18 January 2018
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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for a grouped type II variation for Advocate (EMEA/V/C/000076/II/0039/G)

International non-proprietary name: imidacloprid / moxidectin

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

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Bayer Animal Health GmbH (the applicant), submitted to the European Medicines Agency (the Agency) an application for a grouped type II variation for Advocate.

On 8 September 2016 the CVMP agreed that the data requirements specified in the appropriate CVMP guidelines on "Minor-Use-Minor-Species" (MUMS) are applicable when assessing the application.

1.2. Scope of the variation

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	C.I.4 - Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	II

This grouped variation is to change the current indications for Advocate spot-on solution for cats and ferrets / for dogs to add the following therapeutic indications:
- the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) in cats;
- the treatment of *Eucoleus* (syn. C*apillaria*) *boehmi* in dogs;
- the treatment of the eye worm *Thelazia callipaeda* in dogs.

Furthermore, the Product Information for Advocate for dogs is proposed to be amended with regard to half-life, serum steady state levels, studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications and persistent action. Also, the applicant took the opportunity to update the list of local representatives and the Product Information in line with QRD template v 8.1.

Current	**Proposed**
Part 1 Summary of the Dossier 1.B Summary of Product Characteristics, Labelling and Package Leaflet 1.b.1 Product Information (SPC, PL, Packaging) SPC - Advocate for cats and ferrets 4.2 Indications for use, specifying the target species For cats suffering from, or at risk from, mixed parasitic infections: - the treatment and prevention of flea infestation (Ctenocephalides felis),	Part 1 Summary of the Dossier 1.B Summary of Product Characteristics, Labelling and Package Leaflet 1.b.1 Product Information (SPC, PL, Packaging) SPC - Advocate for cats and ferrets 4.2 Indications for use, specifying the target species For cats suffering from, or at risk from, mixed parasitic infections: - the treatment and prevention of flea infestation (Ctenocephalides felis),

- the treatment of ear mite infestation (Otodectes cynotis), - the treatment of notoedric mange (Notoedres cati), - the prevention of heartworm disease (L3 and L4 larvae of Dirofilaria immitis), - the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of Toxocara cati and Ancylostoma tubaeformae). ...	- the treatment of ear mite infestation (Otodectes cynotis), - the treatment of notoedric mange (Notoedres cati), **- the treatment of the lungworm Eucoleus aerophilus (syn. Capillaria aerophila),** - the prevention of heartworm disease (L3 and L4 larvae of Dirofilaria immitis), - the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of Toxocara cati and Ancylostoma tubaeformae). ...
4.9. Amounts to be administered and administration route Dosage schedule for cats: ... Treatment of notoedric mange (Notoedres cati) A single dose of the product should be administered.	4.9. Amounts to be administered and administration route Dosage schedule for cats: ... Treatment of notoedric mange (Notoedres cati) A single dose of the product should be administered. **Treatment of the lungworm Eucoleus aerophilus (syn.Capillaria aerophila)** **A single dose of the product should be administered.**
Heartworm prevention (Dirofilaria immitis) Cats in areas endemic for heartworm, ...	Heartworm prevention (Dirofilaria immitis) Cats in areas endemic for heartworm, ...
	CORRESPONDING SECTIONS OF THE OUTER CARTON AND THE PACKAGE LEAFLET ARE AMENDED ACCORDINGLY. **In addition the product information has been updated in line with QRD template 8.1. These minor changes are not shown in this "present/proposed" table".**
Part 1 Summary of the Dossier 1.B Summary of Product Characteristics, Labelling and Package Leaflet 1.b.1 Product Information (SPC, PL, Packaging) SPC - Advocate for dogs 4.2 Indications for use, specifying the target species For dogs suffering from, or at risk from, mixed parasitic infections: ... - the treatment of Angiostrongylus vasorum and Crenosoma vulpis,	Part 1 Summary of the Dossier 1.B Summary of Product Characteristics, Labelling and Package Leaflet 1.b.1 Product Information (SPC, PL, Packaging) SPC - Advocate for dogs 4.2 Indications for use, specifying the target species For dogs suffering from, or at risk from, mixed parasitic infections: ... - the treatment of Angiostrongylus vasorum and Crenosoma vulpis,

