficacy standards (i.e. up to 100%) may be imposed for *D. immitis*, it is considered that overall, this study did not substantiate a claim for the prevention of heartworm disease for 12 weeks.
- No worms were recovered at necropsy from any of the animals treated 60 or 90 days before artificial infection. There was inadequate infection of cats in the control group since live worms were recovered from only four cats (only one worm was recovered from each of two cats). In the absence of adequate infection in the control group, the findings of this study are considered inadequate to support a claim for the prevention of heartworm disease for 12 weeks.
- No worms were recovered from any of the treated animals; based on geometric/arithmetic means, both treated groups (60 or 90 days before artificial infection) showed an efficacy of 100%. There was inadequate infection of cats in the control group since live worms were recovered from only four cats (only one worm was recovered from each of three cats). In the absence of adequacy of infection in the control group, the findings from this study are considered inadequate to support a claim for the prevention of heartworm disease for 12 weeks. In this study, moxidectin plasma concentrations were determined at Day 89.
- No worms were recovered from any of the treated animals at necropsy; based on geometric/arithmetic means, both treated groups showed an efficacy of 100% against the establishment of infection with adult *D. immitis*. There was adequate infection of cats in the control group. The infection prevention rate was 100%. This study therefore supports the prevention of heartworm disease caused by *D. immitis* for a period of up to 12 weeks post-treatment.

Three months after administration, the product did not achieve 100% efficacy in all of the studies. The failure of the prevention of infection with *D. immitis* 90 days after a single treatment in a certain percentage of cats was observed in one study. This observation is potentially caused by the variable plasma concentration of moxidectin (and fluralaner) observed in the PK studies.

It is noted that a claim for the prevention of heartworm disease caused by *Dirofilaria immitis* for 8 weeks was accepted, based on the efficacy data provided in support of the original application.

With regard to the adverse events observed in these dose confirmation studies, one animal showed redness and alopecia at the treated area and these were considered treatment related. Alopecia is already listed in section 4.6 of the SPC, whilst redness has been introduced as an adverse event in the product information in the context of the current application.

2.2.2. Pharmacokinetics

The results of the pharmacokinetic studies previously submitted did not show evidence of a biologically relevant interaction between moxidectin and fluralaner and thus the pharmacokinetic profile of moxidectin is similar when administered alone or in combination with fluralaner.

With regard to the pharmacokinetics of moxidectin after topical administration of Bravecto Plus, the applicant (re-)evaluated and (re-)submitted all available data, including previously assessed studies. In addition, the applicant presented a small, supportive, *in vitro* screening study, which evaluated the activity of moxidectin against L3 and L4 larval stages of *D. immitis*.

Following the scientific advice provided by the CVMP, to support the effect of the product against

existing larvae prior to treatment, the applicant determined the PK profile of moxidectin in order to demonstrate that, in all cats, moxidectin plasma concentrations immediately following treatment (one day after treatment) are above or equal to the concentrations observed approximately 60 days following treatment, that is, the concentration considered as the minimal effective concentration at the end of the period for which an acceptable level of efficacy has already been demonstrated.

Justification for an effect against existing larvae of *D. immitis* prior to treatment application is based on the assumption that, if plasma concentrations of moxidectin observed at 60 days post-treatment are accepted as being efficacious, then plasma concentrations above or equal to this at one day post-treatment will also be efficacious against L3 and L4 larvae already present.

Sixty days after treatment can be considered as the time point where an acceptable level (100%) of efficacy was attained in the laboratory dose confirmation studies (that had also demonstrated adequacy of infection). At 56 days after treatment, the highest (worst-case) individual moxidectin plasma concentration, in the dose confirmation study that evaluated plasma moxidectin concentrations and which included an adequate level of infection was 4.18 ng/ml and this can be considered as the minimal effective concentration which should be attained immediately after treatment in order to ensure that *D. immitis* larvae already present in the body are killed.

Data resulting from three previous studies showed that, in all animals dosed at 2 mg moxidectin/kg bw, pharmacokinetic measurements of moxidectin plasma concentration one day after treatment ranged between 5.37 – 86.4 ng/ml, which is clearly above 4.18 ng/ml. The values obtained one day after treatment were significantly higher than the values obtained 56 days after treatment (mean difference: +21.66).

