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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use

# CVMP assessment report for type II variation for Bravecto Plus (EMEA/V/C/004440/II/0003)

International non-proprietary name: fluralaner / moxidectin

**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 on 12 October 2018 an application for a type II variation for Bravecto Plus.

## *1.2. Scope of the variation*

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

The variation is to add a new therapeutic indication: "For the treatment of infestations with ear mites (*Otodectes cynotis*)". Furthermore, the applicant takes the opportunity to amend section 4.5 of the SPC, section 7 of the labelling (outer package) and section 12 of the package leaflet in line with the CVMP conclusion from the recent renewal procedure for the product Bravecto spot-on solution for dogs and cats.

## *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 Plus contains a fixed combination of the active substances fluralaner and moxidectin. Fluralaner is an acaricide and insecticide of the isoxazoline family, efficacious against ticks (*Ixodes ricinus*) and fleas (*Ctenocephalides felis*). Moxidectin, a semisynthetic derivative of nemadectin, belongs to the milbemycin group of macrocyclic lactones and has parasiticidal activity against a range of internal and external parasites, but lacks substantial efficacy against fleas and ticks.

Bravecto Plus is currently indicated for use in cats with, or at risk from, mixed parasitic infestations by ticks and fleas, gastrointestinal nematodes or heartworm. Against ticks (*Ixodes ricinus*) and fleas (*Ctenocephalides felis*), Bravecto Plus provides immediate and persistent killing activity for a period of 12 weeks; the product can be used as part of a treatment strategy for flea allergy dermatitis (FAD). The product is also indicated for the treatment of infections with 4$^{th}$ stage larvae, immature adult and adult gastrointestinal nematodes (*Toxocara cati*, *Ancylostoma tubaeforme*) and for the prevention of heartworm disease caused by *Dirofilaria immitis* for 8 weeks.

Bravecto Plus is presented in three different pipette sizes of spot-on solution with fluralaner and moxidectin administered at a dose of 40-94 mg/kg body weight (bw) and 2-4.7 mg/kg bw, respectively. The frequency of repeat administration is dependent upon the target parasite being treated and the local epidemiological situation. If necessary, cats can be re-treated at 12-week intervals.

The proposed variation is to add a new therapeutic indication: for the treatment of infestations with ear mites (*Otodectes cynotis*).

For this new therapeutic indication, the product is proposed to be administered at the same dose rates as currently authorised, namely "a single dose of the product should be applied. The need for and frequency of re-treatment should be in accordance with the advice of the prescribing veterinarian and take into account the local epidemiological situation. Where necessary, cats can be re-treated at 12-week intervals" (from section 4.9 of the SPC). However, during the assessment of the application, the applicant revised the advice as follows: "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 a re-infestation requiring additional treatment. The choice of the additional treatment (monosubstance or combination product) should be determined by the prescribing veterinarian".

The correct pipette size (dose) is determined by the body weight of the cat, i.e. for small cats (1.2–2.8 kg bw) a pipette containing 112.5 mg of fluralaner and 5.6 mg of moxidectin, for medium-sized cats (>2.8–6.25 kg bw) a pipette containing 250 mg of fluralaner and 12.5 mg of moxidectin, and for large cats (>6.25–12.5 kg bw) a pipette containing 500 mg of fluralaner and 25 mg of moxidectin.

## *2.1. Safety (tolerance, user, environment)*

No new preclinical or 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 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, it can be concluded that the introduction of the proposed indication will not present a different risk than the one currently accepted for the target animals, user or the environment.

## *2.2. Efficacy*

The proposed indication is: "for the treatment of infestations with ear mites (*Otodectes cynotis*)". 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. Justification of combination

A pharmacodynamics summary on moxidectin has been provided. The data indicate that, under clinical conditions, the target sites of action of fluralaner and moxidectin in arthropods and nematodes are sufficiently different for both actives to retain their efficacy. The results of pharmacokinetic studies showed no evidence of interaction between moxidectin and fluralaner. The combination of fluralaner and moxidectin has already been accepted by the CVMP, and data to support the activity of both active

ingredients and their lack of interaction has been evaluated in the procedure for the initial authorisation of Bravecto Plus (EMEA/V/C/004440/0000).

The addition of the target parasite *O. cynotis* to Bravecto Plus indications will increase the range of available treatment possibilities for concurrent ear mite infestations occurring together with tick or flea infestations in cats in Europe. Compliance of the animal owner with the treatment recommendations is critical to ensure that the treatment is effective and efficacious. Spot-on solutions are especially suited for use in cats for ease of administration and thus greatly improve treatment compliance.

On account of the occurrence of *O. cynotis* in Europe, the severity of the resulting clinical condition, the prevalence of the infection in the target species and the zoonotic potential, the CVMP considers the rationale for the proposed new indication as acceptable and to be in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).

### 2.2.2. Dose confirmation studies

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

The first dose confirmation study was conducted to evaluate the efficacy of a single dose of Bravecto Plus 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 Plus was administered at the minimum recommended treatment dose of 40 mg fluralaner/kg bw (and 2 mg moxidectin/kg bw).

Sixteen European mixed breed, short haired cats, weighing 2.28 to 4.32 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 Study Day (SD) -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 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 Plus 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 the treatment were reported during this study, but, after completion of the study at Day 28, 3 cats presented 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.

In conclusion, the results of this study indicate that a statistically significant difference in the number of visible live mites on Day 28 was observed between the treatment and control groups, with an efficacy of 100% following the administration of a single dose of Bravecto Plus.

The second dose confirmation study was conducted to evaluate the efficacy of a single dose of Bravecto Plus 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 Plus was administered at the minimum 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 409 weeks at Day -7, weighing 2.18 to 5.62 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 an European strain (Hungary) of *O. cynotis* mites originating from donor animals.

