15 July 2021
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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

Withdrawal assessment report for a type II variation for Bravecto (EMEA/V/C/002526/II/0047)

International non-proprietary name: fluralaner

Assessment report with all information of a commercially confidential nature deleted.

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1. Introduction

1.1. Procedural steps

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 3 December 2020 an application for a type II variation for Bravecto.

On 3 August 2021, the applicant withdrew the application at day 150 of the procedure. In its letter notifying the Agency of the withdrawal of application, the applicant states that "This withdrawal is based on the reason that the CVMP considers the data provided do not allow the committee to conclude on a positive benefit risk balance."

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

The variation was to add a new therapeutic indication for Bravecto chewable tablets for dogs.

The indication as initially proposed was: "*Provides persistent insecticidal efficacy against sand flies (Phlebotomus perniciosus) for a period of 56 days. Sand flies are killed within 24 – 72 hours. Sand flies need to commence feeding on the host.*"

During the course of the procedure, the proposed indication was amended by the applicant to: "*The product can be used as part of a vector control strategy for dogs infected with leishmaniosis or at high risk of an infection:*

It provides persistent insecticidal efficacy against sand flies (Phlebotomus perniciosus) for a period of 56 days. Sand flies are killed within 24-72 hours which will reduce the risk of transmission of leishmaniosis to other naïve hosts, including humans, living in close proximity with the treated dog. Sand flies must take a blood meal on the host before they are killed."

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. MUMS/limited market status

Not applicable.

2. Scientific Overview

The product Bravecto contains the active substance fluralaner, an insecticide and acaricide of the isoxazoline family. It is currently authorised for use in dogs and cats. Bravecto chewable tablets are only authorised for use in dogs.

Bravecto chewable tablets are currently indicated for use in dogs for the treatment of ticks (*Ixodes ricinus, Rhipicephalus sanguineus, Dermacentor reticulatus* and *D. variabilis*), mites (*Sarcoptes scabiei var. canis* and *Demodex canis*) and flea (*Ctenocephalides felis*) infestations in dogs providing immediate and persistent killing activity, as well as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

The product is presented in five different strengths of chewable tablets for dogs with fluralaner administered at a dose rate of 25–56 mg/kg body weight (bw). For the newly proposed indication the product is to be administered at the same dose rate as currently authorised, namely 25–56 mg fluralaner/kg bw.

The frequency of repeat administration for Bravecto chewable tablets is at 12-week intervals for fleas and *Dermacentor reticulatus*, *D. variabilis* and *Ixodes ricinus* ticks and 8 weeks for *Rhipicephalus sanguineus* ticks. For the treatment of *Demodex canis* mite infestations and sarcoptic mange, a single dose of the product should be administered. For the newly proposed indication, dogs infected with leishmaniosis and dogs at high risk of infection should be treated every 8 weeks, and treatment should be started at the beginning of the sand fly season and continued throughout the season.

The initially proposed indication was as follows: "*Provides persistent insecticidal efficacy against sand flies (Phlebotomus perniciosus) for a period of 56 days. Sand flies are killed within 24 – 72 hours. Sand flies need to commence feeding on the host.*"

During the course of the procedure, this indication was amended by the applicant as follows: "*The product can be used as part of a vector control strategy for dogs infected with leishmaniosis or at high risk of an infection:*

It provides persistent insecticidal efficacy against sand flies (Phlebotomus perniciosus) for a period of 56 days. Sand flies are killed within 24-72 hours which will reduce the risk of transmission of leishmaniosis to other naïve hosts, including humans, living in close proximity with the treated dog. Sand flies must take a blood meal on the host before they are killed."

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 for the newly proposed indication does not differ from that which has already been accepted for the existing target parasites, it can be accepted that no concerns in terms of target animal tolerance/safety are considered to arise.

Further, as the product will be administered to the same target species, using the same route of administration and at the same posology that 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 at 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 would not present an unacceptable risk for the animal, user or the environment.

2.2. Efficacy: insecticidal efficacy against sand flies (Phlebotomus perniciosus)

In support of the proposed indication, the applicant has provided the results of three laboratory efficacy studies that investigated the insecticidal efficacy of Bravecto chewable tablets against sandflies under controlled conditions. The applicant has also referred to published literature in support of the proposed insecticidal efficacy of fluralaner. Pharmacokinetic studies performed upon the initial marketing authorisation application have already demonstrated that, after treatment, fluralaner is quantifiable in hair and skin.