- the prevention of spirocercosis (Spirocerca lupi),	- the prevention of spirocercosis (Spirocerca lupi), **- the treatment of Eucoleus (syn. Capillaria) boehmi,** **- the treatment of the eye worm Thelazia callipaeda,**
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of Toxocara canis, Ancylostoma caninum and Uncinaria stenocephala, adults of Toxascaris leonina and Trichuris vulpis). ...	- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of Toxocara canis, Ancylostoma caninum and Uncinaria stenocephala, adults of Toxascaris leonina and Trichuris vulpis). ...
4.9. Amounts to be administered and administration route	4.9. Amounts to be administered and administration route
...	...
Prevention of spirocercosis (Spirocerca lupi)	Prevention of spirocercosis (Spirocerca lupi)
The product should be administered monthly.	The product should be administered monthly.
	Treatment of Eucoleus (syn. Capillaria) boehmi
	The product should be administered monthly for two consecutive months.
	Treatment of the eye worm Thelazia callipaeda
	A single dose of the product should be administered.
Roundworm, hookworm and whipworm tretament (Toxocara canis, Ancylostoma caninum, Uncinaria stenocephala, Toxascaris leonina and Trichuris vulpis)	Roundworm, hookworm and whipworm tretament (Toxocara canis, Ancylostoma caninum, Uncinaria stenocephala, Toxascaris leonina and Trichuris vulpis)
In areas endemic for heartworm, ...	In areas endemic for heartworm, ...
	CORRESPONDING SECTIONS OF THE OUTER CARTON AND THE PACKAGE LEAFLET ARE AMENDED ACCORDINGLY.
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SPC - Advocate for dogs	SPC - Advocate for dogs
5.1 Pharmacodynamic properties	5.1 Pharmacodynamic properties
...family. It is a parasiticide which is active	...family. It is a parasiticide which is active

against many internal and external parasites. Moxidectin is active against larval stages of Dirofilaria immitis (L3, L4) and Dirofilaria repens (L3). It also active against gastrointestinal nematodes. Moxidectin interacts... 5.2 Pharmacokinetic particulars ... in dogs. Following absorption from the skin, moxidectin is distributed systemically and is slowly eliminated from the plasma as manifested by detectable moxidectin concentrations in plasma throughout the treatment interval of one month.	against many internal and external parasites. Moxidectin is active against larval stages of Dirofilaria immitis (**L1**, L3, L4) and Dirofilaria repens (**L1,** L3). It also active against gastrointestinal nematodes. Moxidectin interacts... 5.2 Pharmacokinetic particulars ... in dogs. Following absorption from the skin, moxidectin is distributed systemically **throughout the body tissues but due to its lipophilicity it is concentrated mainly in the fat.** It is slowly eliminated from the plasma as manifested by detectable moxidectin concentrations in plasma throughout the treatment interval of one month. **The T1/2 in dogs is about 35 days. The drug has a persistent action and protects dogs for 4 weeks after a single application against infection with the following parasites: Dirofilaria immitis, Dirofilaria repens, Angiostrongylus vasorum.** **Studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications have indicated that steady state serum levels are achieved following approximately 4 consecutive monthly treatments in dogs.** **CORRESPONDING SECTIONS OF THE OUTER CARTON AND THE PACKAGE LEAFLET ARE AMENDED ACCORDINGLY.** **In addition the product information has been updated in line with QRD template 8.1. These minor changes are not shown in this "present/proposed" table".**

2. Scientific discussion

2.1. Treatment of the lungworm Eucoleus aerophilus (syn. Capillaria aerophila) in cats

To support the proposed new indication for "the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) in cats", the applicant has presented two GCP field studies conducted in naturally infected cats.

In the first study, 41 *E. aerophilus* positive (egg output) cats were divided in two groups: 20 cats received treatment on study day 0 (Advocate, according to label instructions) and 21 cats were left untreated. The efficacy of the treatment was assessed by Faecal Egg Count Reduction (FECR) against baseline Egg Per Gram of faeces (EPG) for each group. The highest value from the two egg counts performed in the pre-treatment assessments (study days −6 and −2) was used as baseline value. From the two faecal egg counts performed post treatment (study days 7 and 11), the highest value was used for the calculation of efficacy. Arithmetic means were used to calculate FECR. Post treatment, all the treated cats were negative for *E. aerophilus* faecal egg output while all the untreated cats were persistently infested with an average of 195.2 EPG. Differences in mean EPG values were statistically significant at all the time points post-treatment ($p<0.01$).

In the second study, 36 *E. aerophilus* positive cats were divided in two groups: 17 cats received treatment on study day 0 (Advocate, according to label instructions) and 19 cats were left untreated. The primary efficacy criterion was the reduction of post-baseline EPG. From the four egg counts performed in period 0 (days -6±1 and -2±1), the highest value was used as baseline value. From the four egg counts performed in period 1 (days 7 and 11), the highest value was used for the calculation of efficacy. The per cent decrease of the egg count reduction of *E. aerophilus* based on geometric means showed efficacy for cats (99.79%). For cats, the log-transformed counts changed from 4.8 (±0.6) to 0.2 (±1.0) in the treated group and from 4.7 (±0.5) to 4.8 (±0.7) in the untreated control group. Thus, the efficacy of Advocate was proven by statistically significant differences in change of log-transformed counts from baseline ($p<0.0001$).

