EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 June 2019
EMA/359888/2019
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for a type II variation for Advocate (EMEA/V/C/000076/II/0041/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. Introduction

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) on 7 December 2018 an application for a grouped type II variation for Advocate.

1.2. Scope of the variation

Variations requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
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	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

The variation is to add new therapeutic indications: the prevention and treatment of *Aelurostrongylus abstrusus* in cats and the treatment of *Thelazia callipaeda* in cats and to amend the product information with regard to pharmacological properties of moxidectin in cats (persistent action, half-life, steady-state serum levels after multiple applications). Also, the applicant takes the opportunity to update the list of local representatives.

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 in September 2016 that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) would be applied when assessing the application with regard to the indication concerning treatment of *Thelazia callipaeda* in cats. MUMS/limited market status was granted as the treatment of *Thelazia callipaeda* in cats is considered a minor use.

2. Scientific Overview

2.1. The prevention and treatment of Aelurostrongylus abstrusus in cats

2.1.1. Establishment of an artificial infection model

The applicant conducted one study to investigate whether experimental infection with *A. abstrusus* and adult worm counting at necropsy would be feasible for the diagnosis of *A. abstrusus* infection in cats. Six cats were artificially infected with *A. abstrusus* L3 larvae: three cats with 100 larvae each (group 1) and the other three cats with 800 larvae each (group 2). In group 1, two of the three cats became positive for larval shedding and adult worms were found at necropsy; the third cat didn't become positive for larval shedding and no worms were found in the lungs of this cat at necropsy. In group 2, all three cats became positive for larval shedding and adult worms were found at necropsy in all three cats. Both inoculation dosages (100 and 800 larvae) were high enough to induce infections. The group size was too small to estimate the dose-response relationship; however, 800 L3 larvae produced infection in all three cats, whilst one of the infections with 100 L3 larvae was unsuccessful. According to W.A.A.V.P. (World Association for the Advancement of Veterinary Parasitology) guidelines for evaluating the efficacy of anthelmintics for dogs and cats, the quantitative recovery of the nematode species associated with the lungs of dogs and cats is generally impracticable and so indirect means such as monitoring faecal larval excretion and resolution of pathology have to be employed. However, according to the results of this study, there seems to be a poor correlation between larval shedding based on faecal larval counts and the number of adult parasites in the lungs at necropsy. Furthermore, larval shedding is intermittent and therefore tissue dissection of fresh lungs seems to be the most reliable method to determine the total number of worms. To be able to set robust clinical endpoints, post mortem studies are therefore needed. This is in line with a previous assessment in 2009, when the CVMP concluded that this claim could not be approved based on reduction in larval output only.

2.1.2. The treatment (adults) of *Aelurostrongylus abstrusus*

The applicant has presented three dose confirmation studies to investigate the treatment efficacy against adult stage of *A. abstrusus*.

The first study assessed the efficacy of a single treatment against *A. abstrusus* in experimentally infected cats when administered at the minimum therapeutic dose. On SD -36, 24 cats (12 males and 12 females) were experimentally infected with approximately 800 infective L3 larvae. All cats showed excretion of L1 larvae on SD -4 and were randomly allocated to 3 study groups with 8 cats each. On SD 0, group 1 was treated with a placebo, group 2 with Advocate (IVP) and group 3 with a comparator product. On SD 26-30, all cats were necropsied and the nematodes in the lungs were recovered, speciated and counted. The efficacy of the treatment was assessed by comparing *A. abstrusus* worm counts in the IVP-treated cats to those in the control group. The requirement of at least 6 cats adequately infected with *A. abstrusus* in the negative control group was met as all 8 control cats were infected with 11-68 worms (GM 28.8). In the Advocate group, 7 out of 8 cats had 1-18 *A. abstrusus* worms. At necropsy it was found that some of the control cats were co-infected with another lung worm species identified as *Troglostrongylus* sp. Due to the fact that *Troglostrongylus* sp. L1 larvae are undistinguishable from those of *A. abstrusus*, no valid data could be generated concerning faecal larvae reduction of *A. abstrusus* alone. Efficacy against *A. abstrusus* in the Advocate-treated group was 88.3% (based on geometric means). Thus, it was concluded that a single administration of Advocate was insufficiently effective to treat adult stages of *A. abstrusus*.

