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Veterinary Medicines Division

Committee for Veterinary Medicinal Products

CVMP assessment report for a type II variation for Bravecto (EMEA/V/C/002526/II/0051)

INN: fluralaner

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 28 May 2021 an application for a type II variation for Bravecto.

1.2. Scope of the variation

Variation requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

To add a new therapeutic indication for Bravecto chewable tablets for dogs: for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for up to 12 weeks. The effect is indirect due to product's activity against the vector.

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).

Bravecto chewable tablets for dogs is presented in five different strengths, with fluralaner administered at a dose rate of 25–56 mg/kg body weight (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.

The proposed variation is to add a new indication: "For reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for up to 12 weeks. The effect is indirect due to product's activity against the vector."

For this newly proposed indication, the product is to be administered at the same dose rate as currently authorised, namely 25–56 mg fluralaner/kg bw, at intervals of 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 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 substance 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 will not present an unacceptable risk for the animal, user or the environment.

2.2. Efficacy: Reduction of the risk of infection with Babesia canis via transmission by Dermacentor reticulatus for up to 12 weeks

The applicant presented scientific literature, from which it could be concluded that canine babesiosis is a disease caused by the intra-erythrocytic protozoan *Babesia spp*. The dominant species found in Central Europe is *B. canis. B. canis* is transmitted exclusively by the vector *Dermacentor reticulatus*.

Bravecto does not prevent parasites (such as the vector *D. reticulatus*) from taking a blood meal from the treated animal (i.e. there is no repellent effect). Also, routine treatment of animals with Bravecto is not expected to significantly alter the natural density of *D. reticulatus*. However, although minimal transmission time has not been established for all possible natural situations, it appears that in the field, generally about 48h of feeding by the tick on the host animal are required before transmission of *B. canis* occurs.

As such, even though no repellent effect is claimed for the product, a benefit in the reduction of the risk of transmission of *B. canis* is still foreseen from administering Bravecto chewable tablets to dogs.

In support of the claim, the applicant has presented four new GCP-compliant studies: three laboratory studies (in all of which animals were artificially infested with ticks), Lab 1,2 and 3 and a field trial, Field 1. In none of the studies adverse events considered directly attributable to Bravecto chewable tablets were observed, supporting safety of the product when used according to label.

According to the draft 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), at least one well-designed study assessing the reduction of the risk of disease transmission under laboratory conditions is necessary. In the case of the current procedure, laboratory study Lab 1

assessed efficacy of Bravecto in preventing the transmission of *B. canis* by infected *D. reticulatus* ticks. An additional field study, Field 2, also assessed effectiveness of Bravecto in preventing this transmission.

The two remaining laboratory studies, Lab 2 & 3, assessed the speed of kill and efficacy of Bravecto chewable tablets against *D. reticulatus* following a single treatment, thus indirectly measuring the claimed indication. This is considered as supportive information, according to the (draft) Guideline on vector borne diseases (EMA/CVMP/EWP/278031/2015).

The studies were all appropriately designed and conducted, generally in accordance with guideline requirements. All studies were negative control studies, which is considered appropriate. All studies used the formulation as currently marketed, and this is also considered appropriate. In the dose confirmation study, which was presented during the initial marketing authorisation application, dosing was performed at the minimum recommended dose (25 mg/kg bw). It is however noted that of the three additional laboratory studies presented with the current application, only laboratory study Lab 3 had dosed the animals at the minimum recommended dose. In the two remaining laboratory studies, including the pivotal challenge study, animals were dosed at the normal, recommended treatment dose (25-56 mg/kg bw fluralaner). To mimic the worst-case scenario for efficacy determination however, dosing at the minimum recommended dose would be more appropriate and in line with the CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3). Speed of kill of the product at the minimum recommended dose could however be assessed in two of the four laboratory studies (whilst in the two remaining studies, average fluralaner dose was at the lower end of the recommended dose, i.e. 36.4 mg/kg bw and 31.2 mg/kg bw).

It is agreed that the totality of data does not suggest that efficacy of the product will be lower when administered at the minimum dose.

In studies Lab 2 and Lab 3, animals were randomized based on pre-treatment tick counts, which is considered appropriate and in line with the draft guideline EMA/CVMP/EWP/278031/2015. In study Lab 1, no pre-allocation infestation with uninfected vectors was performed. However, in this study, animals had similar baseline characteristics, and inclusion criteria ensured that none of the included animals were recently treated with parasiticide treatments. Overall, it appears unlikely that a significant difference in the animals' capacity of carrying parasites was present in this study.

Tick efficacy was assessed in all newly presented studies.

