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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for type II variation for Advocate (EMEA/V/C/000076/II/0022)

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 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 23 November 2012 an application for a type II variation for Advocate.

1.2. Scope of the variation

Addition of a new therapeutic indication for the treatment of notoedric mange (*Notoedres cati*) in cats, the treatment of circulating microfilariae (*Dirofilaria immitis*) in dogs, the prevention of cutaneous dirofilariosis (L3 and L4 larvae of *Dirofilaria repens*) in dogs, the elimination of circulating microfilariae (*Dirofilaria repens*) in dogs, and the prevention and treatment of spirocercosis (*Spirocerca lupi*) in dogs.

Advocate spot-on solution for cats and ferrets

Current	Proposed
SPC **4.2 Indications for use, specifying the target species** **For cats** suffering from, or at risk from, mixed parasitic infections: For the treatment and prevention of flea infestation (*Ctenocephalides felis*), treatment of ear mite infestation (*Otodectes cynotis*), prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*) and treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara cati* and *Ancylostoma tubaeforme*). The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD). **For ferrets** suffering from, or at risk from, mixed parasitic infections: For the treatment and prevention of flea infestation (*Ctenocephalides felis*) and the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*).	SPC **4.2 Indications for use, specifying the target species** **For cats** suffering from, or at risk from, mixed parasitic infections: For the treatment and prevention of flea infestation (*Ctenocephalides felis*), <u>the</u> treatment of ear mite infestation (*Otodectes cynotis*), <u>the treatment of notoedric mange (*Notoedres cati*), the</u> prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*) and the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara cati* and *Ancylostoma tubaeforme*). The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD). **For ferrets** suffering from, or at risk from, mixed parasitic infections: For the treatment and prevention of flea infestation (*Ctenocephalides felis*) and the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*).
4.9 Amounts to be administered and administration route Treatment of ear mite infestation (*Otodectes cynotis*)…	**4.9 Amounts to be administered and administration route** Treatment of ear mite infestation (*Otodectes cynotis*)… *Treatment of notoedric mange (Notoedres cati)* A single dose of the product should be administered. **<u>Corresponding sections of labelling and package leaflet are amended accordingly</u>**

Advocate spot-on solution for dogs

Current	Proposed
SPC **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*), treatment of biting lice (*Trichodectes canis*), treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*), prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*) and angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*), treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis* and 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).	SPC **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*), treatment of biting lice (*Trichodectes canis*), treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*), prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*), treatment of circulating microfilariae (*Dirofilaria immitis*), prevention of cutaneous dirofilariosis (L3 and L4 larvae of *Dirofilaria repens*), elimination of circulating microfilariae (*Dirofilaria repens*), prevention of angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*), treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis*, prevention and treatment of spirocercosis (*Spirocerca lupi*) and 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).
4.5 Special precautions for use **Special precautions for use in animals** … Although the product may be safely administered to dogs infected with adult heartworms, it has no therapeutic effect against adult Dirofilaria immitis. It is therefore recommended that all dogs 6 months of age or more, living in areas endemic for heartworm, should be tested for existing adult heartworm infection before being treated with the product.	**4.5 Special precautions for use** **Special precautions for use in animals** … Although experimental overdosage studies have shown that the product may be safely administered to dogs infected with adult heartworms, it has no therapeutic effect against adult Dirofilaria immitis. It is therefore recommended that all dogs 6 months of age or more, living in areas endemic for heartworm, should be tested for existing adult heartworm infection before being treated with the product. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. The safety of Advocate has not been evaluated when administered on the same day as an adulticide.
4.6 Adverse reactions (frequency and seriousness) … The product may in very rare cases cause at the application site a sensation resulting in transient behavioural changes such as lethargy, agitation, and inappetence.	**4.6 Adverse reactions (frequency and seriousness)** … The product may in very rare cases cause at the application site a sensation resulting in transient behavioural changes such as lethargy, agitation, and inappetence. A field study has shown that in heartworm positive dogs with microfilaraemia the following clinical symptoms have been observed: respiratory signs (coughing, tachypnoea, dyspnoea), gastrointestinal signs (vomiting, diarrhoea, inappetence) and lethargy.
4.8 Interaction with other medicinal products and other forms of interaction During treatment with Advocate no other antiparasitic macrocyclic lactone should be administered.	**4.8 Interaction with other medicinal products and other forms of interaction** During treatment with Advocate no other antiparasitic macrocyclic lactone should be administered. No interactions between Advocate and routinely used

