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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for type II variation for NEXGARD SPECTRA (EMEA/V/C/003842/II/0019)

INN: afoxolaner / milbemycin oxime

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

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1. Introduction

1.1. Submission of the variation application

In accordance with Article 16 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, MERIAL (the applicant), submitted to the European Medicines Agency on 4 February 2019 an application for a type II variation for NEXGARD SPECTRA.

1.2. Scope of the variation

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

The variation is to add a new therapeutic indication: prevention of eyeworm disease (caused by *Thelazia callipaeda*).

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

Not applicable.

2. Scientific Overview

NEXGARD SPECTRA is currently indicated for the treatment of flea and tick infestations in dogs when the concurrent prevention of heartworm disease, angiostrongylosis and/or treatment of gastrointestinal nematode infestations is indicated; the product is also indicated for the treatment of demodicosis and sarcoptic mange. NEXGARD SPECTRA contains a fixed combination of afoxolaner (an insecticide and acaricide of the isoxazoline family) and milbemycin oxime (an antiparasitic endectocide belonging to the group of macrocyclic lactones) and is presented in five different strengths of chewable tablet.

The proposed variation is to add a new therapeutic indication: prevention of eyeworm disease (caused by *Thelazia callipaeda*).

For the newly proposed indication, the product is to be administered at the same dose rates as currently authorised, namely 2.50–5.36 mg afoxolaner/kg bodyweight and 0.50–1.07 mg milbemycin oxime/kg bodyweight administered monthly.

2.1. Safety (tolerance, user, environment)

No new preclinical or specific target animal safety studies have been conducted by the applicant in the context of this variation application. Given that the posology for the newly proposed indication does not

differ to that which has already been accepted for the existing target parasites, it can be accepted that no concerns in terms of target animal tolerance/safety are considered to arise.

Further, as the product will be administered to the same target species, using the same route of administration and at the same posology that has already been accepted by the CVMP, no concerns in terms of user safety are considered to arise; that is, the user will not be exposed to a greater amount of the active substances or to a greater frequency than that which has been assessed for the existing indications approved for the product. Additionally, no change to the impact on the environment is envisaged.

Therefore, it can be concluded that the introduction of the proposed indication will not present an unacceptable risk for the animal, user or the environment.

2.2. Justification of combination

Data to support the non-interaction between the two active substances in NEXGARD SPECTRA (afoxolaner and milbemycin oxime) was provided and evaluated by the CVMP in the procedure for the authorisation of NEXGARD SPECTRA (EMEA/V/C/003842). Concerning the acceptability of the newly proposed indication for this fixed combination product, it is noted that the applicant claims that the anthelmintic activity against *Thelazia callipaeda* is related to milbemycin oxime only.

Given that the product is to be indicated for the treatment of flea and tick infestations in dogs when concurrent prevention of thelaziosis is required, and on account of the occurrence of *Thelazia callipaeda* in Europe, the resulting clinical conditions arising from infection and the prevalence of the infection and the zoonotic potential, the rationale for the proposed new indication is acceptable and considered to be in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).

2.3. Efficacy data in support of the indication

To support the proposed indication for the prevention of eyeworm disease (caused by *Thelazia callipaeda*) in dogs, the applicant has presented the results of one field study conducted in naturally infected dogs. However, the applicant has not conducted dose confirmation studies and justified their omission due to the unavailability of a reliable model of *Thelazia callipaeda* infection. The justification for omission of dose confirmation studies can be accepted.

The GCP compliant field study investigated the preventive efficacy of multiple doses of the fixed combination product NEXGARD SPECTRA in the prevention of thelaziosis due to *Thelazia callipaeda* infection in client owned dogs presented as veterinary patients in Europe multiple study sites in two disparate geographical regions. The study can be considered sufficiently representative of the European situation, in terms of the geographical location, age, breed and gender of dogs.

The study covered the period during which transmission of *T. callipaeda* is known to occur and the study sites were either considered enzootic for *T. callipaeda* infection or autochthonous cases have been reported in the regions for several years. It is considered that an acceptable level of exposure to *T. callipaeda* was present during the conduct of the study.

An afoxolaner-containing product was used as a negative control and both NEXGARD SPECTRA (IVP) and the control product (CP) were administered as the final formulations at the recommended treatment dose at monthly intervals for 6 treatments.

Eighty-eight dogs were included in the safety population (IVP n=42 and CP n=46) and 79 dogs were included in the efficacy population for the assessment of the primary variable (IVP n=37 and CP n=42).

Both groups can be considered homogenous in terms of environment (indoors/outdoors) and exposure to natural infection.

For the purpose of confirming that none had pre-existing adult *T. callipaeda* infections at Day 0, all animals were examined for the presence of adult *T. callipaeda* by means of an ophthalmologic examination and were administered a milbemycin oxime-containing product administered per label for the treatment of *T. callipaeda* at pre-inclusion. Two dogs in the control group were suspected as having nematodes on Day 0 and were withdrawn from the efficacy analysis. Apart from these two dogs, 24 dogs in the negative control group (out of the 42 dogs in the negative control group that completed the study) were diagnosed with adult *T. callipaeda* infection during the study.