In study Lab 2, 48 clinically healthy, adult dogs (primarily of mixed breed) were included and divided in 8 groups (4 control groups A-D and 4 treatment groups E-H). After treatment with Bravecto at SD 0, multiple challenges were performed throughout the study on SD 7, 28, 56, and 84. Ticks were removed and counted at 4 (group A+E), 8 (group B+F), 12 (group C+G) and 24 (group D+H) hours after infestation. Also, viability of the ticks was re-checked 24 hours after removal. No assessment of the killing efficacy of the product was performed shortly after treatment, as the study objective was to evaluate the progression of killing up to 84 days. Killing effect immediately after the IVP administration was however assessed in a second speed of kill study, Lab 3.

The primary efficacy criterion was percentage of tick efficacy in the treated groups (Groups E-H) compared to the respective untreated control group (Groups A-D) at each assessment time point according to Abbott's formula (as appropriate).

Efficacy rate depended on the time point of assessment. Based on arithmetic means of live tick counts, the IVP was not sufficiently effective (< 90%) at 4 and 8 hours after infestation, but was effective on SD 7 (91.2%) at 12 hours after infestation and on SD 7 (100%), SD 28 (100%) and SD 56 (98.9%) at

24 hours after infestation. Efficacy however did not reach 90% (but was assessed at 80.5%) at SD 84, 24 hours after infestation. This study demonstrated a significant acaricidal effect against *D. reticulatus* on SD 7 (when tick-counts were performed after 8 hours), on SD 7, 28, and 56 (when tick-counts were performed after 12 hours), and on SD 84 (when tick-counts were performed after 24 hours). However, the acaricidal effect did not exceed 90% at SD 84 in any treatment groups (i.e. at any timepoints). Based on the present study, the speed of kill can therefore not be claimed as being 24 hours or less for up to 12 weeks (but only up to 56 days).

In study Lab 3, 14 clinically healthy, adult dogs (mixed breed) were included and divided in two groups (treatment and control). The treatment group received a single treatment with Bravecto tablets at D0 at the minimum recommended dose (25 mg/kg bw) to mimic the worst-case scenario for efficacy determination. Animals were infested twice (at SD 0 and SD 84) with approximately 50 *D. reticulatus* ticks (whilst sedated). Tick *in situ* counts were performed at approximately 36 hours after infestation, tick removal was performed 48 hours after infestation.

In terms of efficacy, the primary efficacy criterion was the percentage of tick efficacy in the treatment group compared to the untreated control group at each assessment time point. Efficacy was calculated using Abbott's formula applying a linear mixed model, as is considered appropriate.

At 36 and 48 hours after the infestation on SD 0, efficacy was 100%. However, efficacy was 88.7% (36h) and 89.7% (48h) after the infestation on SD 84 using arithmetic means and exceeded 90% using geometric means.

Persistent efficacy 86 days after treatment and 48 hours post-infestation was demonstrated to be 89.7% (arithmetic means). When applying geometric means, efficacy did exceed 90%. However, calculation using geometric means was not planned *a priori*.

At 48 hours post-infestation and for up to 12 weeks (86 days), a persistent efficacy against *D. reticulatus* of 89.7% was demonstrated in this study.

In study Lab 1, 24 clinically healthy dogs (adequately representing the target population and proven to be free of infection with *B. canis* (as assessed by PCR and IFAT)) were divided in three groups (8 animals per group). One group was treated with Bravecto chewable tablets (IVP), the 2nd group was treated with a fluralaner spot-on solution (results not assessed in the framework of the current procedure), whilst the dogs in the 3rd group served as negative control.

Animals were allocated to a treatment or a control group, and challenges were performed on Day 2, 28, 56, 70, and 84 with ticks infected with *B. canis*, representing a severe challenge. Following challenge, all dogs were physically examined, and PCR was performed every 7 days, whilst blood samples for IFAT were collected every 14 days. In case an animal was infected with *B. canis*, it was removed from the study, and received rescue treatment.

Infected dogs were replaced by additional (control) animals. Ultimately, an additional 19 control-dogs were introduced throughout the study. Because of the replacement of infected dogs, the denominator changed in the group in which a dog was replaced. It resulted in a proportion of 0/8 infected dogs in the treatment group versus 27/27 dogs in the untreated group (although that group initially also consisted of 8 dogs). The incidence density rate takes into account that not every patient is observed for the same period of time. It is the number of events (infections) 'per observed person-year', or in this case maybe 'per observed dog-week'. The number of observed dog-weeks (the denominator) is similar in both groups, being 8 (dogs) x 12 (weeks), because as soon as one dog became infected, it was replaced by a new dog that was exposed. However, if in this case incidence density rates instead of proportions were compared, the estimate of effect of 100% protection would not change because of zero events in the treated group. Another approach would be to compare the incidence of *Babesia*-

infections after each infestation, but again these comparisons would lead to the conclusion that there is 100% protection at each time point.

