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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a type II variation for Advocate (EMEA/V/C/000076/II/0046)

INN: imidacloprid / 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, Bayer Animal Health GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 24 August 2021 an application for a type II variation for Advocate.

1.2. Scope of the variation

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

To add a new therapeutic indication for the treatment of the lungworm *Troglostrongylus brevior* (adults) in cats. Also, the applicant takes the opportunity to make some editorial amendments to the package leaflet.

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

The applicant requested classification of this application as MUMS/limited market by the CVMP, and the Committee confirmed that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) data requirements would be applied when assessing the application. MUMS/limited market status was granted as the indication for the treatment of the lungworm *Troglostrongylus brevior* in cats is considered a minor use.

2. Scientific Overview

Advocate spot-on solution for cats (and ferrets) is a fixed combination of the two active substances imidacloprid and moxidectin at levels of 10% (w/v) and 1% (w/v), respectively. It was originally approved on 2nd April 2003 according to Council Regulation (EEC) No. 2309/93 (centralised procedure). The minimum effective dose rate has been established at 0.1 ml/kg body weight (bw), providing a minimum dose rate of 10 mg/kg bw imidacloprid and 1 mg/kg bw moxidectin. Advocate spot-on solution is also available for use in dogs (different concentration of the active substances and different dose rates compared to cats and ferrets).

The product is used in animals suffering from, or at risk from, mixed parasitic infections. The applicant is seeking a variation to the marketing authorisation to include approval for the use of Advocate in cats as detailed below:

- the following indication will be added to section 4.2 of the SPC for cats: *the treatment of the lungworm Troglostrongylus brevior (adults)*,
- section 4.9 of the SPC for cats will be amended to add: *Treatment of Troglostrongylus brevior (adults): Advocate should be administered monthly for two consecutive months*.

The applicant has presented literature concerning this emerging parasite in cats. Publications present first reports of *T. brevior* in domestic cats in different countries in Europe, epidemiology and clinical presentation and diagnosis in domestic cats, as well as scientific evidence of the life cycle and epizootiology of *T. brevior*. The literature presented is considered useful and sufficient, albeit it is stated in most of the publications that much about this neglected parasite is still unknown.

To support the proposed indication for the treatment of *Troglostrongylus brevior* in cats, the applicant has presented one study to establish an artificial infection model, two dose confirmation studies and a supportive field study.

2.1. Establishment of an artificial infection model

The establishment of an artificial infection model for *T. brevior* was performed in November 2019. Six cats were divided in three groups of two cats and infected with either 50, 100 or 150 *T. brevior* L3 larvae. Faecal larval output and clinical signs were monitored throughout the study and adult worms counted at necropsy on day 41-42 post-infection. The study results demonstrated that infection with 100 larvae increased the number of adult worms at necropsy compared to the lower dose of 50 larvae. Based on these results, the applicant selected an infective dose of 100 infective larvae to be used in dose confirmation studies. The applicant's choice of infective dose is considered adequately justified.

2.2. Dose confirmation studies

The first dose confirmation study assessed the efficacy of Advocate spot-on solution against induced *Troglostrongylus brevior* infection in cats when administered two times at one-month interval at the minimum recommended dose of 0.1 ml/kg bw. This GCP-compliant study was as a blinded, placebo controlled, single site efficacy study utilizing a randomized block design. Thirty-two European short-haired cats (16 males and 16 females) were divided in four groups:

- Group 1 - untreated control;
- Group 2 - other IVP (not relevant for this variation application);
- Group 3 - other IVP (not relevant for this variation application);
- Group 4 - Advocate spot-on (treatment on SDs 28 and 56).

On SD 0, all cats were experimentally infected with 100 infective L3 larvae of *T. brevior*. Faecal examinations using the Baermann technique to detect the start of patency of the *T. brevior* infection were conducted every other day between SDs 18 and 28 in all study groups. Clinical assessments were conducted pre-treatment and after each treatment. Further individual faecal samples for quantitative examination were collected from all cats on three consecutive days each on SDs 35 to 37, 49 to 51 and 63 to 65, and additionally on SDs 42 and 43. Between SDs 69 and 72 all cats were euthanized and necropsied for adult worm count. The primary efficacy criterion to evaluate the therapeutic efficacy of the treatments against adult *T. brevior* was the number of viable adult worms

counted at necropsy.

The results showed that all cats in all four study groups developed a patent infection according to the faecal examinations prior to the first treatment. At the necropsy on SDs 69 to 72, no *T. brevior* worms were observed in any of the Advocate-treated animals. Four of the eight control animals were found with 10 to 42 adult *T. brevior* worms, whilst for the other four control cats no adult worms were detected at necropsy. According to VICH Guidelines 7 and 20, a minimum of 6 control cats should be infected with a minimum of 5 adult nematodes per cat. As such, efficacy results were considered inconclusive due to inadequacy of infection in the control group and, consequently, no statistical evaluation was performed.