No interactions between Advocate and routinely used veterinary medicinal products or medical or surgical procedures have been observed.	veterinary medicinal products or medical or surgical procedures have been observed. Safety of Advocate when administered on the same day as an adulticide to remove adult heartworms has not been evaluated.
4.9 Amounts to be administered and administration route … *Heartworm prevention* Dogs in areas endemic for heartworm, or those which have travelled to endemic areas, may be infected with adult heartworms. Therefore prior to treatment with Advocate, the advice provided in section 4.5 should be considered. For prevention of heartworm disease, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit heartworm larvae) are present. The product may be administered throughout the year or at least 1 month before the first expected exposure to mosquitoes. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month. When replacing another heartworm preventative product in a heartworm *prevention programme, the first treatment with Advocate must be given within 1 month of the last dose of the former medication.* *In non-endemic areas there should be no risk of dogs having heartworm. Therefore they can be treated without special precautions.* *Treatment of Crenosoma vulpis* A single dose should be administered.	**4.9 Amounts to be administered and administration route** **…** Prevention of heartworm disease (D. immitis) and cutaneous dirofilariosis (D. repens) prevention Dogs in areas endemic for heartworm, or those which have travelled to endemic areas, may be infected with adult heartworms. Therefore prior to treatment with Advocate, the advice provided in section 4.5 should be considered. For prevention of heartworm disease and cutaneous dirofilariosis, the product must be applied at regular monthly intervals during the time of the year when mosquitoes (the intermediate hosts which carry and transmit D. immitis heartworm and D. repens larvae) are present. The product may be administered throughout the year or at least 1 month before the first expected exposure to mosquitoes. Treatment should continue at regular monthly intervals until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month. When replacing another heartworm preventative product in a heartworm prevention programme, the first treatment with Advocate must be given within 1 month of the last dose of the former medication. In non-endemic areas there should be no risk of dogs having heartworm. Therefore they can be treated without special precautions. Treatment of microfilariae (D. immitis) and elimination of microfilariae (D. repens) D. immitis: Advocate should be administered monthly for two consecutive months. D. repens: Advocate should be administered monthly for four consecutive months Treatment of Crenosoma vulpis A single dose should be administered. Prevention and treatment of Spirocerca lupi: Prevention: Advocate should be administered monthly. Treatment: Advocate should be administered weekly until clinical resolution of the lesions. Corresponding sections of labelling and package leaflet are amended accordingly.

2. Scientific discussion

2.1. Assessment

Treatment of notoedric mange (Notoedres cati) in cats

Notoedric mange (feline scabies) is a rare, highly contagious disease of cats. *Notoedres cati* mites can opportunistically infest other animals, including humans.

The applicant submitted one GCP laboratory dose confirmation study conducted in Hungary to evaluate the efficacy and safety of Advocate in the treatment of *Notoedres cati* in naturally infested cats. A total of

16 client owned cats (written consent) with notoedric mange were enrolled in this study; eight cats were initially assigned to the treatment group (treatment at day 0 (D0) with Advocate) and eight cats to the untreated control group. In a second phase 5 control animals were allocated to receive treatment on D30. The primary efficacy variable was the number of viable *N. cati* mites (total of adults, larvae and nymphs) counted after treatment on D28. The secondary efficacy criteria were the presence of viable and dead *N. cati* on study days D28 and D58 or on the day on which the cat was removed from the study. The possibility of spontaneous recovery was taken into account in the study design by acclimatizing the cats for an extended period prior to the start of the study. Study animals were acclimatized to the study site for at least four weeks prior to treatment (D0) during which time cats were kept in two separate environmentally controlled rooms. Then commencing on D0, treated cats were kept in individual cages for three days, and cats in the untreated control group were housed together in a separate room. No contact between cats in the treated and untreated groups was permitted throughout the duration of the study.

There was a good range of disease severity in both groups at the start of the study. Five cats remaining in the control group were still positive for mites at the end of the study on D28; therefore all of them were treated with Advocate. Thus the Advocate group eventually reached a total of 13 cats.

According to the EMA guideline on demonstration of efficacy of ectoparasiticides (7AE17a), the required overall efficacy for this type of product is more than 90%. The calculated primary efficacy in the study, including all animals at D28, was 72.2%. Two cats from the treated group died and were removed from the study (one with a severe infestation and purulent *E. coli* bronchitis resulting in death on D4, and the second with death due to feline infectious peritonitis on D25). In addition three cats from the untreated group were removed from the study (one died, but the pathology examination report missing, two were removed for animal welfare reasons because of severe clinical symptoms of notoedric mange and were then treated off-label with selamectin). After removal of these animals the calculated efficacy was 100% based on the primary efficacy variable. There was no relation between study treatment and withdrawal from the study in the treatment group. One animal in the untreated control group experienced a spontaneous clinical cure (characterised by its *Notoedres* spp. induced skin lesions score being reduced to zero) but was however still positive on the basis of mite counts. Therefore, on the basis of mite counts there was no evidence of self-cure in the control group.

