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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for grouped type II variation for Advocate (EMEA/V/C/000076/II/0026/G)

International non-proprietary name: Imidacloprid / Moxidectin

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

Rapporteur: M. Nevalainen

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Background information on the variation

1.1. Submission of the variation application

In accordance with Article 7.2(b) 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 4-6 November 2014 the CVMP agreed that the data requirements specified in the appropriate CVMP guidelines on "Minor-Use-Minor-Species" (MUMS) are applicable when assessing the indication for Advocate - treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*) in dogs.

1.2. Scope of the variation

Variation(s) 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.II.6.a	Changes to the labelling or the PL which are not connected with the SPC - Administrative information concerning the holder's representative	IAin

To add a new therapeutic indication for Advocate spot-on solution for dogs, i.e. treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*) and to change the administrative information concerning the holder's local representatives.

Current	**Proposed**
SPC - Advocate for dogs 4.2 Indications for use, specifying the target species For dogs suffering from, or at risk from, mixed parasitic infections: • For the treatment and prevention of flea infestation (*Ctenocephalides felis*), • the treatment of biting lice (*Trichodectes canis*), • the treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*), • the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*), • the treatment of circulating microfilariae (*Dirofilaria immitis*), • the prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*), • the reduction of circulating microfilariae (*Dirofilaria repens*), • the prevention of angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*),	SPC - Advocate for dogs 4.2 Indications for use, specifying the target species For dogs suffering from, or at risk from, mixed parasitic infections: • For the treatment and prevention of flea infestation (*Ctenocephalides felis*), • the treatment of biting lice (*Trichodectes canis*), • the treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*), • the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*), • the treatment of circulating microfilariae (*Dirofilaria immitis*), • **the treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*)** • the prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*), • the reduction of circulating microfilariae (*Dirofilaria repens*), • the prevention of angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*),

• the treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis*, • the prevention of spirocercosis (*Spirocerca lupi*), • 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 product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).	• the treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis*, • the prevention of spirocercosis (*Spirocerca lupi*), • 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 product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).
4.9 Amounts to be administered and administration route […]	4.9 Amounts to be administered and administration route ***Treatment of cutaneous dirofilariosis (adult stages of Dirofilaria repens)*** **Advocate should be administered monthly for six consecutive months.** *Corresponding sections of package leaflet have been updated accordingly.*
Package leaflets – Advocate for cats and ferrets / for dogs 15. Other information	Package leaflets – Advocate for cats and ferrets / for dogs 15. Other information Update of local representatives details.

2. Scientific discussion

To support the proposed new indication for "the treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*)" the applicant has presented two dose confirmation studies, one laboratory study and one field study. This is in line with VICH GL19 (Efficacy of anthelmintics: specific recommendations for canines, CVMP/VICH/835/99-FINAL) where it is stated that two dose confirmation studies should be conducted.

CVMP granted MUMS/limited market status for this indication in November 2014. According to the CVMP 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), the requirements for demonstrating efficacy for minor use indications will be determined on a case-by-case basis. During the assessment of this application, the CVMP accepted reduced data, as outlined below.

2.1. Dose justification

The selected minimum dose of 0.1 ml/kg bw Advocate for dogs (i.e. 10 mg/kg bodyweight imidacloprid and 2.5 mg/kg bw moxidectin) was chosen as this is the already authorised dose, which has been shown to be safe to use in the target species. This approach was considered acceptable in view of the minor use nature of the indication.

The applicant justified the proposed treatment schedule of six consecutive monthly treatments with (1) the pharmacokinetic properties of moxidectin (steady-state serum pharmacokinetics approximately after the 6th dose), (2) the knowledge about the tissue location of adult *D. repens* stages that are leading to reduced exposure (hence requiring higher peak levels and longer exposure), and (3) data available from previous studies using different treatment regimens conducted with Advocate to reduce the microfilariae count. Although the applicant has not presented a very solid justification for the treatment schedule of six treatments, the CVMP considered the convincing results of the laboratory dose confirmation study as an acceptable justification for the selected treatment regimen of six monthly treatments, taking into account the minor use nature of the indication.