The second dose confirmation study assessed the efficacy of Advocate spot-on solution against induced *T. brevior* infection in cats when administered two times at one-month interval at the minimum recommended dosage of 0.1 ml/kg bw. This GCP-compliant study was designed as a partially blinded, controlled, single site efficacy study. On SD 0, 20 domestic short hair cats (15 males and 5 females) were experimentally inoculated with 100 *T. brevior* L3 larvae. Faecal examinations using the Baermann technique to detect the start of patency of the *T. brevior* infection were conducted once daily starting on SD 19. On SD 26, all cats shedding *T. brevior* larvae and meeting the other inclusion criteria were included in the study, and randomly allocated to one of the two groups (10 cats each):

- Group 1 - untreated control;
- Group 2 - Advocate spot-on (treatment on SDs 26 and 54).

Clinical assessments were conducted pre-treatment on SDs 26 and 54 (all cats) and approximately 4 and 24 hours after treatment. Individual faecal samples for quantitative examination were collected from all cats three times from SD 48 to 50 and again between SD 57 and 63. On SDs 64 and 65, all cats were euthanized and necropsied to determine the worm burden. The primary efficacy criterion to evaluate the therapeutic efficacy of Advocate against adult *T. brevior* was the number of viable adult worms counted at necropsy.

According to the faecal examinations prior to the first treatment, all 20 cats developed a patent infection. At the necropsy, no *T. brevior* worms were found in any of the Advocate-treated animals. The observed efficacy of two treatments one month apart using Advocate spot-on was 100% (based on geometric means). Four of the ten control animals were found with 16 to 28 adult *T. brevior* worms, whilst for the other six control cats no adult worms were detected at necropsy. According to VICH Guidelines 7 and 20, a minimum of 6 control cats should be infected with a minimum of 5 adult nematodes per cat. As such, adequate infection could not be demonstrated in sufficient control animals and therefore no statistical evaluation was performed.

Macroscopic changes with meat-like consistency and bright colour with purulent mucus in bronchi were observed in most of the lungs of the control group (eight of ten). In the Advocate group, pathological changes (inhomogeneous colour and tissue nodule) were only observed in two animals. Additionally, enlarged lymph nodes in the control group indicated an immunological response, most likely related to the lungworm infection. It can be concluded that pathological changes were clearly visible in the control animals, while they were only mild or absent in the treated animals.

At post-mortem examination in these two dose confirmation studies, only 4/8 and 4/10 control cats were found to harbour adult worms, despite larval evidence that 6/8 and 8/10 of the cats remained infected. It appeared likely that the number of worms was gradually diminishing in the control cats, therefore relatively few worms were recovered at post-mortem.

The applicant conducted a statistical analysis with the two studies combined, which totals 8

adequately infected control cats. According to this statistical analysis, the treatment was 100% effective and significantly different to control group cats. Both VICH GL7 and VICH GL20 allow pooling of data; however, neither the requirement of a minimum of three studies being conducted nor the requirement of a minimum of 12 adequately infected animals in the control group is fulfilled, as the applicant pooled the data from two studies only whereby altogether 8 adequately infected control cats were obtained and included in the statistical analysis. It is acknowledged that the product was 100% effective in treated cats and that terminal studies are the only means of investigating efficacy against *T. brevior*, which is considered a MUMS indication. The applicant provided additional justifications for deviating from the requirements of VICH guidelines. Both dose confirmation studies were very similarly structured and therefore comparable. Also, the results were very similar with regard to the number of adult worms at post mortem examinations and the faecal larval excretion in both control and treated cats. These results are also supported by the field study. Considering the above, the CVMP agreed that additional studies would not be expected to provide novel information and that the pooling of the data was sufficiently justified.

2.3. Field studies

The applicant provided one field study which assessed the efficacy of Advocate spot-on in the treatment of the infection caused by *T. brevior* in naturally infected cats in Greece. The study was a negative control, multi-centre, partially blinded clinical efficacy study utilizing a randomized block design, conducted according to the standards of Good Scientific Practice. Sixteen cats (9 female and 7 males) identified as being positive for *T. brevior* (L1 shedding) were randomly allocated to a non-treatment (control) group (Group 1, n=8) and a treatment (Advocate) group (Group 2, n=8). To test the treatment efficacy, cats assigned to study Group 2 were treated twice at one-month interval with the IVP on SDs 0 and 28 at the recommended dose rate of ≥10 mg imidacloprid/kg bw and ≥1.0 mg moxidectin/kg bw. In order to generate additional information and for ethical reasons (i.e. rescue treatment), cats allocated to Group 1 were treated twice at one-month interval with Advocate on SDs 56 and 84 at the same recommended dose. Cats of both groups were clinically and parasitologically (quantitative Baermann) evaluated on SDs 28 and 56, while cats of Group 1 were additionally examined on SDs 84 and 112.

