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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Trifexis
Type II variation (EMEA/V/C/002635/II/0008)

International non-proprietary name: spinosad / milbemycin oxime

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, Eli Lilly and Company Limited (the applicant), submitted to the European Medicines Agency (the Agency) an application for a type II variation for Trifexis.

1.1.1. Scope of the variation

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

This variation is to add angiostrongylosis as an indication and to update the dosing scheme to allow prevention.

Current	**Proposed**
SPC Text changes: **4.2 Indications for use, specifying the target species** For the treatment and prevention of flea (*Ctenocephalides felis*) infestations in dogs when the concurrent prevention of heartworm disease (L3, L4 *Dirofilaria immitis*),..... . **4.4 Special warnings for each target species** Maintenance of the efficacy of macrocyclic lactones is critical for Dirofilaria immitis control, therefore, to minimise the risk of resistance selection, it is recommended that dogs should be checked for both circulating antigens and blood microfilariae at the beginning of each season of preventative treatment. **4.9 Amounts to be administered and administration route** **Method of administration:** .....Based on the local epidemiological situation, the veterinary medicinal product may be given at monthly intervals throughout the season at the recommended dose as outlined below. This combination product (Trifexis) must, however,	**SPC Text changes:** **4.2 Indications for use, specifying the target species** For the treatment and prevention of flea (*Ctenocephalides felis*) infestations in dogs when the concurrent prevention of heartworm disease (L3, L4 *Dirofilaria immitis*), **prevention of angiostrongylosis (immature adult stages (L5) of *Angiostrongylus vasorum*)** ……. **4.4 Special warnings for each target species** Maintenance of the efficacy of macrocyclic lactones is critical for Dirofilaria immitis control, therefore, to minimise the risk of resistance selection, it is recommended that dogs should be checked for both circulating antigens and blood microfilariae at the beginning of each season **.** **4.9 Amounts to be administered and administration route** **Method of administration:** .....Based on the local epidemiological situation, the veterinary medicinal product may be given at monthly intervals throughout the season at the recommended dose as outlined below. ~~This combination product (Trifexis) must, however, not be given for more than 6 consecutive months~~

not be given for more than 6 consecutive months in any one year. Dogs living in heartworm endemic areas: (…..) It is recommended that heartworm prevention treatment should be continued at regular monthly intervals until at least 1 month after the last exposure to mosquitoes, but not for more than 6 consecutive months using Trifexis in any one year. (…..) Heartworm prevention treatment should be continued monthly, with the last administration being given one month after the dog has left the region, but not for more than 6 consecutive months using Trifexis in any one year.	~~in any one year.~~ Dogs living in heartworm endemic areas: (…..) It is recommended that heartworm prevention treatment should be continued at regular monthly intervals until at least 1 month after the last exposure to mosquitoes. ~~, but not for more than 6 consecutive months using Trifexis in any one year.~~ (……) Heartworm prevention treatment should be continued monthly, with the last administration being given one month after the dog has left the region. ~~but not for more than 6 consecutive months using Trifexis in any one year.~~ **Dogs living in lungworm endemic areas:** **In endemic areas regular monthly administration will prevent angiostrongylosis and patent infections with Angiostrongylus vasorum.**
5.2 Pharmacokinetic particulars Monthly repeated oral administration of spinosad and milbemycin oxime over six months revealed evidence of spinosad and milbemycin oxime accumulation in juvenile dogs. Accumulation cannot be discounted in adult dogs. In juvenile dogs, repeated oral administration of spinosad and milbemycin oxime over six months resulted in the trough plasma concentrations of spinosad and milbemycin increasing throughout the study. Trough concentrations of spinosad doubled monthly up to month 5. The increase in plasma concentrations was strongly correlated with an increase in terminal elimination half-lives.	**5.2 Pharmacokinetic particulars** *This section has been updated to reflect the results of a new chronic PK study.* Monthly repeated oral administration of spinosad and milbemycin oxime over six months revealed evidence of spinosad and milbemycin oxime accumulation in juvenile dogs. ~~Accumulation cannot be discounted in adult dogs.~~ In juvenile dogs, repeated oral administration of spinosad and milbemycin oxime over six months resulted in the trough plasma concentrations of spinosad and milbemycin increasing throughout the study. Trough concentrations of spinosad doubled monthly up to month 5. The increase in plasma concentrations was strongly correlated with an increase in terminal elimination half-lives. **In another study, after repeated oral**