The second study assessed the efficacy of two treatments at 14-days interval in experimentally infected cats at the minimum recommended dose. On SD -43, 24 cats (12 males and 12 females) were orally inoculated with approximately 600 *A. abstrusus* L3 larvae. On SD –5, all 24 cats shed L1 larvae and the treatment was administered on SDs 0 and 14. The cats in group 1 were treated with a placebo spot-on, the cats in group 2 were treated with Advocate 0.1 ml/kg bw, and cats in group 3 were treated with a spot-on comparator product. On SDs 33-36, the cats were euthanized and necropsied and the worms in the lungs were recovered, identified and counted. The efficacy of the treatment was assessed by comparing *A. abstrusus* worm counts in the Advocate-treated cats to those in the control group. All 8 placebo-treated cats were infected with 3-45 viable *A. abstrusus* worms and therefore adequacy of infection was achieved. Six cats in the Advocate-treated group had 1-55 viable *A. abstrusus* worms. Viable and total worm counts for Advocate were not significantly different from the control group; the efficacy was calculated at 36.9%. From this second study it was concluded that two treatments with Advocate at 14-day intervals were insufficiently effective to treat adult stages of *A. abstrusus*.

As in the previous study, it was found at necropsy that some of the control cats were co-infected with another lung worm species identified as *Troglostrongylus* sp. The infective material used for the challenge inoculation was obtained from naturally infected cats and differentiation of faecal larval stages in the infective material is difficult. The inoculum unintentionally contained two lung worm species (*A. abstrusus* and *Troglostrongylus* sp). As the faecal larval counts were only used for monitoring purposes, this had no impact on the efficacy evaluation. However, in the pivotal dose confirmation study ID46213en the inoculum used for infection of the cats contained only *A. abstrusus*.

The third study was performed to assess the therapeutic action of Advocate against an induced *A. abstrusus* infection in cats when administered for 3 consecutive times at monthly intervals at the minimum recommended dose. Twenty-four cats (17 males and 7 females) were infected each with approximately 300 *A. abstrusus* L3 larvae on SD 0. The cats were randomly allocated to three treatment groups, 8 cats in each group: 1) untreated control, 2) treated twice with Advocate on SD -10 and SD 18 (prevention arm of the study), and 3) treated 3 times with Advocate on SD 53, 81 and 109. To detect the start of *A. abstrusus* patency, individual faecal samples were taken between SD 40 and 48 (study groups 1 and 3) or 50 (study group 2). To monitor the development of infection, further individual faecal samples were examined for L1 larvae shedding until the day of necropsy. On SDs 136-140, all cats were necropsied and examined for the presence of viable and dead adult *A. abstrusus* worms, which were collected, identified and counted. For the evaluation of efficacy, worm counts at necropsy were analysed using appropriate statistical procedures. Based on the viable and total worm counts at necropsy, 99.4% efficacy was demonstrated in study group 3 (cats administered Advocate 3 times at monthly intervals in patent infections with *A. abstrusus*) when compared to study group 1 (untreated control). Larval output ceased in group 3 after day 102, whilst 4 of the 8 control cats were still shedding substantial numbers of larvae at the end of the study.

This study was performed according to respective scientific guidelines and the results support the efficacy against adult *A. abstrusus*. It is noted that in this study the infective dose used was 300 L3 larvae, which was lower than in the previous two studies and lower than the higher dose (800 L3 larvae) used in the infection model study, which produced an infection in all three cats. However, a sufficient level of infection was achieved in the control cats with the infective dose of 300 L3 larvae, and no guidance is available on the infective dose specific for this parasite.

The indication has not been granted a MUMS status, and therefore two acceptable dose confirmation studies are required according to VICH GL20 (Efficacy of anthelmintics: specific recommendations for feline). According to the infection model study, there seems to be a poor correlation between larval shedding and the number of adult parasites in the lungs. Also, larval shedding is intermittent and therefore tissue dissection of fresh lungs seems to be the most reliable method to determine the total number of worms. To be able to set robust clinical endpoints, post mortem studies are therefore needed. In a

previous assessment, the CVMP concluded in 2009 that the claim for the treatment of *A. abstrusus* could not be approved based on reduction in larval output only.

The applicant provided only one dose confirmation study fulfilling all requirements relating to efficacy (the third study). Three monthly treatments resulted in 99.4% efficacy in the treatment of *A. abstrusus*. Another dose confirmation study showed that a single dose resulted in 88.3% efficacy, which is very close to the requirement of the relevant guideline (90%).

According to the relevant guideline requirements, supportive field data should also be provided. A non-inferiority field study has been previously provided, where treatment efficacy was measured through a reduction of larval shedding only. This is considered acceptable for this particular indication as post mortem studies are rarely if ever acceptable in field studies.

