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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Bravecto (EMEA/V/C/002526/II/0036)

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 31 May 2019 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 in dogs: "For the treatment of demodicosis caused by *Demodex canis*" (for both the chewable tablets and the spot-on solution). Additionally, the MAH is updating the labelling section for Bravecto spot-on solution for dogs and cats with regard to the information included on the pipette label.

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.

Dogs

Bravecto chewable tablets are currently indicated for use in dogs for the treatment of flea (*Ctenocephalides felis*) and tick (*Ixodes ricinus, Dermacentor reticulatus*, *D. variabilis* and *Rhipicephalus sanguineus*) infestation, as well as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

Bravecto spot-on solution is currently indicated for use in dogs for the treatment of flea (*Ctenocephalides felis* and *Ctenocephalides canis*) and tick (*Ixodes ricinus, Rhipicephalus sanguineus* and *Dermacentor reticulatus*) infestation, as well as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

Bravecto for dogs is presented in five different strengths of chewable tablets and five different pipette sizes of spot-on solution, with fluralaner administered at a dose rate of 25–56 mg fluralaner/kg body

weight (bw).

The frequency of repeat administration for Bravecto chewable tablets is at 12-week intervals for fleas, *Ixodes ricinus, Dermacentor reticulatus* and *D. variabilis* ticks, and 8 weeks for *Rhipicephalus sanguineus* ticks.

For Bravecto spot-on solution for dogs, the frequency of repeat administration is at 12-week intervals for all flea and tick species specified.

Cats

For cats, Bravecto is currently indicated for the treatment of flea (*Ctenocephalides felis*) and tick (*Ixodes ricinus*) infestations, as well as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

Bravecto spot-on for cats is presented in three different pipette sizes, with fluralaner administered at a dose rate of 40-94 mg/kg bw.

The frequency of repeat administration is at 12-week intervals.

The proposed variation is to add a new therapeutic indication: for the treatment of demodicosis caused by *Demodex canis* in dogs.

For this newly proposed indication, the product is to be administered once, at the same dose rate as currently authorised, namely 25–56 mg fluralaner/kg bw for both Bravecto chewable tablets and Bravecto spot-on solution for dogs.

The following treatment regimen is proposed: for the treatment of *Demodex canis* mite infestations in dogs, a single dose of the product should be administered.

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 newly proposed 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 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 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 introduction of the proposed indication will not present an unacceptable risk for the animal, user or the environment.

2.2. Efficacy: treatment of demodicosis (caused by Demodex canis)

The proposed indication against demodicosis in dogs is: "for the treatment of demodicosis caused by *Demodex canis*". In support of the above indication, the applicant has provided the results of two dose confirmatory studies and one field study.

The first dose confirmation study , compliant with US (FDA) GLP standards for nonclinical laboratory studies, investigated the efficacy of the final formulation of Bravecto chewable tablets against

generalised demodicosis in naturally infested dogs in South Africa. This is a parallel group design, blinded, randomized, single centre, positive controlled efficacy study. Study personnel performing assessments were blinded and it can be accepted that the design suitably allowed for adequate blinding and randomization by including a positive control group. Additionally, it can be accepted that a positive control was utilised due to the potentially debilitating nature of the disease. Advocate, which is a topical combination of imidacloprid (10% w/v) and moxidectin (2.5% w/v), can be accepted as a valid control product as it is authorised in the EU with a claim for the treatment of *D. canis* in dogs.

The study recruited privately owned dogs following receipt of informed consent, which were kept under experimental homogeneous conditions. Sixteen mongrel dogs (7 males and 9 females, aged > 1 year, 3.54 to 13.67 kg bw at inclusion) were ranked within sex in descending order of individual pre-administration mite counts on Day -4 and subsequently blocked into eight blocks of two dogs each. Within blocks, dogs were randomly allocated to the two groups (8 dogs per group). The number of study animals is considered adequate. Dogs were healthy except for clinical signs and symptoms of generalised *Demodex canis* mite infestations. All dogs were adult (>1 year) and all were assessed as having generalised demodicosis on the basis of clinical signs and mite counts confirmed from deep skin scrapings prior to treatment. The inclusion criteria can be accepted as being appropriate and resulted in a study sample that is considered to be suitably representative of the target population.