Based on the severity of the infection and also on the potential clinical signs caused by this kind of mange, the low number of animals in the negative control group was justified. Efficacy in the treatment group was confirmed by the 100% mite count reduction which exceeds the guideline recommendations (other ectoparasites: 90%). Furthermore, the inclusion rate was low as the parasite does not occur frequently.

Taking into account that the disease may severely affect susceptible cats, and that no authorised treatment options currently exists, the CVMP considers the justification for the group sizes acceptable.

Although at least two dose confirmation trials and field trials in at least 2 different geographic and climatic regions should be conducted according to EMA guideline 7AE17a. While there had been no request for a MUMS classification for this indication by the applicant, the indication is rare and therefore the CVMP considered specifically whether the deviation from requirements could be acceptable. According to the CVMP's knowledge there are currently no authorised veterinary medicinal products against *Notoedres cati* available in the Community. The clinical disease can be severe and the parasite also has zoonotic potential. Therefore the CVMP considered that the use of only the one study could be acceptable in these particular circumstances.

In conclusion, the indication for the treatment of notoedric mange (*Notoedres cati)* in cats was considered justified.

Concerning target animal safety, Advocate might not prevent a serious lethal outcome of a very severe notoedric mite infestation by using only a miticidal compound as the clinical symptoms are often

aggravated by secondary bacterial infections. It is therefore advisable to also treat the clinical symptoms using concomitant supportive treatment. Therefore the following sentence is necessary to be added in section 4.5 of the SPC: "In certain individual cats *Notoedres cati* infestation may be severe. In these severe cases concomitant supportive treatment is necessary as treatment with the product alone may not be sufficient to prevent death of the animal."

Treatment of circulating microfilariae (Dirofilaria immitis) in dogs

The efficacy against *Dirofilaria immitis* circulating microfilariae was evaluated in two GCP laboratory dose confirmation studies.

Both laboratory studies were parallel group, randomised, masked, single site studies with a negative placebo control. All dogs participating in the studies were classified as either Class 1 or 2 for heartworm disease (animals with no, mild or moderate symptoms) prior to treatment because the study aim was to demonstrate efficacy without undue disease which would have caused significant welfare issues in the affected animals.

In both studies, mineral oil was used as a placebo to achieve masking. Mineral oil had been accepted as placebo in several different target animal safety studies in the original Advocate marketing authorisation dossier. Topical application of mineral oil to a dog imparts the same physical appearance at the application site as an equivalent volume of Advocate. Although Advocate does not contain oil, the solvent system for Advocate has nearly the same physical properties to mineral oil and displays very similar slightly oily "paint brush" appearances on the dog's hair at the site after application. Therefore mineral oil is acceptable as a placebo to achieve masking.

One study showed that dogs in the treated group had significantly fewer *D. immitis* microfilariae compared to dogs in the placebo group on both D42 ($p<0.0001$) and D28 ($p<0.0003$), both with a percentage efficacy of 99.9% respectively when compared to the placebo group.

In this study 10 pairs of adult *D. immitis* worms were implanted into each dog on D–82 prior to treatment with Advocate or placebo on D0 and D28. In the VICH guideline GL19 Efficacy of anthelmintics: specific recommendations for canines (CVMP/VICH/835/99) recommended times of treatment after infection with *D. immitis* are presented. The 82 day time period between implantation and treatment was chosen as it was considered a reasonable time period for recovery of the dogs from the intravenous implantation. This time period allowed the dogs to develop pre-treatment microfilaraemia that were high enough to give scientifically reliable data. Literature references and other information provided the basis for the time period chosen between implantation and treatment both concerning recovery of the dogs from surgery and for the establishment of a sufficiently high microfilarial count.

In this study the geometric means of *D. immitis* microfilaria counts were considerably higher in the placebo group compared to treated group before treatment on D–7 to D–5 (6,111.3, 5,182.8 and 8,078.9 compared to 4,574.7, 4,255.8 and 5,739.1 respectively). The model in the statistical analyses adjusted for the baseline (prior to treatment) microfilaria counts by utilizing an analysis of covariance on D28 and D42. The statistical model adjusted or accounted for baseline differences. The pre-treatment microfilaria count effects where included in the original statistical analysis when testing for treatment group differences. In addition, separate analyses were performed for microfilaria counts (log transformed) on D–7, D–6 and D–5 and the results indicate no statistically significant group differences for each of these days pre-treatment microfilaria counts (p-values of 0.2948, 0.4861 and 0.2015, respectively). Therefore it can be concluded that there were no statistically significant pre-treatment group differences.