Target animal safety of the product was acceptable when used for the treatment of *E. aerophilus* in cats, as no adverse events were observed during these studies.

According to VICH GL7 ("Efficacy of anthelmintics: general requirements", CVMP/VICH/832/1999) and VICH GL20 ("Efficacy of anthelmintics: specific recommendations for felines", CVMP/VICH/545/00-FINAL) a dose finding study, as well as two dose confirmation and field studies should be conducted. However, CVMP granted MUMS status for this indication in September 2016, and reduced data requirements were therefore applied. According to the "Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market" (EMA/CVMP/EWP/117899/2004–Rev.1), a dose determination study might be replaced by other means, and only one dose confirmation study and one field trial might be provided to demonstrate efficacy.

However, no dose confirmation study was provided, and the applicant was therefore requested to justify the absence of dose confirmation study. According to the applicant, there is no valid experimental infection model for this parasite and therefore no laboratory studies can be conducted. For that reason, a field efficacy study conducted by an experienced European scientist was commenced. Later, the applicant tried to establish an experimental model with the University of Hannover in order to conduct a laboratory study. Despite intensive efforts using different inoculation doses, none of the studies resulted in feline infection. For that reason, the applicant decided to omit a laboratory dose confirmation study against *E. aerophilus* and to conduct a second field efficacy study under controlled conditions. The Advocate spot-on dose used in both field efficacy studies was already defined based on the given Advocate spot-on label recommendation with a minimum therapeutic dose. Intention of the present studies was therefore only to confirm the minimum therapeutic dose of Advocate spot-on against *E. aerophilus*. The justification of the applicant is satisfactory.

According to VICH GL20, egg counts/larval identification is the preferred method to evaluate effectiveness in field studies. The applicant has used egg counts in both studies to demonstrate the efficacy, which is acceptable.

The applicant was also requested to justify why, despite similar study designs, group arithmetic mean counts were analysed in one study, whereas geometric mean counts were analysed in the second study. The applicant provided a recalculation of the results of the two studies using both arithmetic and geometric means showing that the FECR results were clear and conclusive and well above the required targets regardless of which mean value was used in the calculation of efficacy. The recalculation demonstrated that in this case the use of different approaches did not lead to markedly different results that would have altered the final conclusion on efficacy. The answer of the applicant is acceptable.

The applicant was requested to justify that the sampling time points post-treatment (FECs at days 7 and 11) allow robust demonstration of a cessation of shedding due to adulticidal efficacy, rather than

a temporary cessation in egg shedding, considering the pharmacodynamic and pharmacokinetic properties of moxidectin and the intermittent faecal egg shedding pattern of *E. aerophilus*. The applicant reiterated efficacy study results and pointed out that the individual EPGs of the untreated control cats show that animals once being positive in FEC stayed consistently positive on high levels. Intermittent faecal egg output with single FEC being zero once patency was reached was therefore highly unlikely. The applicant agrees that confirmation of adulticidal efficacy by necropsy data is missing, however moxidectin plasma levels and also lung tissue levels after topical administration are high for a prolonged time (T_{max} 4-9 days), leading to the assumption that the killing effect against the adult stages in the lungs is sufficiently given. The applicant refers to study results using Advocate for the treatment of *Crenosoma vulpis*, where necropsy data with adult worm counting is available. The results of the study demonstrated a high correlation between the reduction of larval shedding to zero and the absence of live adult worms at necropsy, giving confidence of the adulticidal efficacy.

The applicant concludes that faecal egg counts twice after treatment at 4 days interval were appropriate to demonstrate the adulticidal efficacy of Advocate against *E. aerophilus* in the present filed studies.

Based upon the totality of data provided (confirmed high efficacy demonstrated by FECR in two field studies according to VICH GL19, animals once being positive in FEC stayed consistently positive on high levels and most of the treated cats with clinical signs before treatment fully recovered), the proposed indication for the treatment of *E. aerophilus* in cats is acceptable.

According to VICH GL20, a claim for effectiveness against life stages of each parasite should refer to each stage in the case of natural infections. However, the results of these studies only supported the efficacy of Advocate against adult *E. aerophilus*. Therefore, the claim was restricted to adult parasites only, and the indication has been amended accordingly: "the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) (adults)".