2.2. Dose confirmation study (laboratory)

The GCP laboratory dose confirmation study (201.129) provided by the applicant was well conducted and included 11 dogs in the study group and 12 dogs in the control group, which exceeds the requirement set in VICH GL19 where, i.e. inclusion of at least 6 animals in each experimental group is a minimum. During this study one dog was excluded from the efficacy evaluation but no dog had to be removed from the study.

Experimental infection with approximately 75 infective *D. repens* L3 larvae was done on study day 0 and treatment with Advocate started on study day 228, i.e. approx. 7 months after infection, at the lowest recommended dose that is already authorised for dogs for other Dirofilaria indications (0.1 ml/kg bw). Treatment was repeated monthly over 6 months (D256, D283, D311, D339, and D367). Efficacy against microfilariae was assessed based on blood samples taken 28 days after each treatment, i.e. at D256, D283, D311, D339, D367 and D395. On D403/404, all dogs were subjected to necropsy.

With respect to the total worm count (i.e. the sum of live and dead worms) no significant difference between both groups could be found ($p > 0.05$) indicating a similar degree of initial infection in both groups prior to initiation of treatment. Nine of the 12 control group dogs were adequately infected (i.e. $\geqslant$ 5 live *D. repens* worms were found at necropsy). With respect to the primary efficacy variable

(number of adult live *D. repens* worms at necropsy, D403/405), a significantly lower ($p \leqslant 0.001$) geometric mean worm count was found in dogs of the Investigational Veterinary Product group compared to the control group. The respective geometric mean values were 5.44 and 0.21 live worms in study groups 1 and 2. The calculated effectiveness was 96.2%. Eight of 11 evaluated dogs in the Advocate group showed a negative live worm count. In 3 dogs, only one live worm was found in each dog. The dead *D. repens* worm count was significantly higher in the treated animals of study group 2 compared to the control group 1 ($p \leqslant 0.01$) with respective geometric mean values of 5.9 and 1.4 dead worms. This result also gives evidence that treatment with the IVP was effective.

Advocate was well tolerated in all dogs. No clinical signs of intolerance could be observed.

According to VICH GL19 dose confirmation studies should be conducted using naturally or artificially infected animals; however, at least one study should be conducted in naturally infected animals for each parasite claimed on the label. *Dirofilaria* spp*.* testing may be conducted using animals harbouring induced infections. In this study the dogs were artificially infected, which is considered acceptable.

Adequate parasite infection should be defined in the protocol according to regional prevalence or historic and/or statistic data. There is no recommendation in the VICH GL19 of suitable range of infective stages used to produce adequate infection with *D. repens*, but based on literature cited by the applicant (Genchi et al. 2010, 2013) the infective dose used in this study was deemed sufficient.

The parasite strain used in efficacy studies should be representative for European conditions, and the history of the parasites used in the induced infection studies should be included in the final study report. The applicant provided detailed information on the origin of the *D. repens* strain used in the laboratory study, confirming that the infective material derived from Italy, and could therefore be considered representative for the targeted geographical region, Europe. The strain used complied with the requirements of a World Association for the Advancement of Veterinary Parasitology (WAAVP) guideline for evaluating the efficacy of anthelmintics for dogs and cats (Jacobs *et al*., 1994) stating that if artificially induced infections are used, the infective material should normally be derived from the geographical region in which the trial is being conducted.

According to VICH GL19 the evaluation of the effectiveness data should be based on parasite counts (adults, larvae) in dose confirmation studies. With respect to the primary efficacy variable (number of adult live *D. repens* worms at necropsy), a significantly lower ($p \leqslant 0.001$) geometric mean worm count was found in dogs of the treated group compared to the control group. The calculated effectiveness was 96.2%. According to VICH GL19 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 the WAAVP guideline this is due to the potential pathogenicity of small number of *D. immitis* worms. Although *D. repens* has a zoonotic nature it is not as pathogenic as *D. immitis* in dogs and thus the level of efficacy is considered acceptable.

