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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Bravecto (EMEA/V/C/002526/II/0033/G)

INN: fluralaner

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

Rapporteur: Gerrit Johan Schefferlie

Co-rapporteur: Rory Breathnach

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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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 7 January 2019 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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To add new therapeutic indications: for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei*) in dogs, for the treatment of infestations with ear mites (*Otodectes cynotis*) in cats and for the treatment of infestations with ear mites (*Otodectes cynotis*) in dogs. Additionally, editorial changes are implemented in various languages to correct translation errors not detected in previous linguistic reviews.

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 acaricide and insecticide 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 is presented in five different strengths of chewable tablet and five different pipette sizes of spot-on solution for dogs, 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, *Ixodes ricinus, Dermacentor reticulatus* and *D. variabilis* ticks, and 8 weeks for *Rhipicephalus sanguineus* tick.

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*) infestation, 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 three new therapeutic indications: for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei*) in dogs, for the treatment of infestations with ear mites (*Otodectes cynotis*) in cats and for the treatment of infestations with ear mites (*Otodectes cynotis*) in dogs.

For all three newly proposed indications, the products are to be administered at the same dose rates as currently authorised, namely 25–56 mg fluralaner/kg bw for both Bravecto chewable tablets and Bravecto spot-on solution for dogs and 40-94 mg fluralaner/kg bw for Bravecto spot-on solution for cats.

For the chewable tablets and the spot-on solution for dogs, the following treatment regimens are proposed: a single dose of the product should be applied for the treatment of *Otodectes cynotis* and/or *Sarcoptes scabiei*. The need for and frequency of re-treatment should be in accordance with the advice of the prescribing veterinarian. For the treatment of *O. cynotis* in cats, the proposed recommendation is: "For the concurrent treatment of infections with ear mites (*Otodectes cynotis*), a single dose of the product should be applied. Seek further veterinary examination (i.e. otoscopy) 28 days after treatment to determine whether there is re-infestation requiring additional treatment. The choice of the additional treatment (monosubstance or combination product) should be determined by the prescribing veterinarian."

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 indications 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.

Furthermore, 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, it can be concluded that the introduction of the proposed indications will not present a different risk than the one currently accepted for the animal, user or the environment.

2.2. Efficacy

The proposed indications are: "for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei*) in dogs, for the treatment of infestations with ear mites (*Otodectes cynotis*) in cats and for the treatment of infestations with

ear mites (*Otodectes cynotis*) in dogs". Relevant guidelines recommend that two dose confirmation studies should be provided for each claim and that findings from dose confirmatory studies are supported by field data.

2.2.1. The treatment of sarcoptic mange (caused by *Sarcoptes scabiei*) in dogs

In support of the proposed indication, the applicant has provided the results of one dose confirmation study and one field trial.

The dose confirmation study was conducted to evaluate the efficacy of a single dose of Bravecto chewable tablets and Bravecto spot-on solution using the final formulation against *Sarcoptes scabiei* in naturally infested dogs in South Africa. This is a GCP compliant, parallel group designed, randomised, multi-centre, blinded, controlled efficacy field study. Bravecto chewable tablets were administered at the recommended treatment dose of ≥25 mg fluralaner/kg bw and Bravecto spot-on solution at a dose of 25 mg fluralaner/kg bw. Therefore, the dose administered can be accepted as falling within the lower end of the dose range currently approved for Bravecto (25-56 mg fluralaner/kg bw). Given that this study was conducted outside the EU, the applicant provided additional scientific reassurances that the *S. scabiei* mites against which efficacy was investigated in this study were suitably representative of those found in dogs within the EU (in terms of both geographical representativeness and susceptibility).

Twenty-six privately owned dogs (weighing 5.64 to 25.32 kg bw on Day 0) from rural areas in South Africa were included in the study with their owner's permission. The applicant justifies the use of privately owned dogs on account of the unavailability of a reliable model of *Sarcoptes scabiei* infestation and this can be accepted. Nine animals were included in the placebo group, 9 animals in the Bravecto chewable tablets group and 8 animals in the Bravecto spot-on solution group. The number of study animals is considered adequate (>6 animals per group) and the animals are considered to be representative of the target population. Infestation with *Sarcoptes scabiei* var. *canis* was confirmed by skin scrapings on Day -1/0. The dogs were not kept under homogeneous laboratory conditions, but instead stayed with their owners under their usual housing conditions for the duration of the study.