The guideline "*Demonstration of efficacy against ectoparasiticides*" (7AE17a, 1994) recommends that two dose confirmation studies are provided for each claim and that findings from dose confirmatory studies are supported by field data. As no valid and satisfactory or reliable field model of efficacy assessment against *Phlebotomus perniciosus* is currently available, the applicant presented three well-designed, GCP-compliant laboratory studies. This is considered acceptable, also as artificial sandfly exposure can be expected to demonstrate a product's potentially repellent and insecticidal activity against sand flies under conditions of practical relevance.

All three studies were largely in compliance with the guideline "Demonstration of efficacy of ectoparasiticides" (7AE17a, 1994) and were performed using a near-identical study design. Studies were parallel group designed, single centred, and negative controlled. All studies applied a randomised block design. Veterinary clinical examinations, general health observations and sand fly assessments were performed by persons masked to treatment group assignment. Use of an untreated control group is considered appropriate. Each of all three studies was performed in 12 purpose-bred healthy beagles aged ≥ 6 months old. As the product has a systemic effect, it can be accepted that efficacy in the general target population is sufficiently represented by these beagle dogs. Animals were randomly allocated in two groups of six dogs each. Groups were generally well balanced for all demographic parameters, apart from one study, which only included male animals. As, however, a difference in sex with regards to *Phlebotomus perniciosus* bites is not expected, and the remaining two laboratory efficacy studies did include both male and female animals, this can be accepted. The number of study animals (6 animals per group in all studies) is considered adequate, considering the nature of the study (laboratory efficacy studies).

At Day 0, animals in the treatment group received a single dose of Bravecto chewable tablets. No new dose determination study was performed; treatment was dosed according to the different weight bands for the tablets. Individual doses stayed within the recommended dose range of 25 to 56 mg fluralaner/kg bw, which is appropriate considering that the activity of fluralaner against other ectoparasites was already demonstrated at this dose.

Two studies were performed at a site located in Morocco while the third study was conducted in Ireland. All studies used a different laboratory-bred sand fly strain that originated from specimens initially caught in Spain.

In all studies, animals were sedated, and the head of the animal was exposed to viable, adult, unfed *P. perniciosus* for the duration of approximately one hour. Merely exposure of the head can be accepted, as sand flies frequently bite on the head in natural conditions. The number of sand flies used for the challenges was either approximately 45 (in one study) or approximately 95 (in the other two studies), depending on the availability of the flies. However, in all studies, efficacy could be successfully evaluated and therefore the number of sandflies is considered acceptable in all studies. The experimental setting was well planned and allowed for thorough counting and differentiation of

fed vs. unfed female sand flies as well as dead vs. alive female sandflies. Experimental conditions (such as light management) were designed to achieve maximum fly counts. Unfed female sandflies and male sandflies (that do not blood-feed) were not considered relevant parameters to assess killing efficacy, which is considered appropriate as only fed sandflies had contact with fluralaner. The validity of the efficacy results was confirmed by comparing the proportion of live, fed sandfly counts in the treated group to the proportion of live, fed sandfly counts in the control group, which is considered appropriate.

Prior to treatment, in all studies, a sandfly challenge was performed for randomisation purposes only. Thereafter challenges were performed on several days after treatment up to Day 56 (in one study) or Day 84 (in the other two studies). It is noted that for the newly proposed indication against *Phlebotomus perniciosus*, a persistent insecticidal efficacy for a period of 56 days is claimed. Following each challenge, efficacy was assessed at different timepoints, up to 96 hours after the challenge. In all but one study, assessment of viability was initiated 6 hours after challenge. Following the high effectiveness observed 24 hours after the challenge on Day 1 in the first study, an additional, earlier assessment time point was implemented at 6 hours after each challenge in all following assessment points, and in all following studies.

In all studies, the primary assessment variable was viability of fed female sandflies. The percentage of efficacy was calculated using arithmetic mean counts. The veterinary medicinal product was considered effective when the insecticidal efficacy was ≥ 80% and the number of dead sand flies in the treated group differed significantly from the control group ($p \leq 0.05$). As, according to the guideline "*Demonstration of efficacy of ectoparasiticides*" (7AE17a, 1994), the required minimum threshold for Diptera is 80% (but preferably >90%), the selected threshold is considered acceptable.

The secondary efficacy parameters were the assessment of any repellent efficacy of the product, and survival reduction resulting from the veterinary medicinal product. In none of the studies was any repellent efficacy of the product observed; all dogs experienced sandfly bites. The absence of a repellent action was however expected, considering the mode of action of fluralaner against other ectoparasites.