A further study showed that microfilariae counts in the treated group were significantly lower on both D42 and D28 ($p>0.0001$) with reductions of 100% and 99.9% respectively when compared to the placebo group.

In both studies, all participating dogs were classified as either Class 1 or 2 for heartworm disease prior to treatment and the CVMP therefore considered that the results of these studies do not support the safety of use of the product in dogs with more severe disease. The proof of the safety of Advocate was examined in more severely diseased dogs in a third study.

A field study was conducted in a total of 247 client owned *D. immitis* naturally infected dogs presented as patients in veterinary practices in the US. In this study dogs with heartworm classification 1-3 were included and the safety of Advocate was proven also in class 3 dogs.

After exclusions for compliance issues, a total of 106 dogs were included in a group treated with Advocate on D0 and D28, and 108 dogs in a group treated with Advocate on D0 and D28 and adulticide on D−14 and D14. The efficacy of Advocate alone in reducing circulating *D. immitis* microfilariae counts was 98.8% on D28 and 99.2% on D42 when compared with pre-treatment levels; a similar efficacy was seen following treatment with Advocate plus adulticide where efficacy was 99.6% on D28 and 99.7% on D42.

There were two serious adverse events in the Advocate treated group. The first dog with Class 2 heartworm disease had clinical signs of dyspnoea and difficulty oxygenating and was treated accordingly, including supplemental oxygen for three days. The second dog with Class 1 heartworm disease was treated for pulmonary oedema, possible thromboembolism and bacterial infection and recovered following treatment. The investigator stated that first serious adverse event case was probably related to death of microfilariae following treatment with Advocate and the second serious adverse event was possibly related to treatment with Advocate, either related to the underlying condition (heartworm disease) or from thromboembolism secondary to death of adult heartworms or microfilaria.

Safety in Class 1 and 2 dogs had been shown in two laboratory studies. In the field study only 18 out 108 dogs treated with only Advocate were classified as having Class 3 heartworm disease. Eighteen dogs were considered as a small number to conclude on the safety of this product in Class 3 dogs. Most heartworm infected dogs in the field have class 1 or 2 infections. Class 3 and 4 dogs show obvious symptoms of heartworm disease. It is foreseen that practitioners cannot easily distinguish dogs classified as Class 3 from class 4 dogs. However, the classification between dogs in Classes 1 and 2, and on the other hand dogs in classes 3 and 4, might be more easily distinguished. The CVMP therefore agreed that the following changes to SPC section 4.3 (Contraindications) were necessary: "Do not use in dogs classified as Class 4 for heartworm disease as the safety of the product has not been evaluated in this animal group." and section 4.5 Special precautions for use: "The safety of the product has only been evaluated in dogs classified as either Class 1 or 2 for heartworm disease in laboratory studies and in few Class 3 dogs in a field study. Therefore the use in dogs with obvious or severe symptoms of the disease should be based on a careful benefit-risk assessment by the treating veterinarian".

The safety of the product in treatment of dogs suffering from heartworm disease was considered to warrant further risk management measures because of serious pulmonary adverse events described in the field study. The CVMP proposes to change SPC section 4.6 (Adverse reactions) as follows: "A field study has shown that in heartworm positive dogs with microfilaraemia there is a risk of severe respiratory signs (coughing, tachypnoea and dyspnoea) that may require prompt veterinary treatment. In the study these reactions were common (observed in 2 of 106 treated dogs). Gastrointestinal signs (vomiting, diarrhoea, inappetence) and lethargy are also common adverse reactions following treatment in such dogs."

The CVMP considered the proposed indication acceptable based on the presented studies and the applicant's responses with amendments as indicated in sections 4.3, 4.5 and 4.6 of the SPC.

Prevention of cutaneous dirofilariosis (L3 and L4 larvae of Dirofilaria repens) and elimination of circulating microfilariae (Dirofilaria repens) in dogs

The efficacy against experimental *Dirofilaria repens* infection was evaluated in a laboratory dose confirmation study and a field safety and efficacy study.

The dose confirmation study evaluated the efficacy of Advocate for the prevention of *Dirofilaria repens* infections in dogs. The study was a GCP, parallel group, randomised, masked, single site, laboratory dose confirmation study with a placebo control. A total of 16 dogs were allocated into two groups and treated on D0 with Advocate or placebo in the dorsal neck region, and then inoculated with approximately 75 infective *D. repens* L3 larvae by a single subcutaneous injection in the same dorsal neck region on D28.

