15 June 2022
EMA/601451/2022
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a type II variation for Bravecto (EMEA/V/C/002526/II/0054/G)

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 7 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 2021 an application for a grouped type II variation for Bravecto.

1.2. Scope of the variation

Variations 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
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This grouped variation is to add two new therapeutic indications for Bravecto chewable tablets for dogs: for the treatment of tick infestations with *Ixodes hexagonus* and for reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for up 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

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 tick (*Ixodes ricinus, Rhipicephalus sanguineus, Dermacentor reticulatus* and *D. variabilis*), mite (*Sarcoptes scabiei var. canis* and *Demodex canis*) and flea (*Ctenocephalides felis*) infestations, providing immediate and persistent killing activity. Bravecto chewable tablets are also indicated as part of a treatment strategy for the control of flea allergy dermatitis (FAD) and for reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus*.

Bravecto chewable tablets are presented in five different strengths, with fluralaner administered at a dose

rate of 25–56 mg/kg body weight (bw).

The proposed variation is to add two new therapeutic indications for Bravecto chewable tablets for dogs: reduction of the risk of infection with *Dipylidium caninum* claim (due to product's activity against the vector) and extension of the existing tick indication by adding a new tick species - *Ixodes hexagonus*.

For the treatment of flea (*Ctenocephalides felis*) and most species of tick (*Dermacentor reticulatus*, *D. variabilis* and *Ixodes ricinus*) infestations, the frequency of repeat administration is at 12-week intervals.

For the newly proposed indication for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis*, efficacy for up to 12 weeks has been claimed.

For the newly proposed indication against *Ixodes hexagonus*, an immediate and persistent effect for up to 12 weeks was initially proposed by the applicant. As however the presented data did not demonstrate an immediate effect, only a persistent effect could be accepted by the CVMP.

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 indications 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 indications will not present an unacceptable risk for the animal, user or the environment.

2.2. Efficacy

2.2.1. Reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis*

The applicant presented scientific literature from which it can be concluded that the transmission of the tapeworm *D. caninum* is exclusively linked to a vector. *Ctenocephalides* spp. fleas (of which *Ctenocephalides felis* is the most prevalent) are known to be the main vector of this parasite.

It is evident that Bravecto is not effective against *D. caninum*. However, after an infected flea infests a host in the field situation and ingests a blood meal, it generally takes 24–36 hours before parasite maturation within the flea (i.e. for the hexacanth cestode embryo to develop into an infective cysticercoid stage). As Bravecto is known to provide immediate (within 8 hours) and persistent *Ctenocephalides felis* killing activity, fleas will be killed before parasite maturation is complete. As a result, treatment is expected to prevent an infection with *D. caninum*.

As such, even though no direct parasiticidal effect against *D. caninum* is claimed for the product, a benefit in the reduction of transmission of *D. caninum* is foreseen from administering Bravecto chewable tablets due to its insecticidal effect against the vector *C. felis*.

In support of the claim, the applicant has provided two studies (one GCP compliant laboratory study and one GCP compliant field study assessing the reduction of the risk of transmission of *D. caninum* (due to the effect of the product against the vector *C. felis*) under laboratory- and under field conditions. Both studies were largely performed 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) (Guideline on VBD) as well as the Guideline on statistical principles for clinical trials for veterinary medicinal products (pharmaceuticals) (EMA/CVMP/EWP/81976/2010). Both studies used the formulation as currently marketed. Dosing in both of these studies was according to label, therefore not at the minimum dose. However, the average dose was accepted as being sufficiently close to the minimum recommended dose of 25 mg fluralaner/kg bw.

In addition, the applicant re-submitted two GLP-compliant speed of kill studies, which were previously presented and assessed by the CVMP in the context of the initial marketing authorisation procedure, EMEA/V/C/002526/0000. These studies are considered as supportive information, according to the (draft) Guideline on VBD. In both studies, dogs were dosed at the minimum recommended treatment dose of 25 mg fluralaner/kg bw.

All studies included in the dossier were appropriately designed and executed, generally in accordance with guideline requirements. All studies were negative control studies, which is considered appropriate.

GCP Compliant Laboratory study was a single-site, negative controlled, appropriately blinded, randomised, pivotal laboratory study performed in accordance with GCP, and largely taking into consideration VICH GL7 and the (draft) Guideline on VBD. The study assessed efficacy of the product in preventing infection with *D. caninum* by using a natural flea infestation model and consequently investigated prevention of infection arising from new infestations of fleas (as opposed to existing infestations).

Twenty-four clinically healthy, adult dogs were included and divided in three groups; the number of animals included is considered acceptable, as this is in accordance with VICH GL7. Animals were allocated to three treatment groups: one group (n=8) was left untreated, the second group (n=8) was treated with Bravecto chewable tablets at the recommended treatment dose (average dose 34.9 mg fluralaner/kg bw), whilst the third group (n=8) received a spot-on fluralaner product (results for this group are not discussed within this variation application).