Skin scrapings were taken on Day -2/-1/0 and Day 27/28 from five different body areas suspected of being infested. The clinical signs and the extent of the lesions on each dog were assessed on the days during which scrapings were made and coloured photographs were taken to illustrate the extent and resolution of lesions.

The applicant states that due to the fact that zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution and percentage reduction calculations were based on geometric means rather than arithmetic means. That said, the applicant has presented % efficacy calculations based on both arithmetic and geometric means. Six out of nine animals in the negative control group retained their mite infestation up to Day 27/28 and the number of *S. scabiei* mites recorded from these animals ranged from 0 to 55 (10.0 AM or 3.5 GM). The CVMP considers this to represent adequate infestation intensity in the control group for the duration of the study.

The primary efficacy endpoint was the elimination of *Sarcoptes scabiei* mites, presented as the proportion of dogs with an absence of live mite counts. This is considered appropriate. A 100% efficacy (based on AM and GM) was attained in both treated groups (Bravecto chewable tablets and Bravecto spot-on solution for dogs) on Day 28, which meets the overall efficacy threshold of 100% for *Sarcoptes scabiei* recommended by Guideline on Demonstration of Efficacy of Ectoparasiticides (7AE17a). In terms of secondary efficacy endpoints, a higher percentage of dogs treated with Bravecto had resolution of casts, crusts, erythematous papules and pruritus on Day 28 vs Day 0 values compared to the placebo group. It is noted that the clinical signs associated with sarcoptic mange reduced over the study period; however, the follow up period was not sufficient to evaluate complete resolution of all clinical signs and obvious hair regrowth.

There were 2 protocol amendments and 6 deviations from protocol. It is agreed that none of these impacted on the results of the study.

Regarding safety, three dogs in Bravecto spot-on solution group died between Days 0 and 28. One dog was killed by community members and, therefore, its death is considered to be unrelated to treatment. The deaths of the other two dogs were with high probability caused by *Sarcoptes*-associated sepsis. Due to insufficient information concerning these adverse events, no conclusion can be drawn on a possible association between treatment and death.

In summary, it can be accepted that the results of this study provide evidence that a single administration of Bravecto chewable tablets or a single application of Bravecto spot-on solution at the currently approved dose is effective in the treatment of sarcoptic mange (caused by *Sarcoptes scabiei*) in dogs, with elimination of live mite infestation and reduction in clinical signs.

One GCP-compliant field study evaluated the efficacy and safety of a single administration of Bravecto chewable tablets or a single application of Bravecto spot-on solution using the final formulations at their respective recommended dosages in the treatment of sarcoptic mange in naturally infested dogs presented as veterinary patients in the EU (France, Italy and Portugal) and Albania. The study can be considered representative of the European situation (in terms of both geographical representativeness and susceptibility) and included more than one geographical area (albeit 40% of study animals were enrolled in Albania). A positive control group treated with a comparator product currently authorised in the EU with a claim for the treatment of sarcoptic mange caused by *S. scabiei* was included in this study. Due to the potentially debilitating nature of the disease and therefore on ethical grounds, the CVMP accepts the omission of an untreated control group in this field study.

Skin scrapings of 154 dogs (FAS population) presenting clinical signs of sarcoptic mange were screened to confirm the infestation and to establish *S. scabiei* mite counts. Per Protocol (PP) population consisted of 126 dogs which were treated on Day 0 with Bravecto chewable tablets (n=54), Bravecto spot-on solution for dogs (n=46), or the comparator product (n=26), at their respective recommended treatment doses. The sample size is considered adequate. The study animals (various breeds, privately owned, aged from 10 weeks to 11 years old and weighting 2.8 to 52 kg) in the PP dataset can be considered sufficiently representative of the target population. The dogs were kept at home, under their usual housing conditions, and allocated to treatment groups according to the randomization schedule.