Based on the totality of efficacy data presented, the CVMP accepts that the proposed indication against adult *A. abstrusus* has been adequately supported and is therefore approvable.

2.1.3. The prevention (L3, L4 larvae) of *Aelurostrongylus abstrusus*

The preventive efficacy was investigated in a further fourth dose confirmation study and also in the third dose confirmation study by post mortem worm counts in artificially established infections.

The first of these studies, a GCP partially blinded randomized study, evaluated the preventive efficacy of Advocate against induced *A. abstrusus* infection in cats when administered monthly for 2 consecutive months at the minimum recommended dose. On SD -21, 32 cats (16 males and 16 females) were randomly allocated to 4 groups of 8 cats (4 males + 4 females) each: 1) Advocate administered on SDs -4 and 24; 2) Advocate administered on SDs -10 and 18; 3) Advocate administered on SDs -20 and 8; 4) control group treated with placebo on SDs -4 and 24. Inoculation with approximately 300 *A. abstrusus* L3 larvae was conducted on SD 0. Treatments were phased relative to inoculation in order to demonstrate efficacy against the different larval stages. Based on the life-cycle, *A. abstrusus* were expected to be L3 larvae up to 4 days post-inoculation (dpi), L4 larvae 7 dpi and immature adults 14 dpi. The cats were necropsied on several consecutive days 34-35 days (12 cats) and 48-50 days (20 cats) after inoculation to determine the worm burden in the lungs. The response to treatment was evaluated by comparison of worm counts in cats in the different treatment groups with those in the control group. The requirement of at least 6 adequately *A. abstrusus* infected cats in the control group was met as all 8 control group cats were infected with 3-86 viable worms, and 7/8 cats were infected with >5 worms. At necropsy, no viable *A. abstrusus* worms were found in any of the Advocate treated cats. One dead *A. abstrusus* worm was found in one cat in group 2. Live L1 larvae were found in 6 of 8 control group cats; no live L1 larvae were found in any of the Advocate-treated cats, although one cat in group 3 had one dead larva. All 3 Advocate-treated groups showed a significant reduction in viable and total worm counts as compared to the control group ($p<0.05$). Efficacy based on geometric means of viable worm counts for Advocate was 100% in all 3 study groups.

Another worm species, *Troglostrongylus* sp., was found during necropsy in 7 control group cats and in 2 cats in treatment groups 1 and 2, respectively. As *Troglostrongylus* sp. also sheds L1 larvae very similar to *A. abstrusus* and as no L1 larval differentiation was performed, the larval results during necropsy were only used for information purposes.

The second of these studies is described above in 2.1.2. Group 2 served as a prevention arm in this study. No worms could be detected at necropsy in the prevention group and efficacy was 100%.

The results of these studies support the proposed prevention indication against *A. abstrusus* L3 larvae.

The applicant was asked to justify the inclusion of L4 larvae in the prevention indication as the studies only included challenges performed with L3 larvae. According to the applicant, Group 3 in the fourth study reflects a situation where the second treatment on SD 8 acted on the L4 stage of the parasite, based on the low moxidectin concentration still available from the treatment performed on SD -20. Based on this, it is agreed that the prevention efficacy was shown against both L3 and L4 larvae.

Taking into account all the information provided, the CVMP considers that the proposed indication for the prevention (L3, L4 larvae) of *A. abstrusus* is approvable.

2.2. The treatment of the eye worm Thelazia callipaeda (adults)

The applicant has presented one field efficacy study to support this MUMS indication claim.

This GCP, negative controlled, blinded and randomized field study evaluated the therapeutic efficacy of a single dose of Advocate against natural *T. callipaeda* infection in cats. The study was conducted with 30 privately owned cats (19 females and 11 males) living in a *T. callipaeda* endemic area in Italy and naturally infected with the parasite. On SD 0, the cats were physically examined and the infection level was assessed by examination of both eyes for clinical score and live adult *T. callipaeda* count. Each cat was randomly assigned to one of the treatment groups: 1 - Advocate, 2 - untreated control. Advocate was administered once according to label instructions on study day 0. The dose level was the recommended dose of imidacloprid (10 mg/kg bw) and moxidectin (1.0 mg/kg bw). Clinical assessments and *T. callipaeda* adult counts were performed on SDs 14 and 28. On SD 28, at study completion, the presence of *T. callipaeda* adults and larvae was assessed. All cats were observed daily by their owners and general health was recorded during the entire period of the study. The primary efficacy variable was the efficacy of Advocate against adult *T. callipaeda* by comparing the two study groups of cats with respect to parasitological cure (therapeutic efficacy), i.e. percentage of cats showing a complete elimination of adult eye worms on SDs 14 and 28. Worm count reduction, presence of ocular signs and reduction of severity of ocular signs caused by eye worm infection were evaluated as a secondary variable for efficacy of the IVP. The presence of worm larvae was evaluated on SD 28 using eye flush samples.