L4 larvae are considered the most important larval stage since this is the stage that is predominantly present in cats following infection with *D. immitis*. *In-vitro* data suggested that L4 larvae of *D. immitis* are more susceptible to treatment with moxidectin than L3 larvae, however, L3 larvae are understood to moult quickly into L4 larvae (3-12 days). Even if the *in-vitro* susceptibility of L3 larvae to moxidectin is less than that of L4 larvae, considering that an acceptable level of efficacy *in-vivo* was demonstrated against L4 larvae, then there is no reason to suspect that the product would not be efficacious in preventing heartworm disease.

A parasiticidal effect of Bravecto Plus on *D. immitis* larvae which have developed within the previous 30 days before treatment can therefore be accepted given that plasma concentrations of moxidectin 60 days post-treatment (period for which an acceptable level of efficacy has already been accepted as having been adequately demonstrated) are lower than those present shortly after treatment application.

As a result, an interval of 12 weeks between two treatments is acceptable in order to ensure the appropriate prevention of heartworm disease caused by *Dirofilaria immitis* in cats.

2.2.3. Conclusion

In conclusion, based on the totality of efficacy and pharmacokinetic data available, the indication for the prevention of heartworm disease caused by *Dirofilaria immitis* for 12 weeks has been adequately supported, when treatment is administered repeatedly at 12-week intervals. In this regard, it was considered that the indication as proposed by the applicant initially ("For the prevention of heartworm disease caused by *Dirofilaria immitis* for 12 weeks") suggested a 12-week protection after a single dose, which is not the case; thus, the indication was amended to "When administered repeatedly at a 12-week interval, the product continuously prevents heartworm disease caused by *Dirofilaria immitis* (see details in section 4.9)" and this wording was considered acceptable by the CVMP.

Based on the results obtained from dose confirmation studies and pharmacokinetic data, it is accepted that Bravecto Plus demonstrated persistent efficacy against *D. immitis* larvae for 60 days (demonstrated by the totality of data provided in support for the initial application), and an acceptable level of efficacy against larvae that have developed in the animal 30 days or less before treatment (demonstrated by the totality of data provided in support for this variation).

3. Benefit-risk assessment of the proposed change

Bravecto Plus is a spot-on solution for topical use in cats, containing as active substances a fixed combination of fluralaner (280 mg/ml) and moxidectin (14 mg/ml). Bravecto Plus is intended for use in cats with, or at risk from, mixed parasitic infestations by ticks or fleas and ear mites, gastrointestinal nematodes or heartworm. The product is exclusively indicated when use against ticks or fleas and one or more of the other target parasites is indicated at the same time. The product is available in three pipette sizes to be used according to the body weight of the cat (corresponding to a dose of 40-94 mg fluralaner/kg body weight and 2-4.7 mg moxidectin/kg body weight).

The proposed variation is to modify the approved therapeutic indication for the prevention of heartworm disease caused by *Dirofilaria immitis*, i.e. to extend the duration of prevention from 8 weeks to 12 weeks.

3.1. Benefit assessment

Direct therapeutic benefit

The benefit of this variation will arise from the extension of the period for prevention of heartworm disease caused by *Dirofilaria immitis* from 8 to 12 weeks. This extension is considered as being of benefit for the user/prescriber as well as the patient.

For the remainder of the indications that are already authorised, the benefits of the product remain unaffected by this variation.

Additional benefits

The product would increase the range of available preventive treatment possibilities for *D. immitis* infections in cats.

The extended re-treatment interval would facilitate animal handling by reducing the frequency of applications.

3.2. Risk assessment

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 the remainder of the indications that are already authorised, 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:

Administration of Bravecto Plus in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include skin reactions at the application site. Transient redness at the application site (observed in one dose confirmation study in one cat) has been included in the product information as an additional local adverse event.

Risk for the user:

The frequency of treatment does not change due to the extension of duration of prevention of heartworm disease caused by *Dirofilaria immitis* from 8 weeks to 12 weeks. Therefore, no additional risk for the user arises.

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

Risk for the environment:

Bravecto Plus 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 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, user safety, environmental safety, and target animal safety.

The benefit-risk balance remains positive.

4. Conclusion

Based on the original data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Bravecto Plus can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to modify the approved therapeutic indication for the prevention of heartworm disease caused by *Dirofilaria immitis*, i.e. to extend the duration of prevention from 8 weeks to 12 weeks.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above-mentioned medicinal product.

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

I and IIIB.

As a consequence of this variation, sections 4.2, 4.4, 4.6, 4.9 and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.