The infection method was in accordance with the World Association for the Advancement of Veterinary Parasitology (W.A.A.V.P.) guidelines for evaluating the efficacy of anthelmintics for dogs and cats (Jacobs et al., 1994[1]) and VICH GL19, Efficacy of anthelmintics: specific recommendations for canines (CVMP/VICH/835/99) (Vercruysse et al., 2002[2]). In contrast to detailed requirements and recommendations for *Dirofilaria immitis* (W.A.A.V.P guideline and VICH GL19), no specific recommendations are available about the recommended inoculum for *D. repens* L3 larvae and how to conduct experimental infections. Experiences from published data were therefore used to identify the most reliable method for experimental infection. In both experimental studies (Cancrini et al., 1989[3] and Genchi et al., 2010[4]) found in the literature, adequate infections were obtained and in all untreated control animals adult *D. repens* could be identified. The number of L3 larvae per dog used for experimental infection was 75, and the justification provided for this level of infection was considered adequate by CVMP.

Application of both the challenge and treatment on the same site was considered. Skin biopsies would be an objective way of studying possible interaction between challenge and treatment on the same site, however such data were not provided. The spot-on formulation of Advocate had been specifically developed to guarantee the rapid distribution of imidacloprid over the whole body surface, and rapid systemic availability of the moxidectin by rapid absorption. Kinetic data produced using the final formulation show moxidectin levels in blood 1 hour post dermal dosing. Considering both the parenteral and topical administration routes, moxidectin is rapidly and completely absorbed from the site of administration and will be distributed throughout all body tissues, although the majority of the compound is in the fatty tissues (Löscher et al., 2002[5]). Given this rapid absorption behaviour, it is reasonable to assume that 28 days after dermal application of moxidectin no biologically relevant residues would be available at the application site. On the other hand, it has also been reported that the characteristics of moxidectin encourage more drug depot formation on the skin surface and in the *stratum corneum*. Flip flop kinetics are mentioned, where redistribution from the blood stream into fatty compartments results in building up reservoirs, e.g. in glands, hair follicles or basal cells. Thus it is very likely that the moxidectin in the topically applied Advocate formulation was rapidly and completely absorbed, circulated with the blood stream and redistributed into subcutaneous fat reservoirs over the whole body. In conclusion, it can be stated that no interaction effects could be expected between application of Advocate and the injection of the *D. repens* L3 larvae inoculum on the same site over the 28 days between treatment and the experimental infection.

The CVMP considered that the data presented is sufficient to assume that no interaction takes place over the 28 days between treatment and the experimental infection.

Results showed that a single topical spot-on treatment with Advocate at the recommended dose had a high

[1] Jacobs D.E., Arakawa A., Courtney C.H., Gemmell M.A., McCall J.W., Myers G.H., Vanparijs O., 1994. World Association for the Advancement of Veterinary Parasitology (W.A.A.V.P.) guidelines for evaluating the efficacy of anthelmintics for dogs and cats. Vet. Parasitol., Vol. 52, P. 179-202.

[2] Vercruysse J., Holdsworth P., Letonja T., Conder G., Hamamoto K., Okano K., Rehbein S., 2002. International harmonisation of anthelmintic efficacy guidelines (Part 2). Vet. Parasitol., Vol. 103, P. 277-297.

[3] Cancrini G., Tassi P., Coluzzi M., 1989. Ivermectin against larval stages of *Dirofilaria repens* in dogs. Parassitologia, Vol. 31(2–3), P. 177–182.

[4] Genchi M., Pengo G., Genchi C., 2010. Efficacy of moxidectin microsphere sustained release formulation for the prevention of subcutaneous filarial (*Dirofilaria repens*) infection in dogs. Vet. Parasitol., Vol. 170, P. 167–169.

[5] Löscher W., Ungemach F.R., Kroker R. Pharmakotherpie bei Haus- und Nutztieren, 1.1.5.1 Moxidectin, 5. Aufl., Parey Buchverlag, 2002; S. 265.

level of preventative efficacy against experimental infection with L3 larvae of *D. repens*. All control and treated dogs were negative on D–7 and all treated dogs remained negative at all-time points for the duration of the study, up to and including D238.

Total worm counts in the control group at necropsy were in range of 5 to 21 adult worms in 7 out of 8 dogs (one dog had only three adult *D. repens* worms). With these worm counts in the control group, the preventive efficacy of Advocate against *D. repens* could sufficiently be demonstrated.

In the dose confirmation study, only L3 larvae were used in the challenge while the original proposed indication was the prevention of cutaneous dirofilariosis (L3 and L4 larvae of *Dirofilaria repens*). The CVMP considered that this study design was suitable only to demonstrate the efficacy against the L3 larval stage of *D. repens*, and therefore the following indication was justified: "Prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*)."