Bravecto was administered on D0 and the comparator was administered to the control group at the recommended treatment dose on Days 0, 28, 56 and 85 (optionally). The actual doses of fluralaner (administered as Bravecto) ranged between 25-45 mg/kg bw, which is within the recommended treatment dose range of Bravecto (25-56 mg/kg bw of fluralaner). For the new *Demodex* indication, a single dose of the product is proposed to be administered.

Deep skin scrapings from 5 sites were taken throughout the study on Day -4 (to confirm the presence of *Demodex* spp. mites) and on Days 28, 56, 84 and 112 (optionally). The clinical symptoms and the extent of demodectic lesions on each dog were assessed and overall changes in clinical appearance were illustrated by coloured photographs taken of each dog before treatment on the days during which scrapings were made. The infestation pressure can be considered adequate prior to treatment administration, with 509.4 mites (geometric mean) in the control group and 447.0 mites (geometric mean) in the Bravecto-treated group.

According to Guideline 7AE17a "Demonstration of Efficacy of Ectoparasiticides", the arithmetic mean or geometric mean or other suitably transformed mean may be used, however, such transformation must be justified. The percentage of efficacy was calculated using geometric mean counts as according to applicant's clinical expert, as zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution.

In terms of efficacy, the primary assessment variable was the percentage decrease from the pre-administration mite count to the post-administration mite count in each dog and each group on each assessment point (Days 28, 56, 84). This can be accepted as being an appropriate outcome parameter for demonstrating efficacy. The guideline 7AE17a recommends an overall efficacy of ectoparasiticides of >90% for mange mites other than *Sarcoptes scabiei*. Secondary efficacy variables consisted of the evolution of clinical signs and symptoms assessed during the study.

The results obtained for the primary efficacy criterion showed that a single dose of fluralaner was effective in achieving an acceptable level of efficacy (≥99.8% based on geometric mean and ≥99.7% based on arithmetic mean) at all time points (Days 28, 56 and 84).

Over the course of the study, there was a reduction in erythematous patches, casts, crusts or scales and an improvement in hair re-growth in both study groups. It is noted that the animals were administered antibiotics for pyoderma starting on Day -14, which may also have contributed to the

improvement of clinical signs. That said, in combination with the reduction in mite counts observed during the course of the study, it can be accepted that a clinically-relevant improvement in clinical signs of *D. canis* infestation was observed in both groups. No adverse events directly attributable to Bravecto were reported in this study.

In conclusion, it can be accepted that the results of this study provide evidence that a single administration of Bravecto chewable tablets at the currently approved dose is effective for the treatment of demodicosis caused by *Demodex canis* in dogs.

The second GCP-compliant dose confirmation study investigated efficacy of the final formulation of Bravecto spot-on solution against generalised demodicosis in naturally infested dogs in South Africa. This is a parallel group design, blinded, randomised, single centre, positive controlled efficacy study which included an adequate number of study animals (8 dogs per group). For blinding and randomization purposes and, additionally, due to the potentially debilitating nature of the disease, it can be accepted that a positive control was utilised. Advocate, which is a topical combination of imidacloprid (10% w/v) and moxidectin (2.5% w/v), can be accepted as a valid control product as it is authorised in the EU with a claim for the treatment of *D. canis* in dogs. Study personnel performing assessments were blinded and it can be accepted that the design suitably allowed for adequate blinding.