2.2. Treatment of Eucoleus (syn. Capillaria) boehmi in dogs

To support the proposed new indication for "the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* in dogs", the applicant has presented one GCP field study. In the study, 20 dogs positive for *E. boehmi* eggs in faecal examination were divided in two groups: 10 animals were treated with Advocate once on day 0 and 10 animals remained untreated. For treated dogs, the treatment had to be repeated on day 30±3 in case of positive faecal egg count (samples approx. 24 hours prior to day 28±2) or identification of *E. boehmi* at rhinoscopy (on day 28±2), or both. Two animals in treated group had to be retreated on day 30±3 (one dog had a positive rhinoscopic result and the other dog showed a positive coproscopic result). After re-treatment, they both tested negative for EPG and rhinoscopy. All dogs in the control group had positive coproscopic results for *E. boehmi* on day 28±2. The primary efficacy criterion was the reduction of the faecal egg count of *E. boehmi* (EPG) from baseline to the day of study completion. The mean number (arithmetic mean) of faecal egg counts (EPG) at the day of study completion (day 42±2) was 0 in the treated group and 472.5 in the untreated group. The difference between groups was statistically significant ($p=0.0004$). However, at none of the examination time points the number and percentage of animals with presence of adult stages of *E. boehmi* was significantly different between the groups ($p>0.3$).

As no adverse events were observed during this study, the safety of the product is considered acceptable when used in treatment of *E. boehmi* with the proposed posology of two consecutive monthly treatments.

According to VICH GL7 ("Efficacy of anthelmintics: general requirements", CVMP/VICH/832/1999) and VICH GL19 ("Efficacy of anthelmintics: specific recommendations for canines",

CVMP/VICH/835/99-FINAL), a dose finding study as well as two dose confirmation and field studies should be conducted. However, CVMP granted MUMS status for this indication in September 2016, and reduced data requirements were therefore applied. According to the "Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market" (EMA/CVMP/EWP/117899/2004–Rev.1), a dose determination study might be replaced by other means, and only one dose confirmation study and one field trial might be provided to demonstrate efficacy. However, no dose confirmation study was provided, and the applicant was therefore requested to justify the absence of a dose confirmation study. The applicant stated that based on the rare occurrence of this parasite, currently only few European research groups have experience with this parasite and are capable to conduct field efficacy studies. Moreover, none of these research groups are able to conduct laboratory studies with this parasite, including a valid experimental infection model. The Advocate spot-on dose used in the field efficacy study was already defined based on the given Advocate spot-on label recommendation with a minimum therapeutic dose. Intention of the present study was therefore only to confirm the minimum therapeutic dose of Advocate spot-on against *E. boehmi*. The response of the applicant is satisfactory.

Taking into account the potential direct oral-faecal life cycle of *E. boehmi*, sanitation measures, such as prompt removal of faeces from the environment and prevention of geo- and coprophagic practice, seem to be a crucial procedure for disease control and for reinfection avoidance (Baan *et al*., 2011). Although the life cycle of *E. boehmi* is not known in detail, the presumed recurrence of infection following auto-coprophagia suggests the need for an additional warning sentence in SPC section 4.4 proposed as follows: "When the product is used for the treatment of *E. boehmi* infection, it is advisable to prevent auto-coprophagia between the two treatments in order to prevent possible reinfection". The applicant accepted this suggestion, but proposed to include this information to SPC section 4.9, which is acceptable.

The identification of *E. boehmi* eggs in faecal samples was based on morphometric and morphological characteristics. *Trichuridae* eggs are all quite similar and misdiagnosis among different species can easily occur. The applicant was requested to provide information on how the identification of parasite eggs in faecal samples was done to ensure correct diagnosis. The applicant provided an exhaustive response on how correct coprological diagnosis was ensured. The response of the applicant is acceptable.

In the study, the primary efficacy criterion was the reduction of the faecal egg count of *E. boehmi* (EPG) from baseline to the day of study completion. According to VICH GL19, egg counts/larval identification is the preferred method to evaluate effectiveness in field studies. The efficacy (measured by FECR) in treated group was 100% at study completion (after two monthly treatments with Advocate). According to VICH GL19, effectiveness should be 90% or higher calculated using transformed (geometric means) data. The study methodology concerning faecal egg counts was therefore considered acceptable.

However, the number and percentage of animals with presence of adult stages of *E. boehmi* was not significantly different between the treated and untreated groups at any of the examination time points. In addition, rhinoscopy can reliably be used only to confirm the presence of *E. boehmi*, but not to confirm viability or absence of worms as they can reside apart from the epithelial lining of the nasal turbinates also in the frontal and paranasal sinuses.