The primary variable for the assessment of efficacy was the proportion of dogs free of *T. callipaeda* worms at the end of the study in the IVP-treated group compared to the CP-treated group. A dog was considered positive as soon as *T. callipaeda* nematodes were recovered.

Based on the overall results from two disparate geographical regions, a statistically significant difference ($p \leq 0.0001$) was observed in the proportion of dogs remaining free of *T. callipaeda* worms; in the IVP-treated group, 37/37 (100%) of animals were found to be worm-free compared to 18/42 (42.9%) in the control-treated group at Day 180. Based on the results from one geographical region, a statistically significant difference ($p=0.0001$) in the proportion of dogs remaining free of *T. callipaeda* worms in the IVP-treated group (19/19: 100%) was observed compared to the control-treated group (9/20: 45%). Similarly, based on the results from the second geographical region, a statistically significant difference ($p \leq 0.0001$) in the proportion of dogs remaining free of *T. callipaeda* worms in the IVP-treated group (18/18: 100%) was observed compared to the control-treated group (9/22: 40.9%). Regarding safety, NEXGARD SPECTRA appears to have been well tolerated.

It is noted that the initially proposed indication was for the prevention of eyeworm disease (caused by *Thelazia callipaeda*). However, the results of this study suggest that NEXGARD SPECTRA administered at the recommended treatment dose at monthly intervals is safe and efficacious (100%) in prevention of the establishment of infection with *Thelazia callipaeda* adults under field conditions and therefore the indication is amended accordingly.

Whilst it is acknowledged that the relevant CVMP guidelines indicate that two dose-confirmation studies supported by field data should be provided to be granted a claim, given that the omission of dose confirmation studies is accepted on the grounds that no experimental infection model is currently available and the results from one GCP field study conducted in two different European locations indicate 100% efficacy in preventing the establishment of infection with *Thelazia callipaeda* adults and in consideration of the 'three Rs', the CVMP accepts the omission of a second study in this instance and accepts that an indication for the prevention of establishment of infection with adult *Thelazia callipaeda* with monthly administration has been adequately supported. Indeed, although the field data have been presented as one report, given the inclusion of multiple sites in two disparate geographical regions, the data generated is not dissimilar to two separate field studies having been conducted.

In conclusion, it can be accepted that the findings from this study support an indication for the prevention of the establishment of infection of adult *T. callipaeda.*

3. Benefit-risk assessment of the proposed change

NEXGARD SPECTRA is currently authorised for the treatment of flea (*Ctenocephalides felis* and *C. canis*) and tick (*Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus*) infestations in dogs when the concurrent prevention of heartworm disease (*Dirofilaria immitis* larvae), angiostrongylosis (reduction of the level of infection with immature adults (L5) and adults of *Angiostrongylus vasorum*) and/or

treatment of gastrointestinal nematode infestations (roundworms (*Toxocara canis* and *Toxascaris leonina*), hookworms (*Ancylostoma caninum*, *A. braziliense* and *A. ceylanicum*) and whipworm (*Trichuris vulpis*)) is indicated. The product is also indicated for the treatment of demodicosis (caused by *Demodex canis*) and sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*).

NEXGARD SPECTRA contains a fixed combination of afoxolaner, an insecticide and acaricide of the isoxazoline family, and milbemycin oxime, an antiparasitic endectocide belonging to the group of macrocyclic lactones. The product is presented in five different strengths of chewable tablet with afoxolaner and milbemycin oxime administered at a dose rate of 2.50-5.36 mg/kg bodyweight and 0.50-1.07 mg/kg bodyweight, respectively. The frequency of repeat administration is dependent upon the target parasite being treated and the local epidemiological situation.

The proposed variation is to add a new therapeutic indication: prevention of eyeworm disease (caused by *Thelazia callipaeda*). However, following evaluation of the data submitted, the CVMP agreed to the following indication: "prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection)".

3.1. Benefit assessment

As this is a variation to introduce an additional indication to an existing product, the benefit will arise from the inclusion of the new indication. The indication against adult *Thelazia callipaeda* is considered as being of benefit for the user/prescriber.

3.2. Risk assessment

As this is a variation to introduce an additional indication to an existing product, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indication.

Quality:

Quality remains unaffected by this variation.

Safety:

As the product will be administered to the same target species at the same dose rate and at the same frequency as already approved for existing indications, no new risk is considered to arise in terms of user safety, target animal tolerance, potential for resistance development or for the environment.

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 veterinary medicinal product.

No additional risk management or mitigation measures are considered necessary.

3.4. Evaluation of the benefit-risk balance

Given that it is not expected that any new risk will result from the inclusion of the additional indication considered approvable, it can be accepted that there should be an increased benefit from the use of the product for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection) in dogs.

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

The benefit-risk balance remains positive.

The product has been shown to be efficacious for the prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection).

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 NEXGARD SPECTRA can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows: to add a new therapeutic indication: prevention of establishment of thelaziosis (adult *Thelazia callipaeda* eyeworm infection).

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

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

I and IIIB.

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