The study recruited privately owned dogs and following receipt of informed consent the dogs were kept under experimental homogeneous conditions. The study population consisted of 16 mongrel dogs (7 males and 9 females; 7.7 to 16.2 kg bw). All dogs enrolled in the study were ≥8 weeks and all were assessed as having generalised demodicosis on the basis of clinical signs and mite counts confirmed from deep skin scrapings prior to treatment. The inclusion criteria can be accepted as being appropriate and resulted in a study sample that is considered to be suitably representative of the target population.

Both Bravecto and comparator product were administered at their recommended treatment dose. On Day 0, Bravecto spot-on was administered as a single application and the control product was administered on Days 0, 28 and 56. In case of severe demodicosis, the veterinarian was allowed to prescribe the control product on a weekly basis as per the SPC and this happened in four cases. The actual doses of fluralaner ranged between 26.0 to 43.9 mg/kg bw, which is within the recommended treatment dose range of 25-56 mg fluralaner/kg bw.

Mite counts were performed on samples collected by deep skin scrapings from five different body areas on Days -2, 28, 56 and 84. The clinical symptoms and the extent of demodectic lesions on each dog were assessed on Days -2, 14, 28, 42, 56, 70 and 84. Overall changes in clinical appearance were also illustrated by taking pre- and post-administration photographs from each dog.

It is accepted that the infestation intensity was adequate for the study, with 143.5 live mites (arithmetic mean) in the control group pre-treatment and 186.6 live mites (arithmetic mean) in the Bravecto spot-on solution-treated group before administration. Homogeneity of study groups, based on body weight and mites counts at inclusion time was demonstrated.

In terms of efficacy, the primary efficacy criterion was the decrease in arithmetic mean values of mite counts (immature and adult live mites combined) from pre-administration to each post-administration time point, following treatment administration. This can be accepted as being an appropriate outcome parameter for demonstrating efficacy. Guideline 7AE17a recommends an overall efficacy of ectoparasiticides of >90% for mange mites other than *Sarcoptes scabiei*. Cure rate was assessed as a secondary efficacy variable and was defined as the percentage of treated dogs having two negative scrapings one month apart. Clinical signs (skin lesions: casts, scales, crusts and area(s) of hair loss and erythema) were considered additional parameters and analysed descriptively to assess the efficacy of

the treatment.

The results obtained for the primary efficacy criterion showed that Bravecto administered once was effective in achieving an acceptable level of efficacy (≥99.7% based on arithmetic mean and ≥99.8% based on geometric mean) from D28 to the end of the study on D84.

The cure rate (secondary efficacy parameter) in the Bravecto spot-on solution-treated group was 87.5% at the end of the study, with seven out of eight dogs mite-free for two consecutive scrapings.

Over the course of the study, there was a reduction in erythematous papules, casts, crusts and an improvement in hair re-growth in both study groups. Scales consistently decreased in the group treated with Bravecto. It is noted that animals were administered antibiotics for pyoderma starting on Day -7, which may also have contributed to the improvement of clinical signs. That said, in combination with the reduction in mite counts observed during the course of the study, it can be accepted that a clinically-relevant improvement in clinical signs of *D. canis* infestation was observed in both groups. No adverse events attributable to Bravecto were reported in this study.

Based upon the findings from this study, it is accepted that a single application of Bravecto spot-on solution at the currently approved dose demonstrated an acceptable level of efficacy (>90%) against *D. canis* in dogs.

The GCP-compliant field study investigated the efficacy and safety of the final formulations of Bravecto chewable tablets and Bravecto spot-on solution in the treatment of *Demodex canis* in naturally infested dogs presented as veterinary patients in Europe (i.e. Albania, Germany, Poland, Portugal and Spain). The study can be considered representative of the European situation in terms of the geographical distribution of study sites and the age/breed of study animals.

