EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

## Committee for Medicinal Products for Veterinary Use

# CVMP assessment report for worksharing type II variation for NexGard and NEXGARD SPECTRA (EMEA/V/C/WS1559)

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 20 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, MERIAL (the applicant), submitted to the European Medicines Agency on 29 January 2019 an application for a type II variation for NexGard and NEXGARD SPECTRA, following a worksharing procedure.

## *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: treatment of tick infestations (*Ixodes hexagonus*).

## *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 is currently indicated for use in dogs for the treatment of flea and tick infestations, as well as part of a treatment strategy for the control of flea allergy dermatitis, for the treatment of demodicosis and for the treatment of sarcoptic mange. The product contains the active substance afoxolaner (an insecticide and acaricide of the isoxazoline family) and is presented in four different strengths of chewable tablet.

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: treatment of tick infestations with *Ixodes hexagonus.*

For the newly proposed indication, the products are to be administered at the same dose rates as currently authorised, namely: 2.7-7 mg afoxolaner/kg bodyweight for NexGard and 2.50–5.36 mg afoxolaner/kg bodyweight and 0.50–1.07 mg milbemycin oxime/kg bodyweight for NEXGARD SPECTRA, administered monthly.

Acaricidal activity against *Ixodes hexagonus* is related to afoxolaner only and the absence of interaction between afoxolaner and milbemycin oxime has already been assessed by the CVMP within the context of the application for marketing authorisation for NEXGARD SPECTRA.

## 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 for both products, it can be accepted that no concerns in terms of target animal tolerance/safety are considered to arise.

Further, as the products will be administered to the same target species, using the same route of administration and at the same posology that have 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 for a greater frequency than that which has been assessed for the existing indications approved for the products. 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 the indication for the combination product NEXGARD SPECTRA

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 acaricidal activity against *Ixodes hexagonus* is related to afoxolaner only.

On account of the occurrence of *Ixodes hexagonus* in Europe, the resulting clinical conditions and the prevalence of the infection and the zoonotic potential, the rationale for the proposed new indication is considered acceptable and to satisfy the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).

## 2.3. Efficacy data in support of the indication

In support of the proposed indication for the treatment of tick infestations with *Ixodes hexagonus*, the applicant has provided the results of a single dose confirmatory study and has referred to the results of a field study that was previously submitted for the initial marketing authorisation for NEXGARD SPECTRA.

The GCP-compliant dose confirmation study investigated the efficacy of a single oral administration of afoxolaner alone (NexGard) or in combination with milbemycin oxime (NEXGARD SPECTRA) against induced infestations of *Ixodes hexagonus* on dogs. This was a blinded, randomised, negatively-controlled study conducted in Europe and live attached tick counts were used to calculate efficacy. Twenty-four dogs were randomly assigned into three groups and infested with approximately 50 ticks on Days -2, 7 and 28. Group 1 was the control group and did not receive treatment. Groups 2 and 3 were given a single oral dose of NexGard and NEXGARD SPECTRA respectively on Day 0. Tick counts were recorded on Days 2, 9 and 30 with the numbers of live attached, live free, dead attached and dead free ticks recorded. Efficacy was based upon a threshold of 90% reduction in tick counts for Groups 2 and 3 when compared to Group 1 using arithmetic mean counts.

The percent efficacy using arithmetic means of NexGard (Group 2) and NEXGARD SPECTRA (Group 3) compared to the untreated control group was 100% at all post-treatment counts (Days 2, 9 and 30), apart

from 96.7% for NexGard on Day 30. There were statistically significant differences of the arithmetic mean counts between each treated group and control group for all time points ($p<0.0001$). The overall efficacy for afoxolaner (NexGard and NEXGARD SPECTRA) was 100% on Days 2 and 9 and 98.1% on Day 30.

Based upon the findings from this study, it can be accepted that under laboratory conditions, both NexGard and NEXGARD SPECTRA administered at the recommended treatment dose demonstrated an acceptable level of efficacy (>90%) against the tick species *Ixodes hexagonus*.

The CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.3) recommends that for the demonstration of efficacy of ectoparasiticides two types of studies should be performed, laboratory studies and field studies. Reference has been made to the results of a field study that was provided with the original marketing authorisation application for NEXGARD SPECTRA. Taking into consideration the '3Rs', this is considered acceptable. Although only 6 dogs in that study were identified as being infested with *I. hexagonus* ticks (four treated with NEXGARD SPECTRA and two with the positive control product), it can be accepted that the findings of that study provide supporting evidence for efficacy of both products against *I. hexagonus* ticks under field conditions of use.

CVMP guidelines recommend that two dose confirmation studies are provided for each claim and that findings from dose confirmatory studies are supported by field data. Given that both NexGard and NEXGARD SPECTRA are already indicated for the treatment of *I. ricinus* ticks, and that the applicant has provided data indicating that *I. ricinus* and *I. hexagonus* have similar susceptibility to afoxolaner, the single dose confirmation study provided with this application and reference to the field study previously provided with the application for initial marketing authorisation for NEXGARD SPECTRA are considered adequate for the purpose of supporting the proposed indication against *I. hexagonus* ticks.

# 3. Benefit-risk assessment of the proposed change

The product NexGard contains the active substance afoxolaner (an insecticide and acaricide of the isoxazoline family). NexGard is currently indicated for use in dogs for the treatment of flea (*Ctenocephalides felis* and *Ctenocephalides canis*) and tick (*Dermacentor reticulatus, Ixodes ricinus* and *Rhipicephalus sanguineus*) infestations, as well as part of a treatment strategy for the control of flea allergy dermatitis (FAD), the treatment of demodicosis (caused by *Demodex canis)* and the treatment of sarcoptic mange (caused by *Sarcoptes scabei* var. *canis)*.

NexGard is presented in four different strengths of chewable tablet with afoxolaner administered at a dose of 2.7–7 mg/kg bodyweight. The frequency of repeat administration is at monthly intervals throughout the flea and/or tick seasons, based on the local epidemiological situation.

The product 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). NEXGARD SPECTRA is currently authorised for the treatment of flea (*Ctenocephalides felis* and *Ctenocephalides 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, Ancylostoma braziliense* and *Ancylostoma 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 scabei* var. *canis)*.

NEXGARD SPECTRA 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 and 0.5-1.07 mg/kg bodyweight,

respectively. The frequency of repeat administration is dependent upon the target parasite being treated and the local epidemiological situation.

Both NexGard and NEXGARD SPECTRA are currently indicated for use in dogs for the treatment of *Ixodes ricinus* infestations.

The proposed variation is to add a new therapeutic indication for another species of *Ixodes* tick (*Ixodes hexagonus*).

## *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 *Ixodes hexagonus* is considered as being of benefit for the user/prescriber as efficacy of the products is extended to cover another tick species.

## *3.2. Risk assessment*

As this is a variation to introduce an additional indication to existing products, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indication. Both NexGard and NEXGARD SPECTRA are currently indicated for use in dogs for the treatment of *Ixodes ricinus* infestations.

## Quality:

Quality remains unaffected by this variation.

## Safety:

As the products 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 these veterinary medicinal products.

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 treatment of tick infestations (*Ixodes hexagonus*) 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 treatment of tick infestations (*Ixodes hexagonus*).

# 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 and 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: treatment of tick infestations (*Ixodes hexagonus*).

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 products.

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

I and IIIB.

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