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Veterinary Medicines Division

# CVMP assessment report for a worksharing grouped type II variation for NEXGARD SPECTRA and NexGard (EMEA/V/C/WS1338/G)

International non-proprietary name: afoxolaner / milbemycin oxime; afoxolaner

**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 (the Agency) on 5 January 2018 an application for a grouped type II variation for NEXGARD SPECTRA and NexGard, following a worksharing procedure.

## *1.2. Scope of the variation*

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

To add three new therapeutic indications: for the treatment of demodicosis (caused by *Demodex canis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*) and ear mite infestation (*Otodectes cynotis*). With this procedure, product information of NexGard is aligned with the latest QRD template.

## *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

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 *C. 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). NexGard is presented in four different strengths of chewable tablet with afoxolaner administered at a dose of 2.7–6.9 mg/kg bodyweight. The frequency of repeat

administration is at monthly intervals throughout the flea and/or tick season, based on the local epidemiological situation.

The product NEXGARD SPECTRA contains a fixed combination of afoxolaner 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 *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, Ancylostoma braziliense* and *Ancylostoma ceylanicum*) and whipworm (*Trichuris vulpis*)) is indicated.

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 0.50-1.07 mg/kg, 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 three new therapeutic indications: for the treatment of demodicosis (caused by *Demodex canis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*) and ear mite infestation (*Otodectes cynotis*).

For both products, the following treatment regimens are proposed:

- Demodicosis: monthly administration until two negative skin scrapings are obtained one month apart;
- Sarcoptic mange: monthly administration for two consecutive months;
- Ear mite infestation (*Otodectes cynotis*): single administration with a second administration one month later if required (based upon clinical assessment).

## *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 indications does not differ to that which has been already accepted for the existing target parasites, it is expected 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. No change to the impact on the environment is envisaged.

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

## *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). In the six GCP efficacy studies provided in the current variation application, it is hypothesised that the acaricidal activity against mites is related to afoxolaner only and that afoxolaner keeps its full activity spectrum against ectoparasites as well as milbemycin oxime against nematodes. Furthermore, it is stated that the administration of 0.5 mg/kg bodyweight of milbemycin oxime once a month has not shown any efficacy for the control of *Demodex canis* (only daily administrations for an average of 3 months have an effect) and *Sarcoptes scabiei* (administration every two days for two to three weeks is required). Consequently, it is argued that the results of studies conducted with NexGard (afoxolaner) and assessing the efficacy of afoxolaner at its recommended dose (≥2.5 mg/kg bodyweight) can be extrapolated to NEXGARD SPECTRA. That said, NEXGARD SPECTRA was administered to control animals in some of the clinical studies for an additional direct demonstration with the fixed combination product.

Given that the CVMP accepted that the pharmacokinetic profile of afoxolaner is unchanged by the concomitant administration of milbemycin oxime in the procedure for the authorisation of NEXGARD SPECTRA (EMEA/V/C/003842), it is accepted that the approach whereby the results of studies conducted using NexGard and assessing the efficacy of afoxolaner at a dose rate of 2.50 to 5.36 mg/kg bodyweight can be extrapolated to NEXGARD SPECTRA.

On account of the occurrence of *D. canis, S. scabiei* var. *canis* and *O. cynotis* in Europe, the severity of resulting clinical conditions and the prevalence of the infection and/or the zoonotic potential, the CVMP considers the rationale for the three proposed new indications as acceptable and to be in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).

## *2.1. Treatment of demodicosis (caused by Demodex canis)*

The proposed indication against demodicosis is: "Treatment of demodicosis (caused by *Demodex canis*): Monthly administration of the product until two negative skin scrapings are obtained one month apart. Severe cases may require prolonged monthly treatments. As demodicosis is a multi-factorial disease, where possible, it is advisable to also treat any underlying disease appropriately."

In support of the above indication, the applicant has provided the results of two dose confirmatory studies and one field study.

The first GCP compliant dose confirmation study investigated the efficacy of the final formulation of NexGard when compared to Advocate against generalised demodicosis in naturally infested dogs in South Africa. This was a randomised, positively controlled laboratory study. It can be accepted that a positive control was utilised due to the potentially debilitating nature of the disease. Advocate, which is a topical combination of imidacloprid (10% w/v) and moxidectin (2.5% w/v), can be accepted as a valid reference product in that it is authorised in the Community with a claim for the treatment of *D. canis* in the dog. Study personnel performing assessments were blinded and it can be accepted that the design suitably allowed for adequate blinding.