Presence of ear mites in both ears as confirmed through otoscopic examination on SD -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 SD -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 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 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 Plus 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 the treatment with Bravecto Plus were reported.

In conclusion, the results of this study indicate that a statistically significant difference in the number of visible live mites on Day 28 was observed between the treatment and control groups, with an efficacy of 100% following the administration of a single dose of Bravecto Plus.

## 2.2.3. Clinical field trials

One field study was conducted to evaluate the efficacy of a single dose of Bravecto Plus final formulation 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 Plus (IVP) was administered at the recommended treatment dose of 40-94 mg fluralaner/kg bw and 2-4.7 mg moxidectin/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 thirty-six animals were included into the full analysis set (FAS). The highest participation was seen in Germany (71), Hungary (85) and Spain (77), with only 3 cats participating in France. The per-protocol (PP) set included 167 cats. Animals included in the study were of several breeds, several coat types, aged between 0 and 18 years, and weighed between 1.20 and 8.0 kg. Males and females were included, both intact and neutered. The breeds used consist of a mix of short and longer haired cat breeds, although the majority were short haired (FAS population: 128/149 in fluralaner + moxidectin 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 living mites were seen by otoscopic examination. On SD 28±2, aural debris from both ears of all animals was examined microscopically only if no living mites were seen by otoscopic examination. All living 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 groups. Treatment with Bravecto Plus was considered efficacious at SD 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 (SD 14±2 and SD 28±2). Additionally, a descriptive evaluation of ear examination scores (ear pruritus / scratching, erythema of the pinnae, cerumen at SD 0, SD 14±2 and SD 28±2) was carried out for all cats in the PP population.

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 have 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.

Based on the primary efficacy parameter, efficacy against ear mites was demonstrated in the Bravecto Plus treatment group at SD 14 and 28 (93.6% and 100% respectively). Bravecto Plus spot-on solution for cats was confirmed to be non-inferior to the control product at SD 14 and 28; however, the percentage of ear mite free cats could not be shown to be superior.

In terms of the secondary efficacy endpoints, ear pruritus score, erythema of the pinnae score and the cerumen score were not significantly different between treatment and control groups.

Three of the observed adverse events were considered to be related to the IVP and concerned alopecia and matted coats. These adverse events are already included in the SPC of the product as known adverse events and therefore no update is considered necessary.

In conclusion, the results of this study demonstrate that Bravecto Plus has been shown to have an acceptable level of efficacy (100% at Day 28) for the treatment of *O. cynotis* in cats under natural conditions when administered at the recommended treatment dose.

Given that two dose-confirmation studies and supportive field data have been provided in support of this application, it is considered that the guideline requirements have been met.

# 3. Benefit-risk assessment of the proposed change

Bravecto Plus is authorised for cats with, or at risk from, mixed parasitic infestations by ticks and fleas, gastrointestinal nematodes or heartworm and is exclusively indicated when use against ticks or fleas and one or more of the other target parasites is indicated at the same time. The active substances are fluralaner and moxidectin. The product is a spot-on solution available in three pipette sizes to be used according to the body weight of the cat (corresponding to a dose of 40-94 mg fluralaner/kg body weight and 2-4.7 mg moxidectin/kg body weight).

The proposed variation is to add a new therapeutic indication: "For the treatment of infestations with ear mites (*Otodectes cynotis*)". Furthermore, the applicant takes the opportunity to amend section 4.5 of the SPC, section 7 of the labelling (outer package) and section 12 of the package leaflet in line with the CVMP conclusion from the recent renewal procedure for the product Bravecto spot-on solution for dogs and cats.

## *3.1. Benefit assessment*

### Direct therapeutic benefit

The proposed benefit of this variation to introduce an additional indication to the existing product Bravecto Plus is its efficacy in the treatment of infestations with ear mites (*Otodectes cynotis*), which was established in two well designed laboratory studies and one field study conducted to acceptable standards. Additional information has been added to the product literature to adequately reflect the treatment and the need for re-evaluation after 28 days and the possible necessity to use additional treatments.

### Additional benefits

The product is easy to apply by the owner as it is given as a topical treatment as opposed to other treatments available for this condition which may require application in the affected and painful ears of cats infected with *O. cynotis*. Compliance of the animal owner with the treatment recommendations is

critical to ensure that the treatment is effective and efficacious. Spot-on solutions are especially suited for use in cats for ease of administration and thus greatly improve treatment compliance.

## *3.2. Risk assessment*

As this is a variation to introduce an additional indication to an existing product, 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:*

Administration of fluralaner / moxidectin in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include mild and transient skin reactions at the application site.

*Risk for the user:*

With this variation, the frequency of administration does not change and, therefore, the risk for the user does not change.

*Risk for the environment:*

Bravecto Plus 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.

No additional risk management or mitigation measures are considered necessary.

## *3.4. Evaluation of the benefit-risk balance*

Given that it is not expected that any new risk will result from the inclusion of the additional therapeutic indication, it can be accepted that there should be an increased benefit from the use of the product for the treatment of infestations with ear mites (*O. cynotis*) in cats.

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

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

The product has been shown to be efficacious for the treatment of infestations with ear mites (*O. cynotis*).

The product is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended.

# 4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Bravecto Plus can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add a new therapeutic indication: "For the treatment of infestations with ear mites (*Otodectes cynotis*)". Furthermore, the applicant takes the opportunity to amend section 4.5 of the SPC, section 7 of the labelling (outer package) and section 12 of the package leaflet in line with the CVMP conclusion from the recent renewal procedure for the product Bravecto spot-on solution for dogs and cats.

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, 4.4, 4.5, 4.9 and 5.1 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.