On Days 0, 28, 56 and 84, the dogs were examined to determine the health status, *Sarcoptes scabiei* mites were counted in at least five skin scrapings per dog and the dogs were scored for the presence/extent of specific clinical signs (crusts, hair loss, erythema and/or papules, pruritus).

The primary efficacy endpoint was the percentage of dogs free of live mites at the last evaluation time point (Visit 4, Day 84). The guideline 7AE17a recommends an overall efficacy of approximately 100% for *Sarcoptes scabiei* mites. In this study, the percentage of dogs free of live mites was 100% for all groups.

In terms of the secondary efficacy endpoints (the percentage of dogs free of live mites at Visit 2 (Day 28) and Visit 3 (Day 56)), on D28 94% and 96% efficacy was attained for Bravecto chewable tablets and Bravecto spot-on solution, respectively, whereas on D56 100% efficacy was attained for both treatment groups. The development of pruritus scores and the number of skin lesion areas were evaluated as additional criteria for the PP population. The mean number of lesion areas decreased over time in all treatment groups.

Regarding safety, 8 adverse events were reported during the study in dogs included in Bravecto chewable tablets (3) and Bravecto spot-on solution (5) groups. In the Bravecto chewable tablets group, pyodermatitis and enlarged mandibular lymph nodes may have been related to the sarcoptic mange. In the Bravecto spot-on solution group, one dog was seen with diarrhoea. Mild and transient gastrointestinal effects such as diarrhoea are already adequately addressed in the SPC under section 4.6, adverse reactions.

In summary, it can be accepted that the results of this field study provide evidence that a single administration of Bravecto chewable tablets or Bravecto spot-on solution at the recommended treatment dose is effective in the treatment of sarcoptic mange caused by *S. scabiei* in dogs, with elimination of live mite infestation and

reduction in clinical signs.

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 under field conditions and one clinical field trial. Based on the data provided, the CVMP accepts that a single administration of Bravecto chewable tablets or Bravecto spot-on solution at the recommended treatment dose is effective in the treatment of sarcoptic mange in dogs under field conditions and that a reduction in clinical signs of *S. scabiei* infestation has been shown. Given that 100% efficacy was demonstrated on Day 28 in the dose confirmation study and that 100% of dogs were demonstrated to be mite free on Day 84 in the clinical field trial, the CVMP is of the opinion that additional data from a second dose confirmatory study is unnecessary in this instance.

In terms of safety, although a number of adverse events were observed in treated animals in both studies and due to insufficient information no conclusion can be drawn on an association between treatment and these adverse events, the CVMP accepts that overall, both Bravecto chewable tablets and Bravecto spot-on solution can be considered safe in the treatment of *Sarcoptes scabiei* infestations in dogs.

In conclusion, the indication against *S. scabiei* var. *canis* in dogs can be accepted.

2.2.2. The treatment of infestations with ear mites (*Otodectes cynotis*) in cats

In support of the proposed indication, the applicant has provided the results of two dose confirmation studies and one field trial.

The first dose confirmation study was conducted to evaluate the efficacy of a single dose of Bravecto spot-on solution for cats using the final formulation against *Otodectes cynotis* in experimentally infested cats in South Africa. This is a GCP compliant, blinded, placebo (physiological saline solution) controlled, randomised, three phase, single centre, efficacy study. Although a phased design approach has been used, it can be accepted that the study methods used in each phase were the same and therefore the phased approach is not considered to have negatively impacted upon the study findings. Bravecto was administered at the recommended treatment dose of 40 mg fluralaner/kg bw but no actual doses were reported in the study. Therefore, the dose administered can be accepted as falling within the lower end of the dose range currently approved for Bravecto spot-on solution for cats (40-94 mg fluralaner/kg bw).

Sixteen European mixed breed, short haired cats, weighing 2.42 to 4.68 kilograms at Day -1 were sourced from a colony and housed individually or in groups of up to three animals. The number of study animals (8 cats per group) is considered adequate (>6 animals per group). The study animals were experimentally infested with a South African strain of *O. cynotis* mites originating from donor animals. The timing of the artificial infestation was not provided. At least 1 mite in both ears confirmed through otoscopic examination on Day -7 was used to validate appropriate infestation and animal inclusion. On Day -2, cats were ranked within sex in descending order of individual pre-administration live mite and debris score assessed on Day -2. Otoscopic examinations were performed on Days -7 and -2 to confirm the presence of visible live ear mites (adult or immature) and again on Days 7, 14 and 28. Ear flushing under sedation and mite counts were performed to assess efficacy on Day 28.