	administration of 70 mg spinosad and 1.18 mg milbemycin oxime/kg bodyweight to fed juvenile dogs for thirteen months, steady state for systemic exposure (AUC) was reached by month 7. At this time, the systemic exposure (AUC) in juveniles was comparable to adults. Cmax was comparable between juveniles and adults starting at month 1, indicating no increased risk of acute toxicity
(….) Sufficient data on the Cmax or AUC following repeated oral administration are not available beyond three months of treatment.	(….) ~~Sufficient data on the Cmax or AUC following repeated oral administration are not available beyond three months of treatment.~~ **In another study, after repeated oral administration of 70 mg spinosad and 1.18 mg milbemycin oxime/kg bodyweight to fed juvenile dogs for thirteen months, steady state for systemic exposure (AUC) was reached in month 1 for milbemycin oxime and month 3 for spinosad.**

2. Scientific discussion

The treatment regimen of Trifexis® is in the range of 45-70 mg/kg spinosad and 0.75-1.18 mg/kg milbemycin oxime, which may be given monthly for a maximum of six consecutive months in any one year. The scope of this variation is to delete the restriction in treatment duration and to add a new indication regarding the prevention of angiostrongylosis.

Data on pharmacokinetics and target animal safety

The restriction to a maximum treatment duration of six consecutive months within any one year was based on the data provided with the original dossier. Data showed that repeated administration of the combination resulted in accumulation of both, spinosyns and milbemycin oximes, in blood plasma of juvenile dogs and also of adult dogs without reaching steady state within 6 months. The target animal safety study thus ended before steady state was reached. Field safety data following consecutive dosing was available for six months, with a maximum of the medium label dose, only. In consequence, a reliable margin of safety could not be derived for a treatment duration beyond this time.

A GLP-compliant pharmacokinetic study (PC27), also addressing target animal safety parameters, and a mostly GCP-compliant field safety study (PC28), each lasting one year were provided to support the monthly treatment over an infinite period of time.

In study PC27, 36 beagle dogs were randomized in 3 groups of 12 dogs (6 males, 6 females) per group. The control animals were 12 juveniles treated with a placebo (lactose monohydrate). Two groups (12 juveniles and 12 adults) were treated with capsules individually prepared according to the dog's bodyweight to ensure dosing at the maximum recommended dose of Trifexis (70 mg spinosad/kg

b.w. and 1.18 mg milbemycin oxime/kg b.w.). Capsules were administered every four weeks for thirteen treatment rounds (12 months). The study was not blinded and partly randomized.

The evaluated target animal safety parameters were clinical and ophthalmic examinations, records of body weights and food consumption, clinical pathology including hematology and serum chemistry and pharmacokinetics parameters. After study termination, the animals returned to the research facility's colony.

Pharmacokinetic data generated in this study demonstrate that steady state for systemic exposure (AUC) was reached around month three in adult dogs and around month seven in juveniles. Data reveal that the accumulation effect is likely due to increasing half-life ($T_{1/2}$), confirming the results of studies in the initial file. After the first dose, exposure (AUC_{last}) was approx. 1.5-1.7-fold higher in adult dogs than in juvenile dogs for all analytes. Milbemycin A_3 and A_4 5-oximes exposure remained about 15%-50% higher in adult than in juvenile dogs through month 6 of dosing and about 10% thereafter. Observations for spinosyns A and D were similar.

Accumulation ratios were calculated using the formula $AUC_{last\ (month\ 2\text{-}13)}$ / $AUC_{last\ (month\ 1}$). In juvenile dogs, mean accumulation ratios for milbemycin A_3 and A_4 5-oximes were approx. 1.7-2.3; mean accumulation ratios for spinosyns A and D were approx. 2.1 to 2.6, both indicating a slight accumulation after 13 monthly doses. In general, steady state for all analytes was reached by the seventh cycle in juveniles, as indicated by no further notable changes in the accumulation ratios as well as reaching comparable exposure to adults. In adult dogs, mean accumulation ratios for all analytes were approx. 1.1-1.6 in month 13, indicating a negligible accumulation after 13 monthly doses. Steady state was reached by the third dosing cycle, as indicated by no further notable changes in accumulation ratios.