In terms of efficacy, the primary effectiveness criterion was the protection rate of the IVP against *B. canis*. Dogs which displayed *B. canis* antibodies that were also positive for *B. canis* DNA were regarded as infected (= protection failure). All control dogs tested positive for *B. canis*. None of the treated dogs were infected with *B. canis* during the study, resulting in an efficacy threshold >90%, which is in accordance with the draft guideline requirements (EMA/CVMP/EWP/278031/2015). In this case, with zero events in the treated group, the estimate of effect does not change (but 95% confidence interval and p-value probably do).

Secondary effectiveness criterion was tick efficacy. The efficacy of Bravecto was assessed 48 hours after each challenge, and ranged from 99.2% to 100% (geometric means) throughout the study, a percentage that is in accordance with the guidance for accepting the overall efficacy (EMEA/CVMP/EWP/005/2000-Rev.3). Insecticidal efficacy was not assessed prior to (or after) 48 hours after challenge.

In conclusion, this experimental infection model successfully demonstrated that a single administration of Bravecto chewable tablets was 100% effective in preventing transmission of *B. canis* by infected *D. reticulatus* ticks for up to 12 weeks.

Study Field 1 was the pivotal field study, intended to confirm that Bravecto is capable of preventing the transmission of *B. canis* under field conditions in different European countries.

In total, 152 privately-owned, clinically healthy dogs of various breeds were included in the study. The study was performed in different sites within Europe (Albania, France and Hungary). All sites had a history of tick infestation and babesiosis due to *B. canis.*

Animals were allocated to two groups. One group (n=76) received treatment with Bravecto chewable tablets, whilst the other group (n=76) served as a negative control. On Day 0 and Day 84, animals were treated with the formulation as currently marketed at the recommended treatment dose (25-56 mg/kg bw of fluralaner (mean dose was 32.4 mg/kg bw fluralaner (D0) and 32.6 mg/kg bw fluralaner (D84)). For the efficacy evaluation, 132 dogs were taken into consideration (65 in the treated group and 67 in the control group).

In terms of efficacy, the primary efficacy criterion directly measured the claimed indication: the percentage reduction of the risk of *B. canis* transmission based on incidence rates (relative risk reduction). Treatment efficacy was concluded if the percentage reduction of transmission risk was ≥90%, which is considered appropriate. The secondary efficacy criterion was the percentage reduction of the risk of *B. canis* transmission based on incidence density rates. Dogs which displayed *B. canis* antibodies that were also positive for *B. canis* DNA were regarded as infected (= protection failure).

D. reticulatus ticks were collected during the entire study period, indicating that ticks were active during the entire study period. Of the collected ticks, only a small sample was assessed for infection, and only at the site in Hungary a sample of ticks was tested positive for *B. canis*. However, incidence of *B. canis* was comparable to what is found in literature for these geographical areas when not only considering dogs that were infected during the study (n=5), but also animals that were identified as infected before enrolment (n=9).

None of the dogs included at the sites in France or Albania tested positive for *Babesia*, and the incidence rate was therefore 0%. Out of a total of 40 (20 untreated and 20 treated) dogs included at the site in Hungary, a total of five animals, all of which were untreated, were identified as *Babesia* positive during the study. The calculated absolute risk reduction is 7.46% (the absolute risk in the treated dogs is 0% and in the untreated group 7.46%). This relative low number of infections is

presumably the result of the unpredictability of actual exposure, which is a well-known problem in these types of studies. Also, the difference in incidence rate for Hungary was statistically significant, p=0.0236 (significance threshold was 0.025). Despite the relative low number of cases, this risk reduction is considered statistically significant as well as clinically relevant. The results of this study (100% relative risk reduction) also support the findings of the laboratory challenge study.

The study was conducted between September and March; however, there are no data to confirm that test animals were challenged with *Babesia*-infected ticks after the end of October. Therefore, the field study does not support the persistent effect of up to 84 days post treatment.

However, it can be accepted that, notwithstanding its shortcomings, the study confirms adequate efficacy under field conditions up to day 56 and, based on the findings of the laboratory study (in which it was confirmed that efficacy at day 84 is as good as efficacy achieved at earlier time points), there is no reason to expect that efficacy in the field will wane at later time points.

As such, it can be accepted that overall the field study provides general support for the demonstration of efficacy in the reduction of the transmission of *Babesia canis* for up to 56 days and that the results from the laboratory efficacy study demonstrated 100% efficacy for up to 84 days.