The field safety and efficacy study evaluated the therapeutic and preventive efficacy and safety of Advocate spot-on against dirofilariosis caused by *Dirofilaria repens* in dogs living in an area with high prevalence. The study was a GCP, parallel group, randomised, masked, field safety and efficacy study with an untreated control. A total of 108 dogs were initially allocated into four groups: 18 *D. repens* positive treated dogs, 16 *D. repens* positive untreated dogs, 33 dogs *D. repens* negative treated dogs and 41 *D. repens* negative untreated dogs. The infection status was confirmed.

The primary efficacy criterion for the *D. repens* positive treated group was reduction in the count of *D. repens* microfilaria in the blood samples of the treated *D. repens* positive group vs. the untreated group. The range of *D. repens* microfilaria counts at baseline was considerable (Advocate group: from 2 to 15,550, and untreated control group: from 3 to 8,939) and the data on microfilaria counts were not normally distributed, but right skewed and peaked. The analysis on the basis of log-transformed data, adjusting for baseline values, did not provide confirmatory evidence for demonstrating efficacy and the need for log-transformations in order to normalise the data was questioned in the context of non-parametric analysis, in which normality is not a necessary assumption. However, supplementary analysis of the primary efficacy criterion, based on log-transformed data, supports the efficacy in respect of the reduction of microfilarial counts.

The secondary efficacy criterion was the percentage of animals not testing positive for *D. repens* microfilaria between D28 and D112. From D56 onwards, all animals in the treatment group T01a (*D. repens* positive; Advocate treated) were negative for *D. repens*, whereas in the control group T03 (*D. repens* positive; untreated), the percentages of dogs testing positive for *D. repens* on D28, D56, D84 and D112 was 93.75%, 93.75%, 92.86% and 85.71% respectively. The differences in percentages were found to be statistically significant at each time point. Taking into account the fact that six dogs in treatment group T01a (*D. repens* positive; Advocate treated) only received their first treatment with Advocate on D28 and then tested negative for *D. repens* on D56, all animals treated with Advocate were shown to be *D. repens* negative after a single treatment with the product.

Based on the data presented, the CVMP considered that the initially proposed indication for elimination of circulating microfilariae was not acceptable, however the results show that treatment with Advocate reduces the number of *D. repens* microfilaria in the blood samples of infected dogs. From day 56 onwards there were no *D. repens* microfilaria positive animals in the Advocate group. However, considering that the follow-up period after last treatment was limited (112 days) and that the product has not been shown to have an adulticidal effect against *D. repens,* it is likely that female worms in infected dogs could continue to produce microfilariae after treatment is discontinued.

Therefore the CVMP only accepted the indication for reduction of circulating microfilariae, and the following two additional amendments were made to SPC to make it clear that the product is not efficacious against adult *D. repens* worms:

- Indication (section 4.2): "The reduction of circulating microfilariae (*Dirofilaria repens*)."
- Administration instructions (section 4.9): "The product is administered monthly for four consecutive months. Efficacy against adult worms has not been shown. Adult worms may continue to produce microfilariae."
- Special warnings (section 4.4): "The product has not been shown to have an adulticidal effect against *D. repens*."

In the field safety and efficacy study, multiple dogs from one household could be allocated to either the treatment or the prevention group if all were infested, or free of clinical signs, respectively. The CVMP considered it had been satisfactorily demonstrated that no significant household effect on the microfilaria counts on D0, D28 and D56 exist, and thus no cluster effect can be seen.

The prevention and the treatment of spirocercosis (Spirocerca lupi) in dogs

The efficacy against experimental *Spirocerca lupi* was evaluated in a GCP, parallel group, randomized, single site, laboratory efficacy study using an untreated control group and conducted in three phases.

According to the VICH guideline GL19 Efficacy of anthelmintics: specific recommendations for canines (CVMP/VICH/835/99), two dose confirmation studies should be included in the data for such an indication to be approved.

The laboratory study was conducted in a total of 24 dogs. The study location was in South Africa. Blinding was applied only for parasite recovery assessments during necropsy. Eight dogs were initially allocated to the untreated control group, 8 dogs to a group treated monthly and 8 dogs to a group treated weekly as of D–28. On D2 and D14, D28 and D42 (±2 days) each dog was infected with approximately 10 *S. lupi* L3 larvae. The primary numerical assessment for statistical analysis was the number of worms recovered at necropsy in the groups treated with Advocate compared to the untreated control group. Statistical analysis confirmed that significantly fewer *S. lupi* worms were recovered from groups treated monthly and weekly compared to the untreated control dogs ($P < 0.0001$), whereas there was no statistically significant difference between the treated groups.