Adequate details on the flea strain and characterisation of *D. caninum* were provided. Fleas were infected with *D. caninum* following the CRO's standard operating procedure. Both the cestode *D. caninum* as well as the vector *C. felis* originated from the USA. Both strains were however considered sufficiently representative for Europe, as the genetic differences present in *D. caninum* tapeworms are not related to geographical origin, and the applicant presented scientific support that the efficacy of fluralaner against flea isolates from the EU or USA can be expected to be similar.

The study was conducted in South Africa. Whilst the study was conducted outside the EU, given the design of this laboratory study, the location of the study was not considered to have any consequences for the conclusions that may be drawn.

Multiple challenges were performed throughout the study, as dogs were weekly challenged (12 challenges per dog) with 100 *C. felis* fleas commencing one week after treatment. The fleas were adequately infected with a dog strain of *D. caninum*. No pre-allocation infestation was performed to assess suitability for flea infestation prior to the experiment. However, given that animals were randomly assigned to treatment groups, any differences in ability of study animals to maintain infestations is not expected to bias the results. Further, given that this study has been certified as GCP-compliant, there is no reason to believe that animals have been managed differently in terms of the methods used to infest animals.

It can be accepted that the percentage of fleas (13-67%) harbouring *D. caninum* metacestodes is in excess of infection pressure expected under field conditions.

In terms of efficacy, the primary effectiveness criterion was the proportion of dogs ultimately infected with *D. caninum* in the treated group compared with the proportion of infected dogs in the control group. For this, the presence or absence of *D. caninum* proglottids in the faeces or in the cage environment was determined by macroscopical examination, which served as indication of infection. In case at any timepoint an animal was infected with *D. caninum*, it was treated with a cestodicide and removed from the study.

Effect of treatment was assessed up until 113 days after treatment, i.e. 29 days after the end of the 84-days approved activity of the product against fleas, thus covering the entire period of proposed effect against infection with *D. caninum* being claimed.

By Day 43, all 8 control dogs were positively infected with *D. caninum* (i.e. *D. caninum* proglottids observed in their faeces), whilst none of the 8 treated dogs were infected up to the end of the study (Day 113). The applicant therefore claims that the product is 100% effective in preventing infection with *D. caninum*, thus exceeding the guideline threshold of 90%.

In conclusion, by means of artificial infestation, this study successfully demonstrated that a single administration of Bravecto chewable tablets was 100% effective in preventing the transmission of *D. caninum* by infected *C. felis* fleas for up to 12 weeks.

GCP Compliant Field study was a negative controlled, randomised, examiner-masked, GCP-compliant pivotal field study. The study intended to confirm that Bravecto chewable tablets reduce the risk of transmission of *D. caninum* from infected fleas to dogs under field conditions in three different European countries (Albania, Hungary and Portugal). The study covered the entire relevant period of risk of disease transmission, i.e. it was initiated during summer and finished in autumn (Hungary) or winter (Albania and Portugal).

An acceptable number of 270 privately-owned, clinically healthy dogs of various breeds were included and randomly allocated to a treatment (n=140) or control (n=130) group. For inclusion, animals were required to have daily outside access and at least one dog in the household was required to have ≥4 live fleas for all dogs in one household to be included. There is no report of the type of flea species identified at the examinations. As however the cat flea *Ctenocephalides felis* is the most important ectoparasite of domestic cats and dogs worldwide, presence of the *C. felis* in the study population can be assumed.

On Day 0, animals in the treatment group were administered Bravecto chewable tablets at the recommended treatment dose of 25-56 mg fluralaner/kg bw (mean dose was 34.6 mg/kg).

After treatment, faeces were collected for three consecutive days on two occasions: SD 42 and SD 84 (last day of sampling). Faeces samples were adequately assessed macroscopically as well as by faecal flotation for detecting the presence of *D. caninum*.

In terms of efficacy, the primary efficacy criterion was the percentage reduction of the risk of *D. caninum* transmission based on incidence rates (relative risk reduction). Treatment efficacy was concluded if the percentage reduction of transmission risk was ≥90%. The secondary efficacy criterion was the percentage reduction of the risk of *D. caninum* transmission based on incidence density rates.

Eight out of the 130 untreated control dogs (equating to approximately 6%) were found to be positive for *D. caninum*, of which five were tested positive on Day 42, and three on Day 84. This percentage is consistent with the 5.2% percentage of infection of *C. felis* fleas that was observed in the field. It was noted that all positive dogs were obtained from Albania. It is however acknowledged that infection pressure in the field is hard to predict, and the overall background risk for infection is low.