In response to a question concerning sampling method and selected interval between samplings, the applicant stated that there is only little published information with regard to the exact life cycle and the pattern of faecal egg excretion of *E. boehmi*. The applicant refers to two published studies. In the first study by Perrucci *et al*. (2014), a dog was sampled on a weekly basis for 3 months. All

faecal samples tested positive for *E. boehmi*. In publication by Schoning *et al*. (1993), the egg shedding pattern was found to be periodical with an EPG peaking every 5-7 weeks (one dog sampled on a weekly basis for 24 weeks). At qualitative and quantitative coproscopic examination, all samples except one were tested positive for *E. boehmi.* As a conclusion, the applicant states that the risk of negative results in case of a patent infection can be regarded as negligible.

In response to a request to provide justification to substantiate the efficacy claim against *E. boehmi*, the applicant reiterated the findings of a pilot explorative field efficacy study. In conclusion, the applicant is of the opinion that the efficacy of Advocate against adult stages of *E. boehmi* is sufficiently substantiated by the negative faecal egg count results and the corresponding supportive data of the pilot study.

Based upon the totality of data provided (confirmed efficacy > 90% demonstrated by FECR according to VICH GL19 and literature references demonstrating that the egg shedding pattern of *E. boehmi* is periodical, with EPG peaking every 5-7 weeks and negative faecal samples are very unlikely in infected animals), the proposed indication for the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* in dogs is acceptable.

The applicant proposes to limit the efficacy claim only to adult parasites and has revised the product information as follows: "the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* (adults)", which is acceptable.

2.3. Treatment of the eye worm Thelazia callipaeda in dogs

To support the proposed new indication for "the treatment of the eye worm *Thelazia callipaeda* in dogs", the applicant has presented two GCP field studies.

In the first study, 30 dogs infected naturally with *T. callipaeda* were divided in two groups of 15 dogs each. The treated group was administered Advocate on day 0. Because of protocol deviations, 11 treated and 13 untreated dogs were considered for efficacy evaluation. All dogs were examined for the presence of ocular signs of thelaziosis and the presence of adult live *T. callipaeda* at study days 0, 14±2 and 28±2. The primary efficacy variable evaluated was the efficacy of Advocate against adult *T. callipaeda* by comparing the treated group with the untreated control group with respect to parasitological cure (therapeutic efficacy), i.e. percentage of animals showing a complete elimination of adult eye worms 14±2 and 28±2 days after treatment. The treated group proved to be superior versus the untreated control group at both study visits 14±2 and 28±2. Efficacy in the treated group was 100% at each study day post treatment ($p<0.001$), i.e. starting at day 14±2 after treatment.

In the second study, 47 dogs (infected with at least one adult *T. callipaeda* worm in one eye) were divided in three groups: 16 dogs were treated with Advocate on day 0, 16 dogs were treated with Milbemax and 15 dogs remained untreated. The primary efficacy variable evaluated was the efficacy of Advocate against adult *T. callipaeda* by comparing the Advocate group with the untreated group with respect to parasitological cure (therapeutic efficacy), i.e. percentage of animals showing a complete elimination of adult eye worms 7, 14 and 28 days after first treatment and on day 35 following the second treatment. The mean number of worms at study inclusion was comparable among the groups. The reduction of the number of worms counted in both eyes was 100% for the Advocate group from day 7 onwards. A natural reduction in the control group was observed (29.3%, 24.1%, 34.5%, and 19% on days 7, 14, 28 and 35, respectively). The reduction of the geometric mean worm count for *T. callipaeda* from both eyes was significantly different ($p<0.01$) for the Advocate treated group when compared to the control group at all post-treatment time points.

In this study, the applicant estimated the influence of animal characteristics (i.e. sex, age, weight) on *T. callipaeda* infection to be negligible and concluded that testing of homogeneity of the study groups at baseline in relation to dog data was not necessary. The applicant was requested to justify why the influence of animal characteristics was estimated to be negligible. The applicant provided a post hoc analysis concerning the homogeneity of the study groups in regards of animal characteristics which was supportive of proper random allocation of animals in the study groups. The answer of the applicant is acceptable.

As no adverse events were observed during these studies, the safety of the product is deemed acceptable when used in treatment of *T. callipaeda*.

According to VICH GL7 ("Efficacy of anthelmintics: general requirements", CVMP/VICH/832/1999) and VICH GL19 ("Efficacy of anthelmintics: specific recommendations for canines", CVMP/VICH/835/99-FINAL), a dose finding study, as well as two dose confirmation studies should be conducted in order to be granted a claim (no MUMS classification). The applicant was requested to justify the omission of these studies. According to the applicant, for the new *Thelazia* claim it was not intended to deviate from the already generally adopted optimum dose of moxidectin and thus a dose determination study for this new claim was not deemed necessary. It was however seen necessary to confirm the established minimum therapeutic dosage of 2.5 mg moxidectin/kg bw for the new indication also with respect to the special localisation of the eye worm *T. callipaeda*.