A positive control group was used in this study and the pivotal efficacy parameter was the percentage of dogs free of live mites at the last two evaluation time points: visit 3 (Day 56) and visit 4 (Day 84). According to the Guideline 7AE17a "…*When treatment of groups is intended, preferably 25-50% of the groups under trial should be left untreated. Where this cannot be justified, 25-50% of the groups should be treated with a product established according to Directive 81/852/EEC which is indicated for control of the ectoparasite or groups of ectoparasites claimed...”*. Due to the potentially debilitating nature of the disease and therefore on ethical grounds, the absence of an untreated control group and the use of a positive control group (Advocate) can be accepted. Advocate, which is a topical combination of imidacloprid (10% w/v) and moxidectin (2.5% w/v), can be accepted as a valid control product as it is authorised in the EU with a claim for the treatment of *D. canis* in dogs.

One hundred thirty-four (Full Analysis Set; FAS) client-owned dogs (67 purebred and 67 mixed breed, 63 males and 71 females, aged 10 weeks-13 years, 2.0 to 70.2 kg bw) enrolled in the study were assessed as having generalised demodicosis. Bravecto chewable tablets (n=55), Bravecto spot-on solution (n=54) and control product (n=25) were administered according to their respective SPCs. Bravecto chewable tablets and Bravecto spot-on solution were administered once on D0 and the control product was applied on Days 0, 28, 56 and 84 for mild to moderate cases until 2 negative scrapings 1 month apart; this frequency was increased to once weekly for severe cases at the discretion of the veterinarian. Clinical examinations, skin lesion assessment and skin scrapings (5 scrapings per dog) were performed on Days 0, 28±2, 56±2 and 84±2 in order to evaluate the effect on mite numbers and the resolution of clinical signs.

Two deviations from the study protocol concerning unblinding to treatment were recorded; the applicant has dealt with this by introducing a third group (Unmasked PP population; PPU) for analysis.

The primary efficacy parameter was the percentage of dogs free of live mites at the last two evaluation time points: visit 3 (Day 56) and visit 4 (Day 84). Given the proposed recommendation that a single

treatment with Bravecto is required for the treatment of demodicosis, the evaluation of efficacy at the end of the 12-weeks treatment period can be accepted since this is the authorised re-treatment interval for Bravecto. The overall presence of skin lesions was assessed as secondary efficacy criterion at each visit and for each study group; secondary efficacy was evaluated for the PP and the PPU population only. For the primary efficacy parameter, based upon the complete intention-to-treat data set (FAS), efficacy was 94.55% for Bravecto chewable tablets group and 94.44% for Bravecto spot-on solution group. For the PP population, the efficacy was 96.15% for Bravecto chewable tablets group and 100% for Bravecto spot-on solution group, while for the PPU population the efficacy was 98.00% for both Bravecto chewable tablets and Bravecto spot-on solution groups.

Primary efficacy results in the individual groups were also provided for Day 28: in the per-protocol (PP) population, an efficacy of 91.7% was reached for Bravecto spot-on and 92.3% for Bravecto chewable tablets. In the unblinded per-protocol (PPU) population, these percentages were 92.0% for both Bravecto products. According to Guideline 7AE17a, >90% is an adequate level of efficacy against *D. canis*.

No statistical test results were reported since all comparisons were based on descriptive parameters.

For all study groups in the PP and PPU population, the percentage dogs free of skin lesions increased during the study, reaching 100% for Bravecto chewable tablets and Bravecto spot-on solution in the PP population and 94.0% and 84.0% in the PPU population, respectively, on Day 84. It can be accepted, due to the nature of the disease, that skin lesions do not resolve immediately when mite counts decrease.

Supportive treatment with antiseptics/antibiotics was shown to clear skin lesions faster in both the PP and PPU populations. This can be accepted based on the fact that demodicosis is often accompanied by pyoderma and does not diminish in any way the effect of treatment observed for the control product or Bravecto chewable tablets/spot-on solution.