No serious adverse events occurred. The rate of adverse events was low, and events (emesis containing food, salivation, decreased defecation, diarrhea and mucoid faeces) were mild in nature. Furthermore, liver enzymes (Gamma glutamyl-transferase (GGT), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP)), slightly increased from the second half of the study in adult animals. This increase of liver enzymes cannot be interpreted in the absence of an adult control group and post mortem data. In addition, haemoglobin distribution width (HDW) was increased in the test article-treated adult male and female groups at study weeks 47 and 51, without detected related changes in hematology, e.g. reticulocytes. It has however to be noted that the most relevant parameter, erythrocyte morphology, was not assessed.

Overall, the study demonstrated that 70 mg spinosad/kg b.w. and 1.18 mg milbemycin oxime/kg b.w. administered in a capsule are clinically well tolerated by juvenile and adult beagle dogs of both sexes when given over 12 consecutive months, including several months of treatment in steady state. No clinical adverse events apart from those already known occurred. The observed increase in liver enzymes lacked clinical correlation. However, it is to be noted that no overdoses data and no post mortem examinations were included, therefore, a no-observed-adverse-effect-level (NOAEL), and, in consequence, a reliable margin of safety cannot be derived after steady state is achieved in dogs for a time sufficiently long to allow for conclusions on infinite treatment. Additionally, the study was not blinded and there was no adult control group. It weakens the relevance of the study that bioequivalence of the capsules used with the commercial Trifexis tablets has not been confirmed, since the lower confidence limit of the capsule/tablet ratio for Milbemycin A4, the main component of milbemycin-5- oxime was clearly below 80%. Study PC12, a non-GLP study presented with the original dossier, compared capsules to tablets but was not sufficiently powered to demonstrate bioequivalence of the formulation with the consequence that the upper confidence limits in some pairwise comparisons nearly reached 200%, while lower confidence limits went down close to 50%.

The second study, PC28, is a GCP multicenter, controlled, randomized field safety study which had been conducted in 20 study sites in Hungary and Spain. 210 dogs received Trifexis tablets (158 of these were treated over twelve months within the dose band according to label, being the evaluable case population), and 212 the comparator product, a fixed combination of milbemycin oxime and praziquantel (evaluable case population: 153 dogs). The feeding status of the dogs as required by the label for optimized bioavailability was not strictly followed. Dogs were observed by the owner for adverse events. A monthly clinical examination was performed by a veterinarian. In addition, laboratory parameters were evaluated at approximately 90, 180 and 270 days post-treatment. No adverse events other than those known for Trifexis treatment were reported. However, the study shows considerable flaws with respect to the conduct of the study and data generation regarding clinical adverse events as well as clinical chemistry/haematology, impairing the assessment of the study. Data are not fully reliable, and thus, final conclusions cannot be drawn, especially, but not limited to, neurological and ophthalmological events or slight laboratory changes in, e.g. liver enzymes. The study is rated as for information, only. It has to be kept in mind that irrespective of the validity of this study, field studies in general are not suitable to establish a margin of safety.

In a post marketing study with more than 16.000 Trifexis treated dogs, no related events were detected. This supports the target animal safety of the currently authorized posology. As the vast majority of dogs was treated once or twice, less than 1% were treated for six months, and no dog exceeded six months treatment, this result does not allow for conclusions on treatments beyond 6 months.

In conclusion, for a treatment duration exceeding six months, no overdose data of dogs generated fully in line with VICH GL 43, are available, since they do not cover a period of six months in steady state. Data provided do thus not allow the establishment of a NOAEL at maximum exposure following overdoses in support of infinite treatment. In consequence, a calculation of a margin of safety is not possible.

Changes in laboratory parameters (liver enzymes, haemoglobin distribution width) were observed after six months of continuous treatment, but their relevance in infinite treatment cannot be interpreted due to a lack of data. This is of of special concern with regard to the field population, which is heterogeneous and may include animals that are more susceptible to these kinds of events than the healthy beagle dogs tested. The SPC informs the user about the changes in laboratory parameters which were observed in study PC27.

Clinical part:

In order to support the new indication "prevention of angiostrongylosis (immature adult stages (L5) of *Angiostrongylus vasorum*)" the applicant provided three GCP compliant experimental dose confirmation studies in dogs. These studies were well designed and conducted in line with the relevant VICH anthelmintic guidelines. Trifexis was orally administered to dogs at the lower range of the recommended oral dose range of 0.75-1.18 mg/kg milbemycin oxime and 45-70 mg/kg spinosad on 30 days after artificial infection with L3 larvae of European field isolates of the lungworm *Angiostrongylus vasorum*. The challenge infection failed substantially in one study (CS3) resulting in only 3 out of 8 control dogs which were infected with more than 5 lungworms at necropsy. The number of adequately infected animals was lower than requested as per VICH guideline 19 (efficacy of anthelmintics: specific recommendations for canines) at least 5 worms per control animal is considered adequate. Therefore, the efficacy result of this study (42% only) is not considered any further. It is, however, noted that adult worms were found in 5 out of 8 treated dogs, and apparently 2 treated dogs shed larvae after treatment.