For that reason, the applicant conducted two field efficacy studies both using the recommended dose of Advocate with a minimum therapeutic dose of 2.5 mg moxidectin and 10 mg imidacloprid/kg bw corresponding to 0.1 ml of the spot-on formulation/kg bw.

As already outlined for *Eucoleus aerophilus* and *Eucoleus boehmi*, also for *Thelazia callipaeda* currently only few European research groups have experience with this parasite and are capable to conduct field efficacy studies. However, none of these research groups and to the best of the applicant's knowledge no other research organization has an experimental model available to conduct a dose confirmation study under laboratory conditions using experimental infections. The justification provided by the applicant is acceptable.

The first study did not yield any reliable information concerning the effect of the product on *T. callipaeda* larvae as overall no larvae were detected. Also, the second study did not yield reliable information concerning the effect of the product on *T. callipaeda* larvae, as larvae were detected only in few dogs. According to VICH GL19, a claim for effectiveness against life stages of each parasite should refer to each stage in the case of natural infections. Therefore, the indication was restricted to adult parasites only and the product information has been amended accordingly.

2.4. Persistent action against Dirofilaria immitis, Dirofilaria repens and Angiostrongylus vasorum and other proposed SPC changes

Proposed changes to SPC sections 5.1 and 5.2

The applicant has proposed to include L1-larvae in section 5.1 of the Advocate SPC for dogs in the following sentence (addition in bold): "Moxidectin is active against larval stages of *Dirofilaria immitis* (**L1**, L3, L4) and *Dirofilaria repens* (**L1**, L3)". The inclusion is accepted on the basis that activity against L1 larval stages (microfilariae) of *D. immitis* and *D. repens* has been confirmed in a variation (EMEA/V/C/00076/II/022) submitted previously.

The applicant has also proposed changes/additions to section 5.2 Pharmacokinetic properties of the Advocate SPC for dogs (in **bold**): "Following absorption from the skin, moxidectin is distributed systemically **throughout the body tissues but due to its lipophilicity it is concentrated mainly**

in the fat.", "**The T ½ in dogs is about 35 days. The drug has a persistent action and protects dogs for 4 weeks after a single application against re-infection with the following parasites: *Dirofilaria immitis*, *Dirofilaria repens*, *Angiostrongylus vasorum*. Studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications have indicated that steady state serum levels are achieved following approximately 4 consecutive monthly treatments in dogs."**

In the studies provided by the applicant, there are several estimates and calculations concerning the half-life of moxidectin. In one study, the mean terminal half-life time was estimated at 24.6 days. In another study, it is stated that "[half-life] values ranged from approximately 19 to 38 days, with a mean of 28.4 days". In the view of the CVMP, the provided data does not support the proposed 35 days. The applicant was requested to justify the proposal. The applicant re-examined the material concerning the half-life and, taking all study results into consideration, proposed the following revised wording in section 5.2 of the SPC: "The T ½ in dogs is about 28.4 days". The proposal of the applicant is acceptable.

According to the pharmacokinetic study, moxidectin accumulates in dogs when Advocate is administered according to the label on a monthly basis. The mean half–life was 28.4 days. Based on this half-life, steady state should be reached in approximately 4.5 x 28.4 days, or ~ 128 days. The proposed sentence concerning steady state serum levels is accepted for inclusion in section 5.2 of the Advocate SPC for dogs.

Persistent action against *Dirofilaria immitis*

To support the persistent action against *D. immitis*, the applicant presented one laboratory study. In this study, 16 dogs were randomized to two treatment groups. Eight dogs in group 1 were treated with the investigational veterinary product at study day -30 while eight dogs in group 2 remained untreated. On study day 0, the dogs were infected subcutaneously with approximately 50 infective L3 *D. immitis* larvae. Blood samples were collected from the study animals on study days -37, 120 and 147 for antigen and microfilariae testing. All samples were negative for the presence of *D. immitis* antigens, indicating no prior or unplanned exposure to heartworm infection. All animals were negative for microfilariae at all three time points, except for one dog in group 2 that was positive for the heartworm antigen test on SD 147. Results from the necropsy at study day 148 showed no heartworms in the treated dogs (group 1) compared to 6 of the 8 untreated dogs (group 2) with heartworms (in range of 2-33 worms/dog). The treated dogs had significantly fewer heartworms ($p<0.05$) compared to the untreated controls.