The incidence rate was 0% in the treated group, that is, no dog was positive for *D. caninum* at any post-treatment time point. It can be accepted that the results of this study suggest a reduction in risk of infection

with *D. caninum* based on a statistically significantly lower incidence of *D. caninum* infection in treated compared to untreated study animals using both macroscopical and microscopical techniques.

Overall, although the number of animals infected was low, the results (100% reduction of the risk of *D. caninum* transmission based on incidence rates and also on incidence density rates (secondary efficacy criterion)) do support the claimed indication of reduction of the risk of infection with *Dipylidium caninum* under field conditions over a period of 12 weeks.

Based on both speed of *kill studies against the flea vector, it* can be concluded that Bravecto chewable tablets are effective against adult *Ctenocephalides felis* (effect exceeds the efficacy threshold of 95%), and that the effect persists for in excess of 12 weeks.

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 *C. felis* to fluralaner.

Overall conclusion: Altogether, the totality of the data is considered adequate to support the proposed claim: "For reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for up to 12 weeks. The effect is indirect due to product's activity against the vector."

2.2.2. Treatment of tick infestations with *Ixodes hexagonus*

Ixodes hexagonus is a known vector of various tick-borne pathogens. This parasite has a widespread distribution in Europe and is commonly encountered on dogs. To support the addition of a claim against the tick species *I. hexagonus*, the applicant has provided three (GLP/GCP compliant) dose confirmation laboratory studies (one for *I. hexagonus* and two for *I. ricinus*) and one (GCP compliant) field study. Only one dose confirmation study is newly submitted; the remaining three studies were already submitted and assessed by the CVMP during the initial authorisation procedure, EMEA/V/C/002526/0000.

In support of the claim, the applicant conducted one dose confirmation study for *I. hexagonus*. A high susceptibility for *Ixodes* tick species in general is claimed. Two previous laboratory studies conducted with *I. ricinus* demonstrated that the product is indeed very effective against *Ixodes ricinus* even at the minimum recommended dose of 25 mg fluralaner/kg bw. The study outcome of both a dose confirmation study and a field trial for *I. hexagonus* supported that also *I. hexagonus* appears highly susceptible to fluralaner. As a result, the omission of a second dose confirmation study in support of the claim for *I. hexagonus* can be accepted.

GCP Compliant Laboratory study was a single-site, negative controlled, appropriately blinded, randomised, GCP compliant, well-designed dose confirmation study, conducted in accordance with the 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).

The study investigated the persistent efficacy of a single treatment of Bravecto chewable tablets against *I. hexagonus* for up to 12 weeks.

The study was conducted outside the EU; however, given the design of this laboratory study and the use of a recent (4 years old) tick strain of European origin, the location of the study is not considered to have any consequences for the conclusions that may be drawn. The tick strain used is considered sufficiently representative for the field situation in Europe.

An acceptable number of 16 healthy, adult dogs were included and divided in two groups of 8 dogs each. Study population is considered to be sufficiently representative for the target population.

On Day 0, animals were treated with the formulation as currently marketed at the recommended treatment dose (average dose 31.4 mg fluralaner/kg bw). The dose administered in most animals was close to the

minimum dose of 25 mg/kg bw.

Dogs were sedated and challenged with approximately 50 (40 females and 10 males) viable, adult, unfed *I. hexagonus* ticks on study days -7 to evaluate susceptibility, and on days 7, 28, 56 and 84. The number of challenges and the method of challenge are considered appropriate. In order to assess persistent efficacy of Bravecto chewable tablets, tick counts were performed at Days 9, 30, 58 and 86.

In terms of efficacy, the primary efficacy criterion was the percentage of tick efficacy in the treated group in relation to the control group at each assessment time point. Efficacy was calculated using Abbott's formula, which is considered appropriate.

Infestation in the control dogs was adequate. Also, efficacy based on arithmetic means exceeded 90% (99.4% at Day 30 to 100% at Days 9, 58 and 86), and a significant reduction in mean live tick counts was observed. Overall, the IVP was demonstrated to have a persistent acaricidal effect against *I. hexagonus* tick infestations from day 7, up to 12 weeks following administration.

As the design of this study only permits an evaluation of the persistent efficacy of the product against *I. hexagonus* ticks but not the immediate efficacy (as the first time point when ticks were counted was on study day 9), the results of this study are considered to support only a persistent acaricidal effect against *Ixodes hexagonus* for up to 12 weeks.

One GCP-compliant speed of kill study assessed immediate and persistent effect of fluralaner against *I. ricinus* ticks using a pilot oral formulation containing 6.25% fluralaner. Efficacy was tested against a negative control group. Applying a modified Abbott's formula and arithmetic mean data, this study demonstrated a 12-week efficacy when the product was dosed at 25 mg fluralaner/kg bw. However, it is unclear as to precisely how the findings from this study may be considered to have supported an acceptable immediate and persistent acaricidal effect against *Ixodes hexagonus*.