In the first study, the animals were successfully challenged on Days 1, 28 and 84. This study demonstrated that a single dose of fluralaner was effective in achieving sufficient insecticidal efficacy (100%) against sandflies when assessed from 24 to 96 hours after challenge on Day 1. Insecticidal efficacy was not assessed prior to 24 hours after challenge on Day 1. Adequate persistent insecticidal efficacy (100%) was also observed at challenge Day 28, from 24 to 96 hours after the challenge. The survival reduction reached a maximum of 72.5% at the 96-hour viability assessments on challenge Day 28. Adequate insecticidal efficacy could not be demonstrated after challenge at Day 84. As efficacy could only be demonstrated up to Day 28 following treatment, this study does not support the proposed duration of effect (i.e. up to 56 days).

To replace one timepoint not covered in the first study, the second study assessed persistent efficacy when challenged on Day 56. Based on the results, it can be concluded that a single dose of fluralaner was effective in achieving adequate insecticidal efficacy against sandflies when challenged at Day 56 after treatment from 72 (efficacy 94.2%) to 96 hours (efficacy 99.1%) after challenge. A maximum survival reduction of 81.6% was observed at the 96-hour viability assessment. This study was unable to demonstrate sufficient efficacy prior to 72 hours after challenge at Day 56.

The third study assessed the onset of activity and persistent efficacy of the product up to Day 84. Following treatment on Day 0, animals were successfully challenged at Day 1, Day 28, Day 56 and Day 84. Based on the results, it can be concluded that a single dose of fluralaner was effective in achieving a sufficient insecticidal efficacy against sand flies from 24 up to 96 hours after challenge at

Day 1 (efficacy 98.1 – 98.5%) and Day 28 (efficacy 100%), and from 48 up to 96 hours after challenge at Day 56 (efficacy 80.2 – 85.9%). Sufficient efficacy was however not observed after challenge on Day 84. A maximal survival reduction of 37.6% was reached at the 96-hour viability assessment after challenge on Day 56. The maximum survival reductions in this study were much lower than those observed in the first study (in which a maximal survival reduction of 72.5% was reached at the 96 hour viability assessments on challenge Day 28) and the second study (in which a maximal survival reduction of 81.6% was reached at the 96 hour viability assessments on challenge Day 56). This observed difference was the result of the difference in feeding ratio between the treated groups. Feeding ratio was lower in the third study than in the first two studies.

Based on the presented studies, it was concluded that a single dose of Bravecto chewable tablets administered in accordance with the proposed SPC is effective in killing phlebotomine sandflies within 24 – 72 hours after feeding for at least 56 days.

However, the data presented is not considered robust enough to support a claim as to the product reducing the risk of transmission of leishmaniosis.

It is acknowledged that the active substance fluralaner will not provide protection against *Leishmania* infection in dogs which are bitten by infected sandflies, as leishmaniasis is transmitted by infected female sandflies regurgitating metacyclic parasites into the blood of the dog after biting but before feeding, and the female sandfly has to take a blood meal before dying as a result of exposure to the active substance.

Control of *Phlebotomus perniciosus*, the vector of *Leishmania infantum*, can however be part of *Leishmania* transmission prevention. Although the parasite can occasionally be transmitted by non-vectorial modes, the main transmission route is by the bite of infected phlebotomine sandflies. An extensive treatment of dogs in an endemic area can potentially reduce the pool of *L. infantum*-infected phlebotomine sandflies in endemic settings of (visceral zoonotic) leishmaniasis, causing the interruption of parasite transmission to susceptible hosts. Results of a mathematical model suggesting such an effect in case dogs are treated with a systemic insecticide were presented by the applicant.

However, this modelling was conducted using a different species of sandfly (*Lutzomyia longipalpis*) found in South America and the model did not consider other potential sources of infection. The author states that some aspects of the model could cause bias in the predictions, as for example the sandfly mortality rate. Furthermore, the intended use of the product is as part of a vector control strategy for individual dogs already infected with *Leishmania infantum* and not for the mass treatment of dogs in endemic areas.

In the absence of a validated approach to vector-control modelling, little can be concluded from this information that is directly relevant to the present application, aside from the general assumption that vector control is expected to reduce disease exposure.

In conclusion, the existence of a biologically significant reduction in the number of infected sandflies resulting in vector control as recommended, for example, in 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) has not been demonstrated for Bravecto chewable tablets. Although the guideline is not in effect yet, it reflects the CVMP's latest considerations in this area of assessment, and therefore, any reference to the product reducing the risk of transmission of leishmaniosis was not considered appropriate.