The applicant states that due to the fact that zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution and percentage reduction calculations were based on geometric mean (GM) rather than arithmetic mean (AM). That said, the applicant also presented % efficacy based on arithmetic mean count data. The mite count in animals in the control group ranged from 6 to 1843 (595.1 AM) on Day 28, supporting the fact that the infestations were well established. The applicant provided further scientific information on the source of *O. cynotis* mites and justified how the mites used in this study may be considered suitably representative of those found in cats within the EU (in terms of both geographical representativeness and susceptibility).

The primary efficacy endpoint was the percentage reduction in mite count in the treated group compared to the control group at each assessment day using Abbott's formula. The Guideline on Demonstration of Efficacy of Ectoparasiticides (7AE17a) recommends an overall efficacy of >90% for mange mites other than *Sarcoptes scabiei*. The results from this study indicate a statistically significant difference ($p<0.05$ using GM and AM) in the number of visible live mites on Day 28 between the treatment and control groups, with an efficacy of 100% (AM and GM). In terms of debris and cerumen, a moderate improvement was observed at Day 28 in cats in the Bravecto group compared to control cats. This may be expected as reactions to mites do not resolve immediately once mites die.

No adverse effects attributable to treatment were reported during this study, but, after completion of the study at Day 28, one cat treated with Bravecto spot-on solution presented with clinical signs that could be considered as neurological. These neurological signs were most likely attributable to the ear flushing technique used and therefore no product information update is considered necessary.

The second dose confirmation study was conducted to evaluate the efficacy of a single dose of Bravecto spot-on solution for cats using the final formulation against *Otodectes cynotis* in experimentally infested cats in South Africa. This is a GCP compliant, blinded, placebo (physiological saline solution) controlled, randomized, single centre efficacy study. Bravecto was administered at the recommended treatment dose and the actual dose of fluralaner ranged between 39.59 mg/kg bw and 40.29 mg/kg bw. Therefore, the dose administered can be accepted as falling within the lower end of the dose range currently approved for the product (40-94 mg fluralaner/kg bw).

Sixteen domestic short haired cats (8 females and 8 males, aged between 54 and 407 weeks at Day -7, weighing 2.18 to 5.24 kilograms at Day -2) were sourced from a colony and group housed in one to four cats per cage per sex. The number of study animals (8 cats per group) is considered adequate (>6 animals per group). The study animals were experimentally infested somewhere between Day -90 and Day -7 with a combination of a South African and a European strain (Hungary) of *O. cynotis* mites originating from donor animals.

Presence of ear mites in both ears as confirmed through otoscopic examination on Day -7 with at least one ear with >10 mites was used to validate appropriate infestation and animal inclusion. On Day -2, the acclimatized cats were ranked within sex in descending order of individual pre-administration live mite and debris score assessed on Day -2.

Otoscopic examinations were performed on Days -7 and -2 to confirm the presence of live ear mites and debris. During the study, otoscopic examinations were performed again on Days 2, 7, 14, 21 and 28. Ear flushing under sedation and mite counts were performed to assess efficacy on Day 28.

The applicant states that due to the fact that zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution and percentage reduction calculations were based on geometric mean rather than arithmetic mean. That said, the applicant also presented % efficacy based on arithmetic mean count data. The mite count in animals in the control group ranged from 26 to 1111 (347.0 AM) on Day 28, supporting the fact that the infestations were well established. The applicant provided justification that the mites used in this study were representative of those found in cats within the EU (in terms of both geographical representativeness and susceptibility).

The primary efficacy endpoint was the percentage reduction in mite count in the IVP treated group compared to the control group at each assessment day using Abbott's formula. The Guideline on Demonstration of Efficacy of Ectoparasiticides (7AE17a) recommends an overall efficacy of >90% for mange mites other than *Sarcoptes scabiei*. The results of this study indicate a statistically significant difference ($p<0.05$ using GM and AM) in the number of visible live mites on Day 28 between the treatment and control group, with an efficacy of 100% (AM and GM). In terms of debris and cerumen, a moderate improvement was observed at Day 28 in cats in Bravecto group compared to control cats. This may be expected as reactions to mites do not resolve immediately once mites die.