Another GLP-compliant speed of kill study assessed onset of action for ticks (and fleas). After dosing at the minimum recommended treatment dose, dogs were assessed for persistent efficacy at 4, 8, 12 and 16 weeks, 12 and 24 hours after re-infestation. Fluralaner killed *Ixodes ricinus* ticks in less than 12 hours for a duration of 85 days (12 weeks) and in less than 24 hours for a duration of 112 days (16 weeks). Efficacy calculations were based on arithmetic means. However, it is unclear as to precisely how the findings from this study may be considered to have supported an acceptable immediate and persistent acaricidal effect against *Ixodes hexagonus*.

The aim of the GCP-compliant multi centered field study, conducted in Germany, France and Spain, was to confirm the duration of efficacy of Bravecto chewable tablets for dogs when administered once for the treatment and control of tick and/or flea infestations under field conditions. Animals were dosed according to label, which is appropriate for a field study.

Flea and/or tick counts were conducted on day 0 (prior to treatment), and days 14, 28, 56, and 84.

A total of 1237 ticks (ITT) were collected at inclusion; *Ixodes hexagonus* was the second most frequent tick species found (n=314, 25.38%). In support of current variation, only dogs that presented with *Ixodes hexagonus* ticks on Day 0 were considered for efficacy calculation.

Results indicated that the IVP was 100% effective at all assessment time points, except on day 28 when the efficacy was 98.2%. During unplanned visits following treatment administration, no *I. hexagonus* ticks were identified on any of the dogs. Whilst only a limited number of study animals (n=13) were infested with *Ixodes hexagonus* ticks prior to treatment, it can be accepted that the results of this study demonstrate an acaricidal effect of the product against all ticks identified (including *I. hexagonus*).

On resistance, it is noted that the applicant has performed an extensive literature search using the words "*Ixodes*", "isoxazoline", "fluralaner" and "resistant" (Scopus, 2021) but could not identify any reports on the

resistance of *Ixodes* spp. ticks to fluralaner.

Overall conclusion:

According to the Guideline 7AE17a on the demonstration of efficacy of ectoparasiticides, at least two controlled tests (dose confirmation studies) in addition to clinical field trials are recommended to demonstrate efficacy against each ectoparasite species.

The results of only one dose confirmation study have been provided with this application and this dose confirmation study is supplemented by reference to a previously submitted field study in which *Ixodes hexagonus* was one of the tick species identified (albeit in a limited number of animals (13)).

The outcome of the dose confirmation study and of the field trial supported that *I. hexagonus* appears highly susceptible to fluralaner. As a result, omission of a second dose confirmation study in support of the claim for *I. hexagonus* can be accepted.

However, as an immediate acaricidal effect against *Ixodes hexagonus* has not been demonstrated, only a persistent effect against *I. hexagonus* can be claimed. This is adequately reflected in the product information.

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) and for reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus*.

The proposed grouped variation is to add two new therapeutic indications for Bravecto chewable tablets for dogs: for the treatment of tick infestations with *Ixodes hexagonus* and for reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for up to 12 weeks.

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce two additional indications to existing presentations of the product Bravecto chewable tablets for dogs, the direct benefits would arise from the inclusion of these new indications.

The addition of persistent tick killing activity for a new tick species (*I. hexagonus*) is considered to add to the benefit of the product as this addition increases the range of available tools against this tick in dogs.

It is evident that Bravecto is not effective against *D. caninum*. However, when used at its recommended dose, it provides rapid and sustained efficacy over 12 weeks against *C. felis*, an intermediate host in the life cycle of *D. caninum* and the main vector for this tapeworm. As such, a benefit in the reduction of the risk of transmission of *D. caninum* is foreseen from administering Bravecto chewable tablets.

Additional benefits

D. caninum is a zoonosis. Vector control is therefore an indirect benefit to protect humans.

No further additional benefits are foreseen.

3.2. Risk assessment

As this is a variation to introduce additional indications to existing presentations of the product Bravecto, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indications. As the product will be administered to the same target species at the same dose rate 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 arise from the studies performed in support of the proposed new indications.

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 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 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 *D. caninum*, as it provides rapid and sustained

efficacy over 12 weeks against *C. felis*, an intermediate host in the life cycle of *D. caninum* and the main vector for this tapeworm. The effect is therefore indirect due to product's activity against the vector.

In addition, the product can be accepted as providing a persistent tick killing activity for a new tick species, *I. hexagonus*, for up to 12 weeks.

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 are already included in the SPC and other product information.

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

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for 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 two new therapeutic indications for Bravecto chewable tablets for dogs: for persistent tick killing activity from 7 days to 12 weeks after treatment for *Ixodes hexagonus* and for reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for up 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 these variations, Sections 4.2, 4.4, and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.