It was furthermore hypothesised by the applicant, that treatment may be expected to result in a less severe clinical picture for the individual dog suffering from leishmaniosis and that in *Leishmania*-

infected dogs the frequency of infected sandfly bites would be reduced in treated compared to non-treated animals (prevention of re-infection). It was further hypothesised that additional bites by infected sandflies would increase the *Leishmania* parasite burden and, consequently, worsen the clinical picture. However, none of these benefits for the animal that receives treatment have been demonstrated.

Finally, the CVMP considered that there would be a risk that a claim for insecticidal activity would lead to the expectation that the animal is protected against disease when this product is used, whilst it is clear that treatment will not protect the treated animal from *Leishmania* infection through sandfly bites.

If clinical improvement is claimed for dogs infected with *Leishmania*, the applicant would need to provide robust clinical data in support of this claim.

If no clinical improvement for the treated animal is claimed, but instead some form of vector control is claimed, then robust data, for example in line with the principles in the draft Guideline on vector borne disease (EMA/CVMP/EWP/278031/2015) would need to be provided to support the benefit of the insecticidal efficacy in reducing the risk of transmission of *Leishmania* resulting from the use of the candidate product, including for the treated animal.

Following these major outstanding issues raised by the CVMP, the applicant decided to withdraw the present type II variation application.

3. Benefit-risk assessment of the proposed change

Bravecto is authorised as chewable tablets and spot-on solution for use in dogs and as spot-on solution for use in cats; the dose range is 25–56 mg fluralaner/kg bodyweight in dogs and 40–94 mg fluralaner/kg bodyweight in cats.

Bravecto chewable tablets is authorised for the treatment of tick (*Ixodes ricinus, Dermacentor reticulatus, D. variabilis* and *Rhipicephalus sanguineus*) and flea (*Ctenocephalides felis*) infestations, for the treatment of demodicosis caused by *Demodex canis* and for the treatment of sarcoptic mange (*Sarcoptes scabiei* var. *canis*) infestation in dogs. It can also be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD). The active substance is fluralaner, an acaricide and insecticide.

The initially proposed variation was to add a new indication for Bravecto chewable tablets for dogs: "*Provides persistent insecticidal efficacy against sand flies (Phlebotomus perniciosus) for a period of 56 days. Sand flies are killed within 24 – 72 hours. Sand flies need to commence feeding on the host*".

During the course of the procedure the proposed indication was amended by the applicant as follows:

"*The product can be used as part of a vector control strategy for dogs infected with leishmaniosis or at high risk of an infection: It provides persistent insecticidal efficacy against sand flies (Phlebotomus perniciosus) for a period of 56 days. Sand flies are killed within 24-72 hours which will reduce the risk of transmission of leishmaniosis to other naïve hosts, including humans, living in close proximity with the treated dog. Sand flies must take a blood meal on the host before they are killed*."

3.1. Benefit assessment

Direct therapeutic benefit

As this was a variation to introduce an additional indication to existing presentations of the product Bravecto, the direct therapeutic benefits would arise from the inclusion of this new indication.

According to the applicant, the indication was considered of benefit as treatment potentially provides control against *Phlebotomus perniciosus*, the vector of *Leishmania infantum*.

However, a biologically significant reduction in the number of infected sandflies resulting in vector control has not been demonstrated for Bravecto chewable tablets. Also, a benefit for the animal that receives treatment was not demonstrated, as treatment does not protect healthy dogs from being infected through sand fly bites.

3.2. Risk assessment

As this is a variation to introduce an additional indication to existing presentations of the product Bravecto, the risk assessment focused on potential risks arising from the introduction of the newly proposed indication.

Quality:

Quality remains unaffected by this variation.

Safety:

As the product would have been administered to the same target species, using the same route of administration and at the same posology as already approved by the CVMP for existing indications, no new risks in terms of target animal tolerance, potential for resistance development, user safety or safety for the environment were considered to arise.

3.3. Risk management or mitigation measures

Information already 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 was still considered appropriate.

3.4. Evaluation of the benefit-risk balance

In the presence of major and other concerns, no conclusions can currently be taken on the benefit-risk balance of the product.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for this variation to the terms of the marketing authorisation for Bravecto is not approvable at the present time since "major objections" have currently been identified which preclude a recommendation for the for variation of the terms to the marketing authorisation.