The efficacy of Advocate against *T. callipaeda* after a single administration was 93.3% on SD 14 and 100% on SD 28, which fulfils the requirement set in VICH GL7 Efficacy requirements for anthelmintics: overall guidelines. The *T. callipaeda* claim is supported by a single field study. In general, the study satisfied the requirements of relevant guidelines. Lacrimation was the only milder symptom that seemed to correlate with treatment efficacy. No cat was found to have more severe clinical signs such as keratitis or ulcers, which are generally only seen with chronic and/or infection with a high worm burden. The CVMP has previously been satisfied with the fact that theliaziasis is reliably diagnosed by ocular inspection.

According to the Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/EWP/117899/2004), a dose confirmation study and a field trial should be provided. However, if a field study has been provided and the selected dose justified, dose confirmation studies might not be required. The CVMP finds the selected treatment dose justified; a dose confirmation study is not considered necessary as the product is authorised for the same indication in dogs. The guideline referred to above accepts extrapolation from another species for which the product is authorised as a justification for not providing a dose confirmation study.

The CVMP considers that the results of this field study provide sufficient proof of efficacy against adult *Thelazia callipaeda* to support the proposed indication in cats: "the treatment of the eye worm *Thelazia callipaeda* (adults)".

2.3. Amendments to the product information with regard to pharmacological properties of moxidectin in cats

2.3.1. Month-long preventive efficacy against infection with *Dirofilaria immitis*

The applicant proposes the following amendment to SPC Section 5.1: "The drug has a persistent action and protects cats for 4 weeks after a single application against reinfection with *Dirofilaria immitis*."

To support the claim, the applicant has presented two studies investigating the preventive month-long efficacy ("reach forward effect") of Advocate against *D. immitis* in cats. These are to complement the pharmacokinetic studies demonstrating the persistent month-long presence of moxidectin following treatment with Advocate.

In the first study, which was a non-GCP laboratory study performed in the USA, 20 cats were inoculated with 25 third-stage *D. immitis* larvae/cat, whereas the recommended range of infective stages used to produce adequate infections in felines for anthelmintic evaluation is 30-100, as stated in VICH GL20 Efficacy of anthelmintics: specific recommendations for feline. Three out of nine control cats did not become infected. According to the VICH GL 20, at least six animals in the control group should be adequately infected, generally with 5 to 20 nematodes. Even though in this study adult heartworms (1-6) were found in five cats, the difference between the control and treatment group was statistically significant. The CVMP is of the opinion that the infection can be considered as adequate despite the lower number of infective larvae used. The applicant has justified the use of a non-European isolate of *D. immitis* (Missouri strain) in a previous variation application (EMEA/V/C/000076/II/0039/G), which is acceptable.

All cats in the treated group remained antibody and antigen negative at all examined time points. According to VICH GL20, a compound should be declared effective only when effectiveness against each parasite declared on the labelling stands 90% or above, based on calculation of geometric means. For *D. immitis*, higher efficacy standards (i.e. up to 100%) may be imposed. As no worms were detected at necropsy nor were there any pathological changes in the treated cats and they remained antibody and antigen negative, it is likely that the larvae were eliminated soon after inoculation. The results of this study strongly support the 28-day long preventive efficacy of Advocate against *D. immitis*.

The second study was a GCP laboratory study performed in the USA. Twenty-four domestic cats were acclimated for 7 days. During the acclimation period, on SD -37 a physical examination was performed and blood was collected for heartworm antigen (with and without heat treatment), antibody and microfilarial testing via the modified Knott test (heartworm diagnostics). On SD -33, 20 cats were randomized to 2 treatment groups. Ten cats in group 1 were treated with Advocate according to label recommendations on SD -30, while 10 cats in group 2 remained untreated. On SD 0, each cat was infected in the inguinal region with approximately 100 freshly harvested, infective third-stage "Georgia II" strain *D. immitis* larvae recently removed from infected mosquitoes. Following a question from the CVMP, the applicant has satisfactorily justified the use of this non-European isolate of *D. immitis* ("Georgia II" strain) in this study. The used infection dose of 100 L3 larvae is in line with the recommended range of infective stages, as indicated in VICH GL20. The cats were re-tested again using the same heartworm diagnostic panel on SDs 120 and 180. All treated cats remained negative for *D. immitis* antigen during the entire study period and no worms were found in any of them at necropsy. However, all non-treated cats harboured heartworms and six of them were also antigen positive. The results of this study support the 30-day long preventive efficacy of Advocate against *D. immitis*.

