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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Bravecto Plus (EMEA/V/C/004440/VRA/0023/G)

INN: 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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Intervet International B.V. (the applicant), submitted to the European Medicines Agency (the Agency) on 29 August 2022 an application for a group of variations requiring assessment for Bravecto Plus.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
G.I.18	One-off alignment of the product information with version 9.0 of the QRD templates i.e. major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicinal products placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004

The variation is to add a new therapeutic indication for the prevention of lungworm disease caused by *Aelurostrongylus abstrusus* and to align the product information with version 9.0 of the QRD template.

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. Limited market status

Not applicable

2. Scientific Overview

The product Bravecto Plus spot-on solution for cats is a fixed combination of two active pharmaceutical ingredients, fluralaner (an insecticide and acaricide of the isoxazoline family) and moxidectin (a semisynthetic derivative of nemadectin, belonging to the milbemycin group of macrocyclic lactones). The results of the pharmacokinetic studies previously submitted did not show evidence of a biologically relevant interaction between moxidectin and fluralaner.

Bravecto Plus spot-on solution for cats is currently indicated for use in cats for the treatment of tick (*Ixodes ricinus*) and flea (*Ctenocephalides felis*) infestations, providing immediate and persistent killing activity for a period of 12 weeks and can be used as part of a treatment strategy for flea allergy dermatitis. It is also indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* for a period of 12

weeks, for the treatment of infestations with ear mites (*Otodectes cynotis*) and for the treatment of infections with intestinal roundworm (*Toxocara cati* - 4th stage larvae, immature adults and adults) and hookworm (*Ancylostoma tubaeforme* - 4th stage larvae, immature adults and adults).

Bravecto Plus spot-on solution for cats is available in three different strengths: 112.5 mg fluralaner/5.6 mg moxidectin, 250 mg fluralaner/12.5 mg moxidectin and 500 mg fluralaner/25 mg moxidectin per pipette.

The proposed variation is to add a new therapeutic indication for the prevention of lungworm disease caused by *Aelurostrongylus abstrusus* and to align the product information with version 9.0 of the QRD templates. An updated summary of the product characteristics (SPC) based on QRD template version 9.0 has been provided. In addition, the applicant takes the opportunity to introduce in the product information new standard sentences in line with the updated 'Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products' (EMA/CVMP/EWP/170208/2005-Rev.1).

Aelurostrongylus (A.) abstrusus is a metastrongyloid nematode parasite that can infect both wild as well as domestic felids. In this last decade, the attention for this nematode has dramatically increased, and from a minor species it is now regarded as one of the most important feline parasites. The feline lungworm is endemic in several European countries, such as Bulgaria, Hungary and Italy.

In intermediate hosts, the first stage (L1) parasite-larvae develops to the infectious third stage (L3) larvae within 3 weeks. Cats become infected by ingesting intermediate hosts that harbour infective L3 larvae: terrestrial gastropods (slugs and snails) or, more often, by small preys like reptiles, birds, rodents, amphibians (paratenic hosts). In the cat, L3 larvae migrate from the stomach to the lungs within 24 hours and develop to L4 within 7-11 days. Around 14 days after infection, the pre-adult stages (L5) are present and adult stages can be seen around 1 month after infection. Adult worms live in the bronchioles, alveolar ducts and alveoli. Infected cats may suffer from a subclinical infection to mild or acute or chronic respiratory signs, like coughing, sneezing or nasal discharge. However, severe infections may have detrimental consequences.

Feline aelurostrongylosis can be controlled by preventing the infectious third stage larvae from further development, thus controlling the establishment of the parasite in the lungs. This can be achieved by treatment with macrocyclic lactones such as moxidectin. Fluralaner, being an isooxazoline, exhibits no activity against nematodes.

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 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 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 proposed indication will not introduce an additional risk to the one currently accepted for the animal, user of the environment.

2.2. Efficacy for the proposed indication

In support of the proposed indication `prevention of lungworm disease caused by *Aelurostrongylus abstrusus*´, the applicant has provided the efficacy results of two dose confirmation studies and a clinical trial. Also, as supportive information for the targeted claim, the applicant has provided scientific articles and reports from the public domain concerning the efficacy of moxidectin against *Aelurostrongylus abstrusus*.