According to Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (EMA/CVMP/EWP/117899/2004–Rev.1), pivotal studies used to support applications for products intended for the treatment of infections or parasitic conditions should be ideally conducted in Europe in order to simulate European conditions of use. The applicant was requested to justify the use of a non-European isolate in the study and how its use simulates European conditions of use. The applicant provided an exhaustive response and postulated that the available heartworm prevention data including the recent study allow predicting that Advocate will also show persistent efficacy against European heartworm isolates. Although there are no comparative data available on genotypes from *D. immitis* from Europe or the USA, the 100% efficacy against the resistant *D. immitis* strains (MP3 and JYD-34) from the USA gives confidence that Advocate will be effective also against the *D. immitis* strains present in Europe. The answer of the applicant is acceptable.

The presented laboratory study did not meet the requirements of VICH GL19 ("Efficacy of anthelmintics: specific recommendations for canines", CVMP/VICH/835/99-FINAL) in terms of proving

adequacy of infection. According to VICH GL19, there should be a minimum of 6 adequately infected dogs in control group (non-medicated) and generally the minimal number of nematodes per animal considered to be adequate is in the range of 5 to 20. In this study, six dogs were infected in the control group, but one infected dog had only 2 live worms at necropsy, while other five dogs had 19, 25, 27, 28, and 33 worms, respectively. In this type of study, where persistent action is assessed, it is important to show that infection is adequate in the control group as it is not possible to assess the adequacy of infection in the treated group as in conventional dose confirmation studies.

According to VICH GL19, the effectiveness should be 90% or higher calculated using transformed (geometric means) data. For some parasites with public health, animal welfare/clinical implications such as *D. immitis*, higher efficacy standards (i.e. up to 100%) may be imposed. According to W.A.A.V.P. guideline (World Association for the Advancement of Veterinary Parasitology guidelines for evaluating the efficacy of anthelmintics for dogs and cats), this is due to the potential pathogenicity of small number of *D. immitis* worms.

However, the study was provided without the intent to achieve an additional label claim, but to demonstrate the pharmacokinetic pattern of moxidectin and to confirm/explain this pharmacokinetic behaviour with efficacy data. Advocate has already been proven to be efficacious against *D. immitis* larvae when used as recommended. It can be used for the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*) by regular monthly treatments. Therefore, the study results can be accepted to support the inclusion of the sentence regarding persistent action against *Dirofilaria immitis* in the product information.

Persistent action against *Dirofilaria repens*

To support the persistent action against *D. repens,* the applicant has referred to a previously presented study. On study day 0, a group of 8 dogs was treated with Advocate and a similar group was left untreated as control animals. On day 28, the dogs were infected with approx. 75 infective *D. repens* larvae (L3). The dogs were sampled for blood on days 28, 56, 84, 112, 120,140, 168, 196, 224, and 238 after treatment. On days 245- 246, all dogs were euthanized for necropsy and detection of pre-adult and adult *D. repens* worms.

The same study has been submitted previously to support an earlier variation concerning the claim for the preventive efficacy against *D. repens* L3 larvae; therefore, the study has only been assessed in regards of the claimed persistent action and issues already resolved in earlier assessment have been left out. The study fulfills the requirements of VICH GL19 to prove adequacy of infection. According to GL19, there should be a minimum of 6 adequately infected dogs in control group (non-medicated) and generally the minimal number of nematodes per animal considered to be adequate is in the range of 5 to 20. In this study, adult *D. repens* worms could be detected in each of the eight untreated dogs in the control group, one dog having 3 adult *D. repens* worms at necropsy, for all other seven dogs the worm count was ≥5 worms. In fact, pre-adult and adult *D. repens* worms could be detected in each of the eight untreated control dogs, whereas no pre-adult or adult worm could be detected in any of the eight Advocate-treated dogs.

According to VICH GL19, the effectiveness should be 90% or higher calculated using transformed (geometric means) data. Percent efficacy was calculated as the comparison between the geometric mean worm count in the treated group and the untreated control group. Calculation resulted in 100% efficacy. The treated group was statistically significantly superior versus the untreated control group ($p = 0.0002$).

The results of this study support the proposed persistent action against *D. repens* and the addition of the sentence concerning persistent action in the SPC of Advocate for dogs can be accepted.

Persistent action against *Angiostrongylus vasorum*

To support the persistent action against *A. vasorum*, the applicant presented one laboratory study. In the study, 24 dogs were randomly allocated to three groups of 8 dogs each (4 males and 4 females): dogs of group 1 were treated once with Advocate spot-on at the minimum recommended dose at day 84, dogs of group 2 were treated monthly with Advocate spot-on at study days 0, 28, 56 and 84 at the minimum recommended dose, while dogs of group 3 served as infected but untreated control. All dogs were infected on study day 112 with approx. 250 L3 larvae of *A. vasorum* per dog.

In none of the dogs of study group 1 and study group 2 faecal larval shedding of *A. vasorum* was detected. In group 3 (untreated control), in all eight dogs L1 larvae were observed in faecal samples.