The study recruited privately owned dogs which were kept under experimental homogeneous conditions. 16 mongrel dogs (7 males and 9 females, aged ⩾6 months, 4.48 to 15.13 kg bodyweight at inclusion) were ranked within sex in descending order of individual live mite count on Day -2±1 and subsequently blocked into eight blocks of two dogs each. Within blocks, dogs were randomly allocated to the two groups (8 dogs per group). The number of study animals is considered adequate. The dogs were healthy except for clinical signs and symptoms of generalised *Demodex canis* mite infestations. All dogs were adult (≥ 6 months) and all were assessed as having generalised demodicosis on the basis of clinical signs and mite counts confirmed from deep skin

scrapings prior to treatment. The inclusion criteria can be accepted as being appropriate and resulted in a study sample that is considered to be suitably representative of the target population.

NexGard and Advocate were administered to either the treatment group or the control group at the recommended treatment dose on Days 0, 14, 28, 56, and 84. The actual doses of afoxolaner (administered as NexGard) ranged between 2.83 to 6.67 mg/kg bodyweight, which is within the recommended treatment dose of NexGard (2.7–6.9 mg/kg bodyweight). However, it is noted that the upper end of the dose range of afoxolaner used in this study is higher than the recommended treatment dose of afoxolaner in NEXGARD SPECTRA (2.50–5.36 mg/kg bodyweight). The proposed interval between treatments is monthly administration of the product until two negative skin scrapings are obtained one month apart. However, in this study, NexGard was administered fortnightly on three consecutive occasions followed by a monthly treatment on two consecutive occasions.

Deep skin scrapings from 5 sites were taken throughout the study on Day -2±1 (to confirm the presence of *Demodex* spp. mites) and on Days 28, 56, 83 or 84, and 90. The clinical symptoms and the extent of demodectic lesions on each dog were assessed and overall changes in clinical appearance were illustrated by coloured photographs taken of each dog before treatment on the days during which scrapings were made. The infestation pressure can be considered adequate prior to treatment administration, with 808.1 live mites (geometric mean) in the Advocate treated group and 650.8 live mites (geometric mean) in the NexGard treated group. There was no significant differences (p=0.8103) between the geometric mean number of mites in each group prior to treatment administration.

According to guideline 7AE17a *Demonstration of Efficacy of Ectoparasiticides*, the arithmetic mean (AM) or geometric mean (GM) or other suitably transformed mean may be used; however, such transformation must be justified. The percentage of efficacy was calculated using geometric mean counts and, according to the clinical expert, as zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution. Whilst the applicant has presented efficacy calculations based upon GM count data, the CVMP has also presented efficacy results based on AM count data from the 'Individual mite counts and statistical results'. Although the applicant has not provided results of statistical analyses of the differences in AM counts between test and control products, it is evident from the data provided that the difference in percentage reduction between test and control products is greater when using arithmetic means. Consequently, as a statistically significant difference between test and control products was observed for GM count data, the differences for the AM count data will also have been statistically significantly different.

In terms of efficacy, the primary efficacy criterion was the percentage decrease from the pre-administration mite count to the post-administration mite count in each dog and each group on each assessment day. This can be accepted as being an appropriate outcome parameter for demonstrating efficacy. The guideline 7AE17a recommends an overall efficacy of ectoparasiticides of >90% for mange mites other than *Sarcoptes scabiei.*

Based on the results of this study, it appears that afoxolaner administered fortnightly on three consecutive occasions followed by a monthly treatment on two consecutive occasions was effective in achieving an acceptable level of efficacy (⩾99.2% based on geometric means; ⩾98.35 based on arithmetic means) at all timepoints on Days 28, 56, 83 and 90. It is noted that while parasitological cure was observed in all of the animals in the NexGard treated group at Day 83, three live mites were present on one dog in the NexGard treatment group at the end of the study on Day 90. The percentage efficacy was reported as being statistically significantly different (higher) in the Nexgard group compared to the Advocate treated group.