2.2.1. Dose confirmation studies

In accordance with VICH GL20 Efficacy of anthelmintics: specific recommendations for felines (Revision 1) and VICH GL7 Efficacy of anthelmintics: general requirements (Revision 1), to demonstrate efficacy for the proposed claim, two controlled tests were included in the dossier. The applicant has presented two well-performed dose confirmatory laboratory trials. Both studies were negatively (placebo) controlled and partially blinded, performed in a single site in the EU, using experimentally infected animals. Both studies were GCP compliant and conducted largely in accordance with VICH GL20 Efficacy of anthelmintics: specific recommendations for felines (Revision 1) and VICH GL7 Efficacy of anthelmintics: general requirements (Revision 1).

In both studies, the aim was identical: to evaluate the preventive efficacy of Bravecto Plus against aelurostrongylosis at the minimum recommended dose, applied before experimental infection.

Both studies included approximately 30 (Study 1: n=31, Study 2: n=28) young (6-7 months), healthy European shorthair cats. The animals were considered as representative for the target species with regards to age and breed. Allocation of the animals as well as animal housing were also considered appropriate.

The animals were divided in four well balanced groups consisting of 7-8 animals per group. Total number of animals and group size were considered appropriate.

On study day (SD) 84, all animals were experimentally infected by means of inoculation with 300 L3 of a recent field isolate (2018) of *A. abstrusus* that derived from Italian donor animals (i.e., privately owned cats with a subclinical natural infection by *A. abstrusus*). The infection by *A. abstrusus* was microscopically and molecularly confirmed, and L1 were used to infect intermediate hosts from which ultimately, infectious L3 were harvested. Overall, the isolate was considered adequately characterised. The isolate used for the infections was also considered sufficiently representative of the European field situation.

Although the relevance of the inoculate concentration to the worm burden of naturally infected animals was not mentioned by the applicant and an exact number of infective parasites to be used is not indicated in VICH GL20, it is acknowledged that the number used, 300 L3, is sufficiently high to represent a severe infection in the field, and also in line with the number that is advised for most parasites of the small and large intestines according to VICH GL20.

After infection with *A. abstrusus* L3 at SD 84, the parasite was expected to moult to the fourth larval stage around 7 - 11 days after, to the fifth larval stage (immature adults) around two weeks after, and to adulthood after one month. Experimental infection followed a protocol previously described in peer-reviewed scientific literature.

Appropriateness of the timing was confirmed by the observation that all control cats started to continuously shed L1 between SD 116 and SD 124. Efficacy could be assessed against parasite pulmonary establishment and lung damages, i.e., primarily against early larval stages (group 1) or late larval and immature adults (groups 2 and 3). Therefore, treatments at the different timepoints following inoculation could demonstrate effect against different parasitic stages, which is considered appropriate.

After an appropriate acclimatisation period, cats were treated either 12 (group 1), 8 (group 2) or 4 weeks

(group 3) before experimental infection, demonstrating effectiveness throughout the entire period for which effectiveness is claimed (12 weeks). One group (group 4) was left untreated. The veterinary medicinal product was administered as a single dose, using the formulation currently marketed at the intended minimum recommended dose (40 mg fluralaner + 2.0 mg moxidectin/kg bodyweight), which is considered appropriate. Timing of treatment was based on the observation that after infection with L3 at SD 84, the parasite can be expected to moult to the fourth larval stage around 7 - 11 days after (SD 90 - 94), and to adulthood after one month (SD 113 - 116).

On adverse events, only in Study 1 several adverse events were rated as "related to treatment": slight scaling for 1 day (n=1), and pruritis for 1 day (n=2). These events are already listed as 'common' adverse events in the corresponding section of the SPC. Results of both dose confirmation studies therefore support that treatment is safe and well tolerated, when dosed at the minimum recommended dose.