In addition to the single laboratory study, a published field study report was submitted. The objective of this study was to evaluate the preventive efficacy of a monthly treatment with Advocate administered over a period of 9 months, in young dogs naturally exposed to *S. lupi*. The study investigated the presence of eggs of *S. lupi* in the faeces and the endoscopic detection of gastroesophageal nodules, as well as the possible occurrence of typical clinical signs in dogs. At the end of the study, 57 of 58 dogs in the treated group (98.3%) were *Spirocerca* spp. free according to evaluated parameters whereas only 35 of 54 dogs in untreated group (64.8%) were free. One treated dog was diagnosed with spirocercosis (nodule) however this dog lived close to a river and had very regular swims/baths, so that the 24 hour period without a bath post-treatment could not be respected. This was considered to have a negative impact on the efficacy of the treatment. The CVMP considered this field study to be supportive of the preventive efficacy of a monthly Advocate treatment against *S. lupi*. The evaluation parameters (faecal egg count and endoscopy) in a field study are not as sensitive as study methods that can be used in laboratory studies (e.g. post-mortem examination).

According to the CVMP's knowledge there are currently no EU authorised products against *S. lupi* on the market, and it is acknowledged that the clinical disease can be severe. The omission of a second dose confirmation study was therefore considered adequately justified by the CVMP, given the lack of established treatment options for this disease and in the interest of animal welfare (principles for Replacement, Reduction and Refinement (3Rs) for conducting scientific experiments using animals).

According to VICH guideline GL7 Efficacy of anthelmintics: general requirements (CVMP/VICH/832/99) at least one of the dose confirmation studies should be conducted in the geographic location where

authorisation is being pursued.

The laboratory study submitted was conducted in South Africa. There is no evidence from literature that there is any geographical difference in either genotype of *S. lupi* or susceptibility to moxidectin. Intensive literature searches did not result in any publications describing differences between *S. lupi* found in Europe or South Africa or other regions of the world. Therefore it can be assumed that there is no difference in the genotype between European and South African *S. lupi*. To the CVMP's knowledge there are currently no known morphological, life cycle, epidemiological or pathogenic characters that would be sufficiently different to merit the nomination of different *S. lupi* strains from different geographical regions. The CVMP therefore does not expect relevant differences in the efficacy of Advocate against *S. lupi* originating from South Africa and Europe and thus considers the efficacy data generated in South Africa can be extrapolated to Europe and can thus be considered acceptable.

The CVMP considers the indication for prevention of spirocercosis acceptable based on the presented studies and the information provided, also taking into account 3Rs principles to justify the reduced data requirements.

The proposed posology for treatment of *S. lupi* is different from the posology for all other indications. The proposed posology for treatment of *S. lupi* is once a week, whereas the posology for all the other indications is once a month. Indications formulated as 'mixed infection' should all be treated with the same posology, i.e., posologies for the different components of a 'mixed infection' cannot differ from each other. As a weekly dosing has not been accepted for the other indications, the treatment of *S. lupi* cannot be part of a 'mixed infection' formulated indication. According to CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) every active substance in a fixed combination should be indicated for use at the moment of treatment and administered in the correct dose.

It is acknowledged that Advocate has been approved for use in severe cases and at the discretion of the veterinarian once a week and for a prolonged time to treat *Demodex* spp. infections and hence tolerance of the combination at weekly intervals has been considered acceptable. The CVMP considered whether the use of Advocate to treat spirocercosis could be justified on the basis of the severity of infection and the absence of alternative treatments.

However, as the efficacy of imidacloprid in the treatment of *S. lupi* infections had not been shown, and as this indication cannot be mentioned in section 4.2 as part of a mixed infection (due to a different treatment posology), the CVMP concluded that the indication for treatment of spirocercosis (*Spirocerca lupi*) had not been sufficiently justified and should be rejected.

In conclusion, the CVMP considered the indication for prevention of spirocercosis (*Spirocerca lupi*) in dogs acceptable based on the presented studies and the information provided, also taking into account 3Rs principles to justify the reduced data requirements.

In summary, the CVMP concluded that the following new indications for Advocate had been justified:

- the treatment of notoedric mange (*Notoedres cati*) in cats
- the treatment of circulating microfilariae (*Dirofilaria immitis*) in dogs
- the prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*) in dogs
- the reduction of circulating microfilariae (*Dirofilaria repens*) in dogs
- the prevention of spirocercosis (*Spirocerca lupi*) in dogs.