The presence of *T. brevior* was the primary efficacy criterion. The presence of infection was defined on study day 56 (±2) (post-treatment) according to the detection of *T. brevior* L1 at the copro-microscopic examinations.

The secondary efficacy endpoint was the comparison of the Larvae Per Gram (LPG) values between the pre-treatment (baseline) and post-treatment copro-microscopic evaluation within group 2 and between the pre-treatment and post-treatment copro-microscopic evaluations within groups 2 and 1.

All samples collected at follow-up visits in Group 1 demonstrated continued larval shedding until these cats were rescue treated on SD 56. Follow-up samples collected from cats in group 2 on study days 28 and 56, as well as those collected from cats in group 1 on study days 84 and 112 were all negative. At baseline mean LPG counts in the two groups were comparable (not significantly different, $p=0.505$). The percentage efficacy was 100% (both on SDs 28 and 56) and the difference of the mean LPG counts between treated and untreated groups was highly significant ($p<0.001$). In addition, the LPG mean count for each sample was compared on study days 28 and 56 with the mean LPG count of the same sample at baseline (study day 0). LPG mean counts throughout the study remained comparable in Group 1 while they differed significantly in Group 2 ($p<0.0034$).

Advocate spot-on solution was safe and highly efficacious (100%) under field conditions in the treatment of the natural infection with *T. brevior* in cats. Two treatments one month apart eliminated *T. brevior* L1 shedding as soon as 28 days after the first treatment. However, the safety of the product in cats with severe clinical signs of *T. brevior* has not been studied. This is reflected in the product information and the use of the product in such cases will be at the discretion of the treating veterinarian based on a benefit-risk assessment.

In conclusion, based upon the findings from two dose confirmation studies and a field trial, it can be accepted that administration of Advocate at the currently approved treatment dose for two consecutive months is efficacious for the treatment of the lungworm *Troglostrongylus brevior* (adults) in cats. Consequently, the new indication can be accepted.

3. Benefit-risk assessment of the proposed change

This product is authorised in cats, ferrets and dogs suffering from, or at risk from, mixed parasitic infections. The active substances are imidacloprid (an ectoparasiticide belonging to the chloronicotinyl group of compounds) and moxidectin (a macrocyclic lactone of the milbemycin family, active against many internal and external parasites). The recommended minimum doses in cats are 10 mg/kg bodyweight imidacloprid and 1.0 mg/kg bodyweight moxidectin, equivalent to 0.1 ml/kg bodyweight Advocate for cats. Advocate for cats is presented as pipettes containing 0.4 ml (for small cats) and 0.8 ml (for large cats) spot-on solution.

The proposed variation is to add a new therapeutic indication for the treatment of the lungworm *Troglostrongylus brevior* (adults) in cats.

The product has been classified as MUMS/limited market and therefore reduced data requirements apply that have been considered in the assessment.

3.1. Benefit assessment

Direct therapeutic benefit

This is a variation for the addition of a new indication for treating adult *Troglostrongylus brevior* infection in cats. The efficacy of Advocate against adult *T. brevior* in cats was investigated in two well designed laboratory studies and one non-pivotal field study; all three studies were conducted to an acceptable standard.

Additional benefits

The approval of the proposed indication increases the range of available treatment possibilities for *T. brevior*, which is an indication classified as MUMS/limited market.

3.2. Risk assessment

The product has been used for almost 20 years and the tolerance when used as recommended in the SPC is well known. No new adverse events were recorded in current studies. No new resistance issues were identified when the product was used for the proposed new indication.

Quality:

Quality remains unaffected by this variation.

Safety:

Measures to manage the risks identified below are included in the risk management section.

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

Risks for the target animal:

Due to the exclusion criteria in the field study, the safety of the product has not been established in cats with severe clinical signs of *T. brevior*. This is reflected in the product information and the use of the product in such cases will be at the discretion of the treating veterinarian based on a benefit-risk assessment.

3.3. Risk management or mitigation measures

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal and to provide advice on how to prevent or reduce these risks.

3.4. Evaluation of the benefit-risk balance

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

The benefit-risk balance remains positive.

The product has been shown to be efficacious for the treatment of *Troglostrongylus brevior* (adults) in cats.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Veterinary Medicinal Products (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), as follows: to add a new therapeutic indication for the treatment of the lungworm *Troglostrongylus brevior* (adults) in cats. Also, the applicant takes the opportunity to make some editorial amendments to the package leaflet.

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 and IIIB.

As a consequence of this variation, sections 4.2, 4.5 and 4.9 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly. Furthermore, the applicant

has made editorial corrections in sections 6 and 12 of the package leaflet.