In two dose confirmation studies (CS1 and CS2) lungworm isolates of different European origin (Denmark and Switzerland) were used. Both were below the age of 10 years at each study beginning which is considered acceptable.

In the first study (CS1) the reduction of lungworm burden in the treated group (immature L5 of *Angiostrongylus vasorum*) is 98.8% based on geometric mean 30 days after treatment (i.e. 60 days after inoculation of L3 larvae). In the second study (CS2) the lungworm reduction was 88.7% compared to controls, i.e. slightly below the given threshold of 90% according to the VICH guideline 7 (efficacy requirements for anthelmintics: overall guidelines) and the VICH guideline 19; and some of the treated dogs still shed larvae of *A. vasorum* on a low level after single treatment. The combined efficacy of both studies, however, was reported to be 95.1% (based on geometric means) with a statistically significant difference between the control and treatment groups ($p<0.0001$). Such pooling of the data is considered acceptable since both studies have a comparable study protocol, used the same number of dogs per group (n=8), and nearly the same number of L3 larvae of *A. vasorum* (250 and 266 L3) for the experimental inoculation.

No field studies have been provided to confirm the efficacy of the product under field conditions. This is considered acceptable given the low prevalence of natural infection with *A. vasorum*.

In summary, a single treatment dose of Trifexis reduces but do not fully prevent clinical manifestations of angiostrongylosis which is most likely due to its exclusive activity against the late premature adult lungworm stages, and only when the migrating L5 larvae have reached their final predilection site in the heart and lung vessels. Based on the data provided the following indication is considered justified: "prevention of angiostrongylosis by reducing the level of infection with immature adult (L5) *Angiostrongylus vasorum*".

In addition, further advice is added in section 4.9 of the SPC specifying the conditions for reasonable treatment of dogs living in lungworm endemic areas.

3. Benefit-risk assessment

3.1. Benefit assessment

This is a variation to introduce the new indication "prevention of angiostrongylosis (immature adult stages (L5) of *Angiostrongylus vasorum*)" and to extend the treatment duration from 6 month to lifelong monthly treatments.

Three GCP compliant controlled clinical studies were submitted in support of the prevention of angiostrongylosis claim. Data demonstrate a significant reduction of the level of infection (>90% on average) with immature adult (L5) of *A. vasorum* following single administration of Trifexis at the recommended treatment dose, thereby preventing clinical signs of angiostrongylosis in treated dogs. Appropriate advice for the treatment of dogs living in lungworm endemic areas is provided.

3.2. Risk assessment

The extension of treatment duration from the currently approved six consecutive months in any one year to a potentially infinite treatment calls for an assessment of target animal safety beyond the currently approved time. From the data presented it is not possible to derive a margin of safety for long-term treatment in dogs. Additionally, concerns regarding a potential hepatopathic effect of long-term treatment with Trifexis, as well as an influence on red blood cell parameters could not be ruled out.

3.3. Evaluation of the benefit-risk balance

The new indication "prevention of angiostrongylosis by reducing the level of infection of immature adult (L5) *A. vasorum*" has been sufficiently substantiated by data.

The product has not been shown to have a positive benefit-risk balance with regard to extended (potentially lifelong) treatment. Sufficient information on accumulation and steady state is provided. However, the safety of an infinite treatment is not sufficiently characterised, since, due to a lack of sufficient overdose data, a margin of safety still cannot be derived for a duration of treatment beyond six months. Furthermore, concerns on potential hepatopathic effects or influence on red blood cell parameters in long-term treatment with Trifexis could not be ruled out. The benefit-risk balance regarding the extension of the maximum treatment duration is negative.

No change of the risk for the user or for the environment is envisaged from this variation application.

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 partly approvable. The new indication prevention of angiostrongylosis has been sufficiently proven by data, but the safety of an extended (potentially life long administration of the products was not sufficiently substantiated by data. Therefore, the treatment duration must be restricted to 6 months in any one year.

4.1. Changes to the Community marketing authorisation

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

I, IIIA and IIIB