3. Benefit-risk assessment

3.1. Benefit assessment

The product was considered effective for the treatment of notoedric mange (*Notoedres cati*) in cats on the basis of one laboratory dose confirmation study also taking into account the rare occurrence of the disease and the lack of available treatments.

The product was considered effective for treatment of circulating *Dirofilaria immitis* microfilariae in dogs on the basis of two GCP laboratory dose confirmation studies and a field safety and efficacy study.

The product was considered effective for reduction of circulating *Dirofilaria repens* microfilariae in dogs on the basis of a laboratory dose confirmation study and a field safety and efficacy study.

The product was also considered effective for the prevention of spirocercosis (*Spirocerca lupi)* based on a laboratory efficacy study and a published field study. The CVMP took into account the rare occurrence of this disease and the principles for Replacement, Reduction and Refinement (3Rs) for conducting scientific experiments using animals in the justification for the reduced data requirements for this indication.

3.2. Risk assessment

The product has previously been shown to be safe in regards of treatment intervals and dosing of the product.

Concerning target animal safety, the presented studies indicate an increased risk of serious pulmonary adverse events in dogs suffering from heartworm disease (*Dirofilaria immitis*). Treatment with Advocate only might not prevent a serious lethal outcome of a very severe notoedric mite infestation in cats with concomitant secondary bacterial infections.

No changes to user safety or environmental safety are afforded by this variation.

3.3. Evaluation of the benefit-risk balance

The CVMP considers that the overall benefit-risk balance remains favourable when used as recommended in the SPC.

No change to the impact on the environment is envisaged due to this variation.

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.

The CVMP also recommends updating the SPC and appropriate parts of the product information as follows:

1. Section 4.2:

- the treatment of notoedric mange (*Notoedres cati*) – in cats
- the treatment of circulating microfilariae (*Dirofilaria immitis*) – in dogs
- the prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*) – in dogs

• the reduction of circulating microfilariae (*Dirofilaria repens*) – in dogs

• the prevention of spirocercosis (*Spirocerca lupi*) – in dogs

2. Section 4.3:

Do not use in dogs classified as Class 4 for heartworm disease as the safety of the product has not been evaluated in this animal group. – in dogs

3. Section 4.4:

To add: Therefore, the use of this product should be based on the assessment of each individual case and on local epidemiological information about the current susceptibility of the target species in order to limit the possibility of a future selection for resistance.

The use of the product should be based on the confirmed diagnosis of mixed infection (or risk of infection, where prevention applies) at the same time (see also sections 4.2 and 4.9). – in cats and dogs

To add: The product has not been shown to have an adulticidal effect against *D. repens*. – in dogs

4. Section 4.5:

To add: In certain individual cats *Notoedres cati* infestation may be severe. In these severe cases concomitant supportive treatment is necessary as treatment with the product alone may not be sufficient to prevent death of the animal. – in cats

The safety of the product has only been evaluated in dogs classified as either Class 1 or 2 for heartworm disease in laboratory studies and in few Class 3 dogs in a field study. Therefore the use in dogs with obvious or severe symptoms of the disease should be based on a careful benefit-risk assessment by the treating veterinarian. – in dogs

To add: At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. The safety of Advocate has not been evaluated when administered on the same day as an adulticide. – in dogs

5. Section 4.6:

To add: A field study has shown that in heartworm positive dogs with microfilaraemia there is a risk of severe respiratory signs (coughing, tachypnoea and dyspnoea) that may require prompt veterinary treatment. In the study these reactions were common (seen in 2 of 106 treated dogs). Gastrointestinal signs (vomiting, diarrhoea, inappetence) and lethargy are also common adverse reactions following treatment in such dogs. – in dogs

6. Section 4.8:

To add: Safety of Advocate when administered on the same day as an adulticide to remove adult heartworms has not been evaluated. – in dogs

7. Section 4.9:

To update: The treatment schedule should be based on individual veterinary diagnosis and on the local epidemiological situation. – in cats

To add: Treatment of notoedric mange (*Notoedres cati*)

A single dose of the product should be administered. – in cats

To update: The treatment schedule should be based on individual veterinary diagnosis and on the local epidemiological situation. – in dogs

To add regarding microfilariae: Treatment of microfilariae (*D. immitis*)

Advocate should be administered monthly for two consecutive months.

Reduction of microfilariae (*D. repens*)

The product should be administered monthly for four consecutive months. Efficacy against adult worms has not been shown. Adult worms may continue to produce microfilariae. – in dogs

To add: Prevention of *Spirocerca lupi*:

The product should be administered monthly. – in dogs

4.1. Changes to the community marketing authorisation

Changes are required in the following annexes of the Community marketing authorisation:

- Annexes I, IIIA and IIIB.