One adverse event (flaking/scaling and dry skin at administration site 2 days after treatment, which resolved within 2 days) possibly related to treatment with Bravecto was reported.

In conclusion, both dose confirmation studies showed 100% efficacy for Bravecto spot-on solution for the treatment of infestations with *O. cynotis* in cats.

One field study was conducted to evaluate the efficacy of a single dose of Bravecto spot-on solution for cats against *Otodectes cynotis* in naturally infested cats in Europe. This is a GCP compliant, multi-centred, positive-controlled, randomised and examiner-blinded study, with one study group and one positive control group, conducted in 22 veterinary practices located in France, Germany, Hungary, and Spain.

Bravecto (IVP) was administered at the recommended treatment dose of 40-94 mg fluralaner/kg bw calculated from the body weight of the cats. Due to rounding, minor deviations have been introduced but no actual doses have been provided in the study. A selamectin-containing product (CP) authorised in the EU for treatment of ear mite infestation (*O. cynotis*) was administered at the recommended treatment dose of at least 6 mg selamectin/kg bw as comparator (positive control).

Two hundred and sixty-eight animals were included into the full analysis set (FAS). The per-protocol (PP) set included 176 cats (IVP group, n=118; CP group, n=58). The highest participation was seen in Hungary (78), Spain (51) and Germany (43), with only 4 cats participating in France. Animals included in the study were of several breeds, several coat types, aged between 0 and 15 years, and weighed between 1.20 and 7.5 kg. Males and females were included, both intact and neutered. The breeds used consist of a mix of short haired and longer haired cat breeds, although the majority were short haired (FAS population: 142/181 in fluralaner group and 72/87 in selamectin group).

Presence of ≥5 ear mites per cat as confirmed through otoscopic examination or microscopically was used to validate appropriate infestation and animal inclusion.

The included households were randomly allocated to study groups stratified by site in blocks (2:1 ratio for IVP and CP), using computer generated randomization lists (one per investigational site).

Bilateral otoscopic examinations were performed on Days 0, 14±2 and 21±2. Otoscopic assessments were quantitative and the presence or absence of moving ear mites was recorded according to the parameters: no mites, less than 5 mites, 5 or more mites. In addition, on Days 0 and 14±2, microscopic examination of aural debris was done in cases where zero or less than five live mites were seen by otoscopic examination. On Day 28±2, aural debris from both ears of all animals was examined microscopically only if no live mites were seen by otoscopic examination. All live mites were counted on Day 28±2.

Primary efficacy was evaluated for the PP population only and was based upon the percentage of cats free of mites (parasite free cases) within study group. Treatment with Bravecto was considered efficacious at Day 14 or 28 if the percentage of cats free of mites in the respective study group was >90% at this time point. This is considered appropriate and in line with the guideline 7AE17a. Secondary efficacy was evaluated for the FAS population. The number of parasite free households was determined for each study group and each follow-up visit post-treatment (Day 14±2 and Day 28±2). Additionally, a descriptive evaluation of ear examination scores (ear pruritus / scratching, erythema of the pinnae, cerumen at Day 0, Day 14±2 and Day 28±2) was carried out for all cats in the PP population.

With regard to the primary efficacy parameter, on Day 14±2, 106/118 cats (89.8%) and on Day 28±2, 113/115 cats (98.3%) in Bravecto-treated group were free of mites. As for secondary efficacy parameter, on Day 14±2, 62/69 (89.9%) households and on Day 28±2, 66/69 (95.7%) households in the Bravecto-treated group were free of mites.

The applicant has tested for superiority in both the FAS and the PP population. However, in superiority trials the full analysis set should be used in the primary analysis as it tends to avoid over-optimistic estimates of efficacy. In this study, the percentage of ear mite free households could not be shown to be superior.