In autopsy, all eight dogs of the untreated control (study group 3) harbored more than 5 live worms (min: 23, max: 99, geo mean: 56.7). The infection level was considered to be adequate as a minimum of 6 control animals are required to carry at least 5 worms according to VICH GL19. None of the eight dogs of the study group 1 or the eight dogs of study group 2 had any live worms. Differences in the live adult worm count between study group 1 as well as study group 2 and the untreated control group 3 were highly significant ($p \leq 0.001$).

In none of the treated dogs of groups 1 and 2 any macroscopic changes of the lungs were detected, whereas 7 of 8 dogs of the untreated control group showed mild to severely affected lungs.

Both a single application 4 weeks before inoculation and 4 applications at monthly intervals before inoculation were efficacious. The results demonstrate that the persistent efficacy of the product against L3/L4 of *A. vasorum* over a four week period can be achieved with a single application of the product.

The persistent efficacy against *A. vasorum* has been sufficiently demonstrated by the results of this study and the proposed addition of the sentence concerning persistent action in the SPC of Advocate for dogs can be accepted.

In conclusion, the data provided by the applicant support the inclusion in the product information of Advocate for dogs of the sentence: "**The drug has a persistent action and protects dogs for 4 weeks after a single application against re-infection with the following parasites: *Dirofilaria immitis*, *Dirofilaria repens*, *Angiostrongylus vasorum*.**" However, considering that this sentence concerns pharmacodynamic rather pharmacokinetic properties, it was agreed this sentence to be included in section 5.1 of the SPC of Advocate for dogs, and not in section 5.2.

3. Benefit-risk assessment

This grouped variation application is to change the current indications for Advocate spot-on solution for cats and ferrets / for dogs by adding the following therapeutic indications:
- the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) in cats;
- the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* in dogs;
- the treatment of the eye worm *Thelazia callipaeda* in dogs.

Furthermore, the Product Information for Advocate for dogs is proposed to be amended with regard to half-life, serum steady state levels, studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications and persistent action. Also, the applicant took the opportunity to update the list of local representatives and the Product Information in line with QRD template v 8.1.

3.1. Benefit assessment

As this is a variation to introduce additional indications to an existing product, the benefit will arise from the inclusion of the new indications.

To support the proposed indication "the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) in cats", the applicant presented two GCP field trials. However, no dose confirmation study was provided, but the applicant provided an acceptable justification for the absence of the study. The results of these studies only supported the efficacy of Advocate against adult *E. aerophilus*. Therefore, the claim was restricted to adult parasites only. Overall, this claim is acceptable.

To support the proposed indication "the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* in dogs", the applicant has presented one GCP field study. However, no dose confirmation study was provided, but the applicant provided and acceptable justification for the absence of the study. The efficacy against *E. boehmi* has been demonstrated according to VICH GL19 and therefore the proposed indication is acceptable. The applicant proposes to limit the efficacy claim only to adult parasites, which is acceptable.

To support the proposed indication "the treatment of the eye worm *Thelazia callipaeda* in dogs", the applicant has presented two GCP field studies. However, dose finding and dose confirmation studies are required as this indication has no MUMS classification. The applicant provided an acceptable justification for the omission of these studies and the claim is acceptable. However, the presented studies did not yield reliable information concerning the effect of the product on *T. callipaeda* larvae and therefore the indication was restricted to adult parasites only.

There is direct benefit to animal health because the proposed indications include parasites that currently have very few efficacious therapeutic options. As some of them are also of zoonotic importance, the benefits also extend to public health. *Eucoleus aerophilus* has zoonotic potential and sporadic cases of human capillariosis have been described worldwide. *Thelazia callipaeda* can also infect humans.

3.2. Risk assessment

The indications that are subject of this grouped variation do not include changes in posology that differ from the accepted treatment regimen, which has been shown to be safe for target animals, users, and environment. In the studies presented by the applicant, no adverse events occurred that would require changes in existing product information.

No additional risks than those already mentioned in the product information are foreseen as a result of this variation and no actions are therefore considered necessary.

3.3. Evaluation of the benefit-risk balance

The benefit-risk balance remains unchanged. No change to the impact on the environment is envisaged. The proposed changes are not expected to alter the risk to the user.

The proposed administration schedule / posology does not differ from the previously accepted regimen where continuous monthly administration is advised for certain indications. In the original application, the tolerance of multiple overdoses of Advocate administered in six occasions at fortnightly intervals at up to five times the maximum recommended dose rate was evaluated and found to be well tolerated.

4. Overall conclusions of the evaluation and recommendations

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 Advocate can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008).

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.

4.1. Changes to the community marketing authorisation

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

I, IIIA and IIIB