In addition to the studies that were performed in support of the present application, the applicant presented a GCP-compliant dose confirmation study, that had been submitted during the initial marketing authorisation procedure, EMEA/V/C/002526. Based on the outcome of this study, the CVMP accepted a claim for persistent efficacy against *Dermacentor reticulatus* up to Day 84 post treatment. Results of this study support an adequate acaricidal effect (speed of kill) of 48 hours after dosing. As this study only assessed tick efficacy at 48 hours after infestation, no information can be derived on effectiveness prior (or after) this time period.

Taking into consideration the totality of the data provided, it can be accepted that sufficient efficacy has been demonstrated to support the indication for the reduction in the transmission of *Babesia canis* for up to 84 days, when the product is administered at the recommended treatment dose.

On resistance, it is noted that the applicant has performed an extensive literature search (Scopus, 2021) but could not identify any reports on the resistance of *D. reticulatus* to fluralaner.

Overall conclusion: Based on results of study Lab 1and (previously submitted) the dose confirmation study (and in addition, efficacy close to 90% (89.7%) in study Lab 3), a speed of kill of 48 hours for the duration of 84 days can be claimed. A speed of kill lower than 48 hours cannot be claimed (though it is noted that in Study Lab 3, tick efficacy was very close to the threshold of 90%, being 88.7% 36 hours after tick infestation, and in Study Lab 2, 84 days following treatment and 24 hours after infestation, efficacy was 80.5%). Also, it is noted that the speed of kill decreased with time after the product was administered.

In current procedure, laboratory study Lab 1(which is considered a severe challenge study) successfully demonstrated that a single administration of Bravecto chewable tablets was effective in preventing transmission of *B. canis* for up to 12 weeks. This outcome was supported by the results of a well-designed field study, albeit in this study the number of control dogs infected with *B. canis* was low as a result of the well-known unpredictability of actual exposure.

Altogether, the totality of the data is considered adequate to support the proposed claim for the reduction of the risk of infection with *B. canis* via transmission by *D. reticulatus* for up to 12 weeks. For accuracy purposes, the protozoan agent has been referred to as *Babesia canis canis* in the product information in order to differentiate from other *Babesia* subspecies transmitted by other ticks.

3. Benefit-risk assessment of the proposed change

This product is authorised as chewable tablets and spot-on solution for use in dogs and as spot-on solution for use in cats. The active substance is fluralaner, an acaricide and insecticide. The dose range is 25–56 mg fluralaner/kg bodyweight in dogs and 40–94 mg fluralaner/kg bodyweight in cats.

Bravecto chewable tablets are 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. The product can also be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

The proposed variation is to add a new therapeutic indication for Bravecto chewable tablets for dogs: for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for up to 12 weeks. The effect is indirect due to product's activity against the vector.

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce an additional indication to existing presentations of the product Bravecto, the direct benefits arise from the inclusion of this new indication: reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for up to 12 weeks.

Bravecto does not prevent the vector *D. reticulatus* from taking a blood meal from the treated animal (i.e. there is no repellent effect). Also, routine treatment of animals with Bravecto is not expected to significantly alter the natural density of *D. reticulatus*. However, though no minimal transmission time appears to have been established for all possible natural situations, it appears that in the field, generally about 48 hours of feeding by the tick on the host animal are required before transmission of *B. canis canis* occurs.

As such, a benefit in the reduction of the risk of transmission of *B. canis canis* is foreseen from administering Bravecto chewable tablets.

Additional benefits

No additional benefits are foreseen.

3.2. Risk assessment

As this is a variation to introduce an additional indication to existing presentations of the product Bravecto, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indication. As the product will be administered to the same target species at the same dose rate 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:

No increased frequency of treatment administration is proposed. Consequently, no additional risk for the target species is foreseen.

Administration of Bravecto 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 were reported in the studies performed in support of the proposed new indication.

Risk for the user:

The CVMP previously concluded that user safety for this product is acceptable when used according to the SPC recommendations. The frequency of treatment does not change due to the addition of the new indication. Therefore, no additional risk for the user arises.

Risk for the environment:

Bravecto is not expected to pose a risk for the environment when used according to the SPC recommendations.

3.3. Risk management or mitigation measures

Information 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 is considered appropriate.

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, target animal safety.

The product provides a reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for up to 12 weeks. The effect is indirect due to product's activity against the vector.

The product is well tolerated by the target animals and presents an acceptable risk for users and the environment, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk is deemed positive.

4. Conclusion

Based on the original and complementary 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 can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add a new therapeutic indication for Bravecto chewable tablets for dogs: for reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for up to 12 weeks. The effect is indirect due to product's activity against the vector.

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, and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.