Over the course of the study, there was a reduction in erythematous papules, casts, crusts and an improvement in hair re-growth in both study groups. It is noted that animals were administered antibiotics for pyoderma starting on Day -7, which may also have contributed to the improvement of clinical signs. That said, in combination with the reduction in mite counts observed during the course of the study, it can be accepted that improvement in clinical signs of *D. canis* infestation were observed in both groups. No adverse events attributable to NexGard were reported in this study.

In conclusion, given that the product has not been administered in accordance with the proposed SPC (in terms of the proposed treatment dose of afoxolaner for the product NEXGARD SPECTRA and the re-treatment interval), the relevance of the study findings for the proposed indication is unclear. Specifically, it is unknown whether monthly administration (i.e. omitting initial fortnightly treatment on three consecutive occasions) is adequate or how the dose of afoxolaner administered (2.83 – 6.67 mg afoxolaner/kg bodyweight) may be considered sufficiently representative for the product NEXGARD SPECTRA for which a lower dose rate range is approved (2.50 – 5.36 mg afoxolaner/kg bodyweight).

In light of the above, the CVMP is of the opinion that the results of this study cannot be considered adequate for the purpose of confirming the proposed posology.

The second GCP compliant dose confirmation study investigated efficacy of the final formulations of NexGard and NEXGARD SPECTRA against generalised demodicosis in naturally infested dogs in South Africa. It is accepted that this was a well-designed negatively controlled laboratory study which included an adequate number of study animals (8 dogs per group). Although a phased design approach has been used, it can be accepted that the study methods used in each phase were the same and therefore the phased approach is not considered to have negatively impacted upon the study findings.

The study recruited privately owned dogs and the dogs were kept under experimental homogeneous conditions. The study population consisted of 24 mongrel dogs (6 males and 14 females; 6.08 to 17.7 kg bodyweight). All dogs enrolled in the study were adult ($\geqslant$6 months) and all were assessed as having generalised demodicosis on the basis of clinical signs and mite counts confirmed from deep skin scrapings prior to treatment. The inclusion criteria can be accepted as being appropriate and resulted in a study sample that is considered to be suitably representative of the target population. It is reported that codes (A, B, C) were randomly assigned to the treatment groups to facilitate blinding. Whilst it is noted that study personnel involved with assessing effectiveness of the treatments were blinded to treatment allocation, it is unclear as to whether this meant that they were unaware of the treatment group code as well. If not, then only part-blinding is considered possible as study personnel would have been aware of which animals were in the same group (albeit that the actual treatment was unknown). That said, given the relatively non-subjective nature of the pivotal efficacy outcome parameter (mite count), the above is not considered to have invalidated the study findings.

Both NexGard and NEXGARD SPECTRA were administered at their recommended treatment dose on Days 0, 28 and 56. Actual doses of afoxolaner ranged between 2.55 to 3.59 mg/kg bodyweight in the NexGard-treated group and 2.54 to 3.39 mg/kg bodyweight in the NEXGARD SPECTRA-treated group. Therefore, it can be accepted that both test products were administered at as close a dose to the minimum recommended treatment dose currently approved for each product.

The text proposed in section 4.9 of the SPCs does not explicitly state the minimum number of treatments and instead indicates that treatment should be administered monthly until two negative skin scrapings are obtained one month apart. Although the number of treatments has not been specified, this is interpreted as a minimum of two treatments at monthly intervals. It is noted that in

this study, both products were administered on 3 occasions at monthly intervals.

Mite counts were performed on samples collected by deep skin scrapings from five different body areas on Days -2, 28, 56, and 84. The clinical symptoms and the extent of demodectic lesions on each dog were assessed based on the following parameters: body areas covered by casts, scales, crusts, hair loss and erythema on Days -7, -2, 28, 56, and 84. Overall changes in clinical appearance were also illustrated by taking pre- and post-administration photographs from each dog.

The mite count recorded in the negative control group decreased slightly throughout the study from 357.1 (AM) on Day -2 to 315.7 (AM) on Day 84. According to the clinical expert, this was very likely as a result of the better husbandry conditions these dogs were subjected to during the study. It is unclear to the CVMP why the mite count reduced to 182.9 (AM) on Day 28 and increased again to 314.4 (AM) on Day 56. That said, mite infestations persisted in 7/8 dogs in the control group up to the end of the study (Day 84). The CVMP accepts that the infestation intensity in the control group was adequate for the duration of the study. Homogeneity of study groups, based on body weight and mite counts at inclusion time was demonstrated.