Overall, the therapeutic efficacy of Advocate when administered at the minimum dosage of 0.1 ml/dog monthly for 6 consecutive months against the adult stages of *D. repens* after experimental infection of dogs was considered demonstrated.

2.3. Dose confirmation study (field study)

The field study was conducted in Czech Republic and designed for evaluation of the therapeutic and preventive efficacy and safety of Advocate against dirofilariosis caused by *Dirofilaria repens* in dogs living in an area with high prevalence. This study had already been submitted and accepted in support of a previous variation application (EMEA/V/C/000076/II/0022) that resulted in the following indication for microfilaricidal efficacy being granted: the reduction of circulating microfilariae (*Dirofilaria repens*).

During the aforementioned procedure it was determined that this field study could not be used to reliably assess adulticidal efficacy. Microfilaricidal efficacy cannot be used as a surrogate measure of adulticidal efficacy for a product where direct microfilaricidal efficacy has already been demonstrated (based on both laboratory and field trials).

The product has previously been shown to be well tolerated when administered as recommended. The proposed administration schedule / posology (six times monthly) does not differ from the previously accepted regimen (continuous monthly use); therefore, no further justification in regard to safety was needed. In both the laboratory and field study submitted in support of this application, no adverse events were recorded. Based on the above the CVMP considered that there is no need to restart the periodic safety update report (PSUR) cycle for Advocate.

2.4. Conclusions

The CVMP considered that the laboratory dose confirmation study fulfills the requirements set in respective guidelines and the applicant has convincingly shown the efficacy of Advocate at a dose of 0.1 ml/kg bw with six consecutive administrations at monthly intervals against adult stages of *Dirofilaria repens* in laboratory conditions.

The field study presented had already been submitted and accepted in support of a previous variation application that resulted in the reduction of circulating microfilariae (*Dirofilaria repens*) indication being granted. However, microfilaricidal efficacy cannot be used as a surrogate measure of adulticidal efficacy for a product where direct microfilaricidal efficacy has already been demonstrated. The CVMP therefore did not consider that this field trial could be used in support of adulticidal efficacy in this application.

Nevertheless, the CVMP considered the dose confirmation study alone as an acceptable proof for adulticidal efficacy of the product, considering the minor use nature of the indication. It is acknowledged that a field study to confirm the adulticidal efficacy is not feasible with patient dogs as post mortem examinations are not possible. An additional field study with test animals is not deemed necessary based on the 3Rs principle of Replacement, Reduction and Refinement of methods in animal testing.

In conclusion, the CVMP is of the opinion that adequate data have been provided to support the proposed indication "the treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*)" and recommends this variation application.

3. Benefit-risk assessment

3.1. Benefit assessment

To support the proposed new indication for "the treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*)" the applicant presented two dose confirmation studies, one laboratory study and one field study extrapolating from the effect of Advocate in reducing circulating microfilariae to the efficacy against adult *Dirofilaria*.

While the field study was not considered adequate to support the proposed claim, the CVMP considered the results of the laboratory dose confirmation study sufficient to demonstrate the efficacy of the proposed dose of 0.1 ml/kg bw Advocate for dogs (i.e. 10 mg/kg bw imidacloprid and 2.5 mg/kg bw moxidectin) administered six times in monthly intervals for the treatment of cutaneous dirofilariosis (adult stages of *Dirofilaria repens*), taking into account the minor use nature of the indication.

Additional benefit:

The proposed indication has currently very few efficacious therapeutic options and is of zoonotic importance.

3.2. Risk assessment

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

3.3. Evaluation of the benefit-risk balance

No change to the impact on the environment is envisaged.

The benefit-risk balance remains unchanged. The proposed administration schedule / posology (six times monthly) do 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

The CVMP considers that this variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, is approvable.

4.1. Changes to the community marketing authorisation

Changes are required in the Annexes to the Community marketing authorisation.

I, IIIA and IIIB