In Study 1, the primary effectiveness criterion was the geometric mean in necropsy worm count in each treated group in comparison to the negative-controlled group. Secondary, non-pivotal efficacy criteria (evaluated in the full analysis set population) were lung pathology scores at necropsy (scores 0 to 4); faecal larvae counts (L1 shedding assessed between SD 114 and SD 130 via copromicroscopic examinations) and respiratory parameters.

Necropsy was performed 47 to 50 days post infection. Necropsy worm counts were formally analysed using two-sided two sample t-tests for the pairwise comparison of each treatment group to the control group. The level of significance was set to alpha = 0.05. Before the formal analysis was performed, data was log-transformed.

Using geometric means is considered appropriate as the VICH GL7 states that geometric means should be chosen as the initial estimate of the central tendency of parasite counts for most dose confirmation studies. It is however noted that both arithmetic as well as geometric means were calculated, which is considered appropriate and also in line with VICH GL7, which states that calculation of efficacy based on geometric means should be complemented by efficacy determination based on arithmetic means.

A purposed in-depth clinical respiratory assessment was performed for all cats the day before experimental infection (SD 83), and then from SD 85 until necropsy (SD 130). Between SD 114 - SD 130, faecal samples were collected daily from all study cats. Each faecal sample was subjected daily to the Baermann's method. On SD 131-134, parasitological necropsies were performed on all animals. Parasites were identified and counted, and lungs were examined; pathological findings were rated.

In accordance with VICH GL7 and GL20, treatment was considered effective if it resulted in a ≥90% reduction in necropsy worm count, and mean worm count in each treated group was significantly different to placebo-controlled group ($p \leq 0.05$). Secondary efficacy criteria were lung pathology scores at necropsy, faecal larvae counts (counted between SD 114 and SD 130) and respiratory parameters.

All cats were eligible for statistical analyses. The success of the artificial infection was confirmed by calculating the number of (pre-)adult worms recovered at necropsy. Adequacy of infection was confirmed as per the VICH guidelines, as all untreated control cats were infected with an average (GM) parasitic burden of 26.57 worms and a range of 10 - 64 parasites. An acceptable level of infection was reached as defined in VICH GL7 and GL20.

Based on both geometric- as well as arithmetic means, worm count reduction was ≥99.60% in groups 1-3. Efficacy both in terms of geometric- as well as arithmetic means was therefore adequate, meeting the efficacy threshold of more than 90%, as recommended by VICH GL7 and GL20.

In terms of secondary efficacy criteria, lung pathology scores in the negatively controlled group were significantly higher compared to the groups treated with the veterinary medicinal product. Lungs in the control group showed severe pathological findings. In the treated groups, cats in groups 1 to 3 had no (n =

4, 5 and 5 cats) to mild (n = 4, 2 and 2 cats) pathological findings. One cat from group 2 had moderate damages. This indicates that also some treated cats had (a small number of) worms in their lungs causing some damage during parasite migration.

Between SD 116 and SD 124, all cats in the negatively controlled group started to continuously shed larvae whereas only in one animal of group 1, larvae were present on several consecutive days. Another seven animals in the treated groups were positive on one day. However, larvae counts in the treated groups ranged from 1 to 31 larvae, whereas in the untreated group, counts were as high as 45,900 larvae. Faecal larvae count reduction was 99.99% in study groups 1 and 3 (treated on SD 0 and 56, respectively) and 99.98% in study group 2 (treated on SD 28). No clear difference between study groups was observed for the intensity or quality of respiratory sounds. None of the cats showed severe respiratory sounds. However, it is noted that recurring episodes of feline upper respiratory infection occurred in several animals, potentially resulting in the absence of clear differences in respiratory parameters.

In the second study (Study 2), cats were not necropsied. Instead, the primary effectiveness criterion was the reduction of faecal larvae counts (i.e., L1 shedding assessed via copromicroscopic examinations) in each treated group in comparison to the negative controlled group. Between SD 114 - SD 130 (i.e., 30-45 days post infection), daily faecal samples from all study cats were collected and subjected to the Baermann's method. The log-transformed individual maximum values of faecal larval counts of the treated groups were compared to those of the control group using a two-sided two sample t-test. Also in this study, the reduction of faecal larval counts was calculated in percentage using geometric as well as arithmetic means of the individual maximum counts, which is considered appropriate and in line with VICH GL7, which states that calculation of efficacy based on geometric means should be complemented by efficacy determination based on arithmetic means. The abandonment of necropsy is considered appropriately compensated by additional examinations (i.e., CT and serology).