The applicant also performed non-inferiority studies to show that the efficacy of the IVP was not lower than that of the comparator. A study by Six (2000) has been provided, in which the efficacy and safety of selamectin against *O. cynotis* in cats has been studied. This study reports an efficacy of 94-100% against ear mites in cats by Day 30. Similar results were obtained in this field study for selamectin on day 28±2. Therefore, it can be accepted that the observed efficacy of the active comparator in this study was similar to what was to be expected.

One of the observed adverse events was considered to be related to the IVP and concerned alopecia. This adverse event is already included in the SPC of the product as known adverse events.

In conclusion, the results of this study demonstrate that Bravecto spot-on solution for cats has been shown to have an acceptable level of efficacy (>90% at Day 28) for the treatment of infestations with *O. cynotis* in cats under natural conditions when administered at the recommended treatment dose.

Given the guideline requirements for two dose-confirmation studies and supportive field data, the applicant has met guideline requirements and therefore the indication against *O. cynotis* in cats can be accepted. However, for the purpose of clarity, treatment recommendation proposed initially by the applicant has been amended to: "For the treatment of ear mite infestations (*Otodectes cynotis*), a single dose of the product should be applied. A further veterinary examination 28 days after treatment is recommended as some animals may require further treatment with an alternative product."

2.2.3. The treatment of infestations with ear mites (*Otodectes cynotis*) in dogs

In support of the proposed indication, the applicant has provided the results of one dose confirmation study and some field evidence in the form of a case study.

The dose confirmation study was conducted to evaluate the efficacy of a single dose of Bravecto spot-on solution for dogs and Bravecto chewable tablets using the final formulation against *Otodectes cynotis* in experimentally infested dogs in South Africa. This is a GCP-compliant, parallel group design, blinded, randomised, single centre, placebo controlled efficacy study. Although a phased design approach has been used, it can be accepted that the study methods used in each phase were the same and therefore the phased approach is not considered to have negatively impacted upon the study findings. The dose of fluralaner administered in the Bravecto chewable tablet group and the Bravecto spot-on solution for dogs group ranged between 25.41 to 32.7 mg/kg bw and 25.14 to 25.41 mg/kg bw, respectively. Therefore, the dose administered can be accepted as falling within the lower end of the dose range currently approved (25-56 mg fluralaner/kg bw).

Twenty-four mongrel dogs (weighing 8.80 to 24.21 kg) were sourced from a colony and housed individually. The number of study animals (8 dogs per group) is considered adequate (>6 animals per group). The study animals were experimentally infested with a South African strain of *O. cynotis* mites originating from donor animals. The timing of the artificial infestation was not provided. A total of >10 mites in both ears confirmed through otoscopic examination on Day -7 was used to validate appropriate infestation and animal inclusion. The dogs were ranked within sex in descending order of individual pre-administration live mite and debris score assessed and subsequently blocked into eight blocks of three dogs each. Otoscopic examinations were performed on Days -7 and -2 to confirm the presence of visible live ear mites and again on Days 14 and 28. Ear flushing under sedation and mite counts were performed to assess efficacy on Day 28.

The applicant states that due to the fact that zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution and percentage reduction calculations were based on geometric mean (GM) rather than arithmetic mean (AM). That said, the applicant also presented % efficacy based on arithmetic mean count data. The mite count in animals in the control group ranged from 24 to 664 (123.50 AM) on Day 28, supporting the fact that the infestations were well established. The applicant was requested to provide further information on the source of *O. cynotis* mites and justify how the mites used in this study may

be considered suitably representative of those found in dogs within the EU (in terms of both geographical representativeness and susceptibility).

The primary efficacy endpoint was the number of live mites collected from the treated groups on Day 28 compared to that of the placebo control group using Abbott's formula. Guideline 7AE17a recommends an overall efficacy of >90% for mange mites other than *Sarcoptes scabiei*. The results from this study indicate a statistically significant difference ($p<0.05$ using GM or AM) in the number of visible live mites at Day 28 between the treatment groups and control group, with an efficacy of 99.8% (GM) or 99.9 % (AM) attained in both treatment groups at Day 28. In terms of debris and cerumen, a moderate improvement was observed in dogs in both Bravecto groups compared to control dogs. This may be expected as reactions to mites do not resolve immediately once mites die.