No spit-out or vomiting was observed during treatment with Bravecto chewable tablets. Local spreading (where the product does not run off but creates a larger than usual spot on the treated dog after application) was observed for one dog during visit 1 for Bravecto spot-on solution. It can be accepted that no adverse events related to the administration of Bravecto chewable tablets or Bravecto spot-on solution were recorded.

In summary, it can be accepted that the results of this field study demonstrate that a single administration of Bravecto chewable tablets or Bravecto spot-on solution at the recommended treatment dose provides an acceptable level of effectiveness against *D. canis* in dogs under field conditions in Europe.

According to guideline 7AE17a, at least two controlled dose confirmation studies in addition to EU clinical field trials should be provided to demonstrate efficacy. The applicant has provided one dose confirmation study conducted with Bravecto chewable tablets and one dose confirmation study conducted with Bravecto spot-on solution. The applicant justifies the omission of a second dose confirmation study for each pharmaceutical form on the grounds that: no valid laboratory model of demodicosis is available; the pharmacokinetic data for both formulations indicate that fluralaner has a high volume of distribution, a low plasma clearance and a long half-life thereby demonstrating persistence of fluralaner and ensuring high exposure of *Demodex* mites; both formulations demonstrated a high level of efficacy against *D. canis* in the one dose confirmation study provided for each and reduction of the number of studies is in accordance with the 3R principles.

In light of the above and given that an acceptable number of animals were included in each treatment group in the field study and the fact that efficacy has been based upon parasitological cure (two

negative skin scrapings one month apart), the CVMP accepts the omission of a second dose confirmation study for the proposed indication for each of the Bravecto formulations in this instance and concludes that further confirmatory data to support efficacy of the product is unnecessary.

In conclusion, the indication against *Demodex canis* in dogs can be accepted.

With this procedure, the MAH is updating Annex IIIA for Bravecto spot-on solution for dogs and Bravecto spot-on solution for cats with regard to the information included on the pipette label, i.e. new pipette labelling sections are included in the product information.

3. Benefit-risk assessment of the proposed change

Bravecto is currently authorised for the treatment of tick and flea infestations in dogs and cats; also, the product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD) in both dogs and cats. The active substance is fluralaner, an acaricide and insecticide; fluralaner is a potent inhibitor of parts of the arthropod nervous system by acting antagonistically on ligand-gated chloride channels (GABA-receptor and glutamate-receptor). Bravecto is presented as chewable tablets and as a spot-on solutions for dogs and a spot-on solution for cats; the dose range is 25–56 mg fluralaner/kg bw for dogs and 40–94 mg fluralaner/kg bw for cats.

The proposed variation is to add a new therapeutic indication in dogs: "For the treatment of demodicosis caused by *Demodex canis*" (for both the chewable tablets and the spot-on solution). Additionally, the MAH is updating the labelling section for Bravecto spot-on solution for dogs and cats with regard to the information included on the pipette label.

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 benefit will arise from the inclusion of the new indication. The indication against *D. canis* in dogs is considered as being of benefit for the user/prescriber and patient. The direct therapeutic benefit of Bravecto is its efficacy in the treatment of demodicosis in dogs, which was established in 3 well-designed laboratory and field studies conducted to an acceptable standard.

Additional benefits

No additional benefits 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 and at the same frequency 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:

The frequency of treatment administration does not differ for the proposed indications in the target species when compared to that already approved for the existing indications. 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 indication.

Risk for the user:

The frequency of treatment does not change due to the addition of the new indication against *D. canis* in dogs. 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 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 is 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.

3.4. Evaluation of the benefit-risk balance

No change to the impact of the product is envisaged on the following aspects: quality, safety, user safety, environmental safety, target animal safety.

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

4. Conclusion

Based on the original data presented on safety and 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 in dogs: "For the treatment of demodicosis caused by *Demodex canis*" (for both chewable tablets and spot-on solution). Additionally, the MAH is updating the labelling section for Bravecto spot-on solution for dogs and cats with regard to the information included on the pipette label.

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, IIIA and IIIB.

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