The primary efficacy endpoint was the percentage reduction in mite count in each individual animal and for treated groups compared to the control group at each assessment day using Abbott's formula. This is considered appropriate and in line with the guideline 7AE17a. Similar to the previous study, the primary efficacy results were based on geometric mean (GM) count data. The applicant justifies this approach by stating that due to the fact that small and even zero mite counts could be recorded, it could be expected that the mite counts would not follow a normal distribution. That said, the applicant also presented % efficacy based on arithmetic mean (AM) count data.

Efficacy of 96.7% GM (or 97.2% AM) on Day 28, >99.9% GM (or 99.9% AM) on Day 56 and 99.9% GM (or 99.9% AM) on Day 84 was observed in the NexGard treated group. Three mites were recovered from one dog in the NexGard group at Day 84.

Efficacy of 98.4% GM (or 98.6% AM) on Day 28, >99.9% (GM and AM) on Day 56 and 100% (GM and AM) on Day 84 were observed in the NEXGARD SPECTRA group.

There was a reduction in the occurrence of crusts, casts, scales and an improvement in hair re-growth in both the NexGard and NEXGARD SPECTRA treated groups by Day 84. While it is noted that all animals were administered concurrent antibiotics for pyoderma starting on Day -7, which may also have contributed to the improvement of clinical signs in combination with the reduction in mite counts observed during the course of the study, the CVMP accepts that an improvement in clinical signs of *D. canis* infestation was observed in both the NexGard and NEXGARD SPECTRA treated groups and that as the antimicrobial therapy was also administered to animals in the control group that were not administered afoxolaner, it can be accepted that this improvement resulted from afoxolaner administration. No adverse events attributable to treatment were reported in this study.

Based upon the findings from this study, the CVMP accepts that under laboratory conditions, both NexGard and NEXGARD SPECTRA administered monthly at the recommended treatment dose on three consecutive occasions demonstrated an acceptable level of efficacy (>90%) against *D. canis*.

While the study was conducted outside the EU, taking into account the results of field study which demonstrated an adequate level of efficacy according to guideline 7AE17a (>90%) against *D. canis* mites found in dogs under natural conditions within the EU, the CVMP concludes that further dose confirmatory data is unnecessary.

The GCP compliant field study investigated the efficacy and safety of the final formulations of

NexGard and NEXGARD SPECTRA in the treatment of demodicosis caused by *Demodex canis* in naturally infested dogs presented as veterinary patients in Europe (i.e. France, Italy, and Poland). The study can be considered representative of the European situation in terms of the geographical distribution of study sites and the age/breed of study animals.

No control group was used in this study and the pivotal efficacy parameter was percentage reduction in live mite counts compared to pre-treatment counts based on arithmetic mean data. According to the guideline 7AE17a, "…*When treatment of groups is intended, preferably 25-50% of the groups under trial should be left untreated. Where this cannot be justified, 25-50% of the groups should be treated with a product established according to Directive 81/852/EEC which is indicated for control of the ectoparasite or groups of ectoparasites claimed*..." Due to the potentially debilitating nature of the disease and therefore on ethical grounds, the absence of an untreated control group is accepted. Whilst it is acknowledged that guideline 7AE17a states *"When treatment of individual animals is intended, more specifically small companion animals, studies without the use of control may be performed if justified",* in the opinion of the CVMP, the absence of a control group is a significant deficiency in this study's design and, as a consequence, the conclusions that may be reached are considered to be somewhat limited by the absence of a comparator group on the basis that, without a control group, it cannot be concluded that the differences in outcome parameters when compared between study days 84 and 0 are solely attributable to the administration of afoxolaner. Furthermore, the absence of a control group has the potential to result in biased assessment of clinical parameters by the study investigators.