Two adverse events for which the relationship to the treatment with Bravecto was classified as "unknown" were reported during this study. They included anxiousness and red/congested mucous membranes. Due to insufficient information, no definitive conclusion can be drawn on an association between treatment and these adverse events.

Since the representativeness of the infestation for the EU was not established, no conclusion could be drawn on the findings of this study and how it can be considered supportive of the proposed indication for the treatment of *O. cynotis* infestations in dogs.

Field evidence to support the efficacy of fluralaner against *O. cynotis* in dogs was provided in the form of a case study by Field and Hasselman (2016). Briefly, sixteen, 13-week old Harrier hound puppies weighing 8–13 kg were treated with Bravecto chewable tablets against infestation with *O. cynotis*. No control group was included in the study. The puppies were treated with a clinical dose of 25–56 mg fluralaner/kg bw. On Days 0, 7, 14 and 35 the pups' ear canals were examined visually using an otoscope. The number of mites in each ear was estimated and the scores for both ears averaged together to generate the mite score. Similarly, the amount of debris/cerumen observed in the ear canal was scored. On Days 14 and 35, no mites were found in any of the pup's ears.

Concomitant treatment on Day 14 included an ear cleaner. During the study, 8 pups were rehomed and did not participate in the final examination on Day 35.

As a field study, this case study is very limited. Firstly, only 16 puppies were included and only 8 remained in the study until the end due to rehoming of the other 8 puppies. Secondly, the study took place in New Zealand and it has not been clarified how these *O. cynotis* mites are suitably representative of those found in dogs within the EU (in terms of both geographical representativeness and susceptibility).

Taking into account a number of significant deficiencies in this study, particularly the lack of a control group and the inclusion of a small number of animals, the CVMP considers that the findings of this study could only provide limited evidence to support the efficacy claim of Bravecto against *O. cynotis* under field conditions.

Considering the guideline requirements for two dose confirmation studies and supportive field data and the fact that only a single dose confirmation study in dogs has been provided and the field data is very limited, the CVMP was of the opinion that, for *O. cynotis* infestations in dogs, the applicant did not meet guideline requirements. In summary, the indication against *O. cynotis* in dogs was considered to have been inadequately supported in accordance with guideline requirements. Consequently, the applicant was requested to provide additional information to justify this claim; in light of the above, the applicant decided to withdraw the proposed indication for Bravecto chewable tablets and Bravecto spot-on solution for dogs against *Otodectes cynotis* infestations in dogs.

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 or spot-on solution for dogs and spot-on solution for cats; the dose range is 25–56 mg fluralaner/kg bodyweight in dogs and 40–94 mg fluralaner/kg bodyweight in cats.

The proposed variation is to add three new therapeutic indications: for the treatment of sarcoptic mange (caused by *Sarcoptes scabiei*) in dogs, for the treatment of infestations with ear mites (*Otodectes cynotis*) in cats and for the treatment of infestations with ear mites (*Otodectes cynotis*) in dogs. However, following receipt of questions from the CVMP on the adequacy of the data package provided in support of the proposed indication against *Otodectes cynotis* in dogs, the applicant decided to omit this indication in dogs.

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce additional indications to existing products, the benefit will arise from the inclusion of new indications. The indications against *S. scabiei* var. *canis* in dogs and *O. cynotis* in cats are considered as being of benefit for the user/prescriber. The direct therapeutic benefit of Bravecto is its efficacy in the treatment of sarcoptic mange in dogs and otodectic mange in cats, which was established in a number of 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 additional indications to existing products, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indications. As the products 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 include gastrointestinal effects (chewable tablets) or skin reactions at the application site (spot-on solution).

Risk for the user:

The frequency of treatment does not change due to the addition of the new indications against S. *scabiei* var. *canis* in dogs and *O. cynotis* in cats. 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 and complementary 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 new therapeutic indications: for the treatment of sarcoptic mange (*Sarcoptes scabiei* var. *canis*) infestation in dogs and for the treatment of infestations with ear mites (*Otodectes cynotis*) in cats.

However, the proposed indication for the treatment of infestations with ear mites (*Otodectes cynotis*) in dogs is considered to have been inadequately supported and this claim has been withdrawn by the applicant during the procedure.

Taking into account the two accepted claims, 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 as outlined above.

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

I and IIIB.

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