Based on the results of the two studies, the CVMP considers that the addition of the sentence "The product has a persistent action and protects cats for 4 weeks after a single application against reinfection with *Dirofilaria immitis*." in section 5.1 of the SPC is acceptable.

2.3.2. Amendments to the product information with regard to pharmacokinetic properties of moxidectin in cats

The applicant has submitted 9 studies altogether in support of moxidectin pharmacokinetics (PK) in cats, most of those being already submitted in the original marketing authorisation dossier. Moxidectin is lipophilic and has a high volume of distribution, and therefore that the t½ is long. The individual variation in the kinetics is extensive, with a t½ range of approximately 12-35 days (considering all PK studies submitted). The studies presented point to a mean terminal elimination t½ of 18.7-25.7 days. The applicant proposed to mention in the SPC section 5.2 only the t½ calculated in two reports, i.e. 23.6 days. The CVMP considered that the applicant should justify the choice of t½ taking into account all PK study results presented for the target species cat. Consequently, it was agreed to include the reported range of mean t½ (18.7-25.7 days) in the SPC.

Based on the information provided, it is agreed that steady state is achieved after 4-5 half-lives, and therefore the applicant's proposal for wording concerning steady state in the SPC section 5.2 is acceptable: "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 cats".

3. Benefit-risk assessment of the proposed change

This product is authorised in cats suffering from, or at risk from, mixed parasitic infections: treatment and prevention of flea infestation (*Ctenocephalides felis*), treatment of ear mite infestation (*Otodectes cynotis*), notoedric mange (*Notoedres cati*), lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) (adults), gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara cati* and *Ancylostoma tubaeforme*) and prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*). Advocate can be used as part of a treatment strategy for flea allergy dermatitis (FAD) in cats. Also, the product is indicated in dogs and ferrets 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. 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 new therapeutic indications: the prevention and treatment of *Aelurostrongylus abstrusus* in cats and the treatment of *Thelazia callipaeda* in cats and to amend the product information with regard to pharmacological properties of moxidectin in cats (persistent action, half-life, steady-state serum levels after multiple applications). Also, the applicant takes the opportunity to update the list of local representatives.

The product has been classified as MUMS/limited market and therefore reduced data requirements apply that have been considered in the assessment of the application with regard to the indication concerning treatment of *Thelazia callipaeda* in cats.

3.1. Benefit assessment

Direct therapeutic benefit

The benefit of Advocate related to this grouped variation is its efficacy in the prevention and treatment of *Aelurostrongylus abstrusus* in cats and the treatment of *Thelazia callipaeda* in cats.

Control of a zoonotic agent can be obtained by use of this product as it has effect against *Thelazia callipaeda*, which is the etiological agent of human thelaziasis. The product can be used to treat infected domestic animals, which may act as reservoirs for human infection.

Additional benefits

The product has a persistent action and protects cats for 4 weeks after a single application against reinfection with *Dirofilaria immitis*.

3.2. Risk assessment

The risks pertaining to product use are unchanged by this variation and no reassessment is needed.

Quality:

Quality remains unaffected by this variation.

Safety:

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

3.3. Risk management or mitigation measures

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

3.4. Evaluation of the benefit-risk balance

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

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.

The product has been shown to be efficacious for the treatment of *Thelazia callipaeda* in cats and for the prevention and treatment of *Aelurostrongylus abstrusus* in cats.

The amendments of the product information with regard to pharmacological properties of moxidectin (half-life and persistent efficacy) are accepted.

The benefit-risk balance remains positive.

4. Conclusion

Based on the original and complementary data presented on efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for variation to the terms of the marketing authorisation for 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 new therapeutic indications: the prevention and treatment of *Aelurostrongylus abstrusus* in cats and the treatment of *Thelazia callipaeda* in cats and to amend the product information with regard to pharmacological properties of moxidectin in cats (persistent action, half-life, steady-state serum levels after multiple applications). Also, the applicant takes the opportunity to update the list of local representatives.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommends the approval of the variation to the terms of the marketing authorisation for the above mentioned medicinal product.

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

I, IIIA and IIIB.

As a consequence of these variations, sections 4.2, 4.9, 5.1 and 5.2 of the SPC for Advocate spot-on solution for cats (and ferrets) are updated. The corresponding sections of the package leaflet are updated accordingly.