The three secondary efficacy criteria were respiratory parameters (a purposed in-depth clinical respiratory assessment was performed for all cats before experimental infection, and then twice weekly after infection), CT examination findings (performed prior to treatment, before infection (approx. SD 75) and on SD 131, and assessed and classified based on an already described system for lung pathologies modified to fit for feline lungworm image assessment) and serology, by means of an enzyme-linked immunosorbent assay (ELISA) for the detection of serum antibodies against *A. abstrusus*, between SD 96 and SD 162. Blood samples were obtained before infection and weekly post-infection. The CT assessment is considered an appropriate approach to evaluate and compare the damages caused by *A. abstrusus*.

In accordance with VICH GL7 and GL20, treatment was declared effective if treatment resulted in a ≥90% reduction in worm count, and mean worm count in each treated group was significantly different to the negative control group ($p \leq 0.05$).

One control cat was excluded from the study at SD 79 due to a concomitant disease, thus the full analysis set (FAS) and per protocol (PP) populations consisted of 28 and 27 cats, respectively. Adequacy of infection was met in terms of larval counts in untreated cats compared to values in treated cats; that is a statistically significant difference ($p<0.0001$) was found between the log-transformed individual maximum larval counts in each of the treated groups and the control group. Also, all cats of the placebo group demonstrated larval shedding, indicating a patent infection. It can be agreed that an acceptable level of infection was reached, and that larval output was high and comparable with counts in the first study, i.e., GM maximum counts of 7380.89 and 7574.29, respectively.

Based on both geometric- as well as arithmetic means, reduction of faecal larvae counts exceeded 99.9% in all treated groups. Efficacy (both in terms of geometric- as well as arithmetic means) was therefore adequate, meeting the efficacy threshold of more than 90%, as recommended by VICH GL7 and GL20.

In terms of secondary efficacy criteria, no meaningful clinical difference in mean respiratory frequencies,

respiratory sounds or quality of respiratory sounds was seen between study groups.

Results of the CT examination showed that mean overall lung severity scores were significantly lower in all treated groups when compared to the control group ($p \leq 0.0022$). No significant differences between treated groups and control group could be observed pre-enrolment and before experimental infection. Post-infection, scores were significantly lower in all treated groups when compared to the control group ($p \leq 0.0022$). It is noted that post-infection, lungs in the treated groups were normal (4 cats), or mildly (11 cats) or moderately (5 cats) affected, indicating that also some treated cats had some worms in their lungs causing some damage during parasite migration. Severely affected lungs were however only seen in the untreated group, and only in the untreated group all cats showed lung abnormalities in all lung zones after infection and abnormalities considered typical for infection with *A. abstrusus*, as described in scientific literature.

No antibody increase was observed in any treated group. In the untreated group, titers rose, then decreased after anthelmintic treatment.

In summary, it can be accepted that the results of both dose confirmation studies show that administration of Bravecto Plus at the minimum recommended dose is safe and effective against *A. abstrusus* for a duration of 12 weeks. However, it is not strictly accurate to conclude that treatment prevents lungworm disease, noting that in some of the treated animals lung pathology was detected that may have been attributable to migrating larvae.

2.2.2. Clinical trial

To demonstrate the efficacy of Bravecto Plus against *Aelurostrongylus abstrusus*, the applicant also presented a (GCP-compliant) multi-centered, negative-controlled, randomised and examiner-blinded clinical trial. This third study was also conducted largely in accordance with VICH GL20 and VICH GL7.

Aim of this trial was to demonstrate that Bravecto Plus spot-on prevents aelurostrongylosis in cats under field conditions in different European countries, i.e., Bulgaria, Hungary and Italy, appropriately representing different geographic regions where the parasite is endemic.