The applicant was requested to provide further reassurances to demonstrate that the clinical presentation of animals with demodicosis is unlikely to have changed significantly over the course of the 84 days follow-up period in the absence of treatment. Based on a review of published literature, the applicant concludes that while self-cure may occur in a limited proportion of dogs with juvenile onset and/or localised demodicosis, spontaneous self-cure of generalised demodicosis in dogs > 1 year of age is very unlikely to occur. Given that 31/50 (62%) dogs in this study were older than 1 year and all animals had been diagnosed with generalised demodicosis prior to treatment, the applicant considers the risk of spontaneous self-cure in the study population to have been limited.

While it is acknowledged that 38% of dogs in the study were younger than 1 year of age, the CVMP considers the changes in outcome parameters such as the rapid reduction in mites count and the significantly lower skin lesion scores, lesion extension and pruritus on Day 28 compared to Day 0 to support the applicant's conclusion that the improvement in generalised demodicosis was more likely to be attributable to the administration of afoxolaner than as a result of spontaneous resolution in the majority of cases. In light of the above, the omission of a control group in this instance can be accepted as having limited impact in terms of the study's findings.

50 client-owned dogs (44 purebred and 6 mixed breed, 21 males and 29 females, aged 0.25-15 years, 2.4 to 46 kg, ⩾8 weeks) included in the study were assessed as having generalised demodicosis (5 or more areas of disease present, or podo-demodicosis on two or more feet, or an entire body region affected) and ⩾5 live *D. canis* mites (adult, nymph, or larvae) confirmed at skin scraping on Day 0.

NexGard (n=31) or NEXGARD SPECTRA (n=19) were administered orally at the recommended treatment dose in accordance with the SPC at monthly intervals on 3 consecutive occasions on Days 0, 28±4, and 56±4 (inclusive). Clinical examinations, skin lesion assessment and skin scrapings (5 scrapings per dogs) were performed on Days 0, 28±4, 56±4, and 84±4 (inclusive) in order to evaluate the effect on mite numbers and the resolution of clinical signs.

The primary efficacy criterion was the reduction of live mites on Day 84±4 compared to the baseline

(pre-treatment) mite burden. Global percent efficacy (combination of results from both treatment groups) was calculated for each timepoint (i.e Day 28, 56, and 84) using arithmetic mean values. Based on the global score (a combination of results from both the NexGard and NEXGARD SPECTRA treatment groups), an adequate level of efficacy according to guideline 7AE17a (>90%) against *D. canis* was not achieved on Day 28 (global score 87.6%); however, adequate efficacy was attained on Day 56 (96.5% AM) and Day 84 (98.1% AM).

In terms of % efficacy in the individual treatment groups, adequate efficacy was also attained for each treatment group (NexGard: 98.2% AM and NEXGARD SPECTRA: 97.5% AM) on Day 84. Efficacy results in the individual groups were not provided for Days 28 or 56. For the purpose of assessment, the CVMP has calculated % efficacy for individual treatment groups on Days 28 and 56 using the following calculation: % efficacy = 100 x [(C-T)/C], where C = arithmetic mean of the Baseline count and T = arithmetic mean of the Day 84±4 count. Based on the CVMP's calculation, efficacy (>90%) was not achieved for either individual treatment group on Day 28 (NexGard: 88.49%; NEXGARD SPECTRA 84.25%); however, adequate efficacy was achieved for each group on Day 56 (NexGard: 96.77%; NEXGARD SPECTRA 95.51%).

Given the recommendation that monthly re-treatment is required for the treatment of demodicosis until two negative skin scrapings a month apart have been achieved, the CVMP is of the opinion that the lower level of efficacy observed on study days 28 for the global parameter (and for each product individually) is not unexpected. Concerning use of the global parameter (combined data from both NexGard-treated and NEXGARD SPECTRA-treated animals), the CVMP is prepared to accept that no interaction between afoxolaner and milbemycin oxime is to be expected (as previously accepted by the CVMP during the assessment for initial marketing authorisation for NEXGARD SPECTRA) and therefore no difference in efficacy against *D. canis* between NexGard and NEXGARD SPECTRA is to be expected. In support of this assumption, percentage efficacy for each individual product has been presented, suggesting that both products attained an acceptable level of efficacy (>90%) on study Days 56 and 84.

When the results of both NexGard and NEXGARD SPECTRA treatments are combined, there were significantly lower skin lesion scores, lesion extension and pruritus on Days 28 and