The study included a well-balanced group of 161 privately-owned, healthy cats of various breeds, recruited in 6 veterinary facilities. The number of animals included was adequately justified and considered to adequately represent the target species. Included cats were required to spend a significant amount of time outside, having the opportunity to demonstrate relevant hunting behaviour, therefore ensuring that animals were at factual risk of infection. The cats were randomly allocated into two well-balanced groups. To ensure cats were free of potentially existing intestinal and lungworm infections worms, all cats were treated twice with a product authorised for the treatment of infestations with feline lungworms (L3 larvae, L4 larvae and adults of *Aelurostrongylus abstrusus)*, prior to initiation of the study (SD -44 and SD -16). Thus, cats were lungworm free on the day of inclusion, which was confirmed by coproscopic examination of faeces.

Cats of group 1 were treated with Bravecto Plus on SD 0 and SD 84 (12 weeks following first treatment). Study duration is considered appropriate, as this would allow identification of cats infected at the end of the 12-week period. Cats of group 2 were left untreated. The product used was the formulation currently marketed, dosed according to label, which is considered appropriate under field conditions of use. Ultimately, cats received a minimum of 2 mg moxidectin/kg body weight and a maximum of 4.7 mg moxidectin/kg body weight. Faecal samples were collected pre-treatment (SD-6 to SD-2) and after treatment (at SD 42, SD 84, SD 126, SD 168). Faecal larvae counts were performed using the Baermann method, and a species-specific PCR was performed on the Baermann's sediment. Cats were adequately treated as soon as a lungworm infection was diagnosed (rescue treatment). Non-pivotal parameters were an analysis of faecal material by means of a qualitative flotation method, and screening (PCR) for *Troglostrongylus brevior*.

In accordance with VICH GL7 and VICH GL20, treatment was considered effective if the percentage of

parasite free cats was ≥90% on SD 168 and differed significantly from the control group. Faecal larvae counts were compared using a two-sided two sample t-test (α=0.05). To compensate for the skewed distribution, the faecal larvae count was log-transformed and shifted prior to the statistical test.

The primary effectiveness criterion was based upon the percentage of *A. abstrusus* free cats post-treatment (no faecal larvae and PCR-negative for *A. abstrusus*). It is noted that VICH GL7 refers to egg counts/larval identification to be the preferred method to evaluate the effectiveness in field studies, and assessment of presence of faecal larvae in combination with a PCR method can therefore be accepted as a primary effectiveness criterion.

For each post-treatment observation time point, the relative frequency of parasite free cats in the treated group was compared to the control group using Fisher's exact test with a two-sided level of significance of α = 0.05.

Secondary efficacy was based upon the reduction of faecal larvae counts (*A. abstrusus*) in the treated group in comparison to the negative controlled group (with and without applying the last observation carried forward (LOCF) method). Reduction of faecal larvae counts was calculated from the geometric means, but was also calculated based on arithmetic means, which is considered appropriate and in line with VICH GL7, which states that calculation of efficacy based on geometric means should be complemented by efficacy determination based on arithmetic means.

Ultimately, 152 cats were eligible for statistical analysis in the PP population. Nine cats (6 in the treated group, 3 in the negative controlled group) were excluded from the PP population.

In terms of larval shedding and PCR results (primary efficacy endpoint), the percentage of cats negative for *A. abstrusus* was higher in the treated group at all post-treatment evaluation SDs. However, a significant difference was only present on SD 168 (p=0.0134). In the untreated control group, there were four cats PCR-positive (Baermann negative) for *A. abstrusus*. These cats however did not shed detectable L1 at the faecal examinations.

For the secondary efficacy criterion, i.e., the percentage reduction of L1 output in the treated group in relation to the untreated group, data showed a 100% reduction at each time point, with statistically significant differences between groups by SD 84 onwards.

The observed discrepancy between the primary and secondary criteria is considered caused by the observation that the DNA-based assay can reveal cats with a nil to very low faecal larval shedding (due to a very low worm burden).

It is noted that only 15 of the control cats tested positive for *A. abstrusus* infection, thereby indicating an infection pressure of approximately 19.48%. Though the overall prevalence of *A. abstrusus* was therefore lower than what was expected based on literature, it can be agreed that the study demonstrated ≥90% efficacy (based on the primary efficacy parameter) of the product against *A. abstrusus* for up to 12 weeks, thus meeting the efficacy threshold as recommended by VICH GL7 and GL20. It can therefore be accepted that the results of this clinical trial provide supportive evidence that Bravecto Plus, administered as a single dose at the recommended dose, can prevent the establishment of the parasite in the lungs and therefore lungworm disease (caused by *Aelurostrongylus abstrusus)* for the duration of 12 weeks.

In terms of safety, no adverse event was recorded throughout the study in the treated group. Results therefore support that treatment is safe and well tolerated, when dosed according to the recommendations in the product information.

Altogether, the available data package confirms an effect of the product against *A. abstrusus.* However, it is not strictly accurate to conclude that treatment prevents lungworm disease, noting that in some of the treated animals lung pathology was detected that may have been attributable to migrating larvae. To more accurately

reflect the data presented, the indication has therefore been slightly modified and reads "Prevention of aelurostrongylosis (by preventing the establishment of adult *Aelurostrongylus abstrusus* responsible for clinical disease)". Furthermore, the following sentence has been added to Section 3.9 of the SPC: "To prevent the establishment of adult lungworms responsible for clinical aelurostrongylosis, cats need to be retreated at 12-week intervals."

2.3. Alignment of the product information with version 9.0 of the QRD template

In order to align the product information of Bravecto Plus spot-on solution for cats with version 9.0 of the QRD template, the information has been largely transcribed directly from the relevant sections of the previously approved product information for the product to the relevant sections of the newly proposed product information presented with this application. A number of minor amendments, mostly editorial, have also been made.

In addition, new standard sentences in line with the updated 'Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products' (EMA/CVMP/EWP/170208/2005-Rev.1) have been introduced in the product information.

3. Benefit-risk assessment of the proposed change

Bravecto Plus is a spot-on solution for topical use in cats, containing as active substances a fixed combination of fluralaner (280 mg/ml) and moxidectin (14 mg/ml). Bravecto Plus is intended for use in cats with, or at risk from, mixed parasitic infestations by ticks or fleas and ear mites, gastrointestinal nematodes or heartworm. The product 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 product is 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 variation is to add a new therapeutic indication for the prevention of aelurostrongylosis (by preventing the establishment of adult *Aelurostrongylus abstrusus* responsible for clinical disease) and to align the product information with version 9.0 of the QRD templates, as well as to update the product information in line with the 'Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products' (EMA/CVMP/EWP/170208/2005-Rev.1), i.e., the introduction of several standard sentences.

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce an additional indication to existing presentation of the product Bravecto Plus spot-on solution for topical use in cats, the direct benefits would arise from the inclusion of this new indication.

The proposed benefit is its efficacy in the prevention of aelurostrongylosis (by preventing the establishment of adult *Aelurostrongylus abstrusus* responsible for clinical disease).

Additional benefits

No further additional benefits are foreseen.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation

Safety:

Risks for the target animal:

Administration of Bravecto Plus spot-on solution for cats 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.

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

Risk for the user:

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

Risk for the environment:

Bravecto Plus spot-on solution for cats is not expected to pose a risk for the environment when used according to the SPC recommendations.

Resistance:

A literature search (Scopus, 2022) did not reveal any data on resistance of *Aelurostrongylus abstrusus* against moxidectin.

3.3. Risk management or mitigation measures

Information already included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, and environment and to provide advice on how to prevent or reduce these risks is considered appropriate.

3.4. Evaluation of the benefit-risk balance

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

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

The product has been shown to be efficacious for preventing lungworm disease caused by *Aelurostrongylus abstrusus*. For this indication, the product provides sustained efficacy over 12 weeks.

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Bravecto Plus can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: to add a new therapeutic indication for the prevention of aelurostrongylosis (by preventing the establishment of adult *Aelurostrongylus abstrusus* responsible for clinical disease) and to align the product information with version 9.0 of the QRD templates.

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, II, IIIA and IIIB.

As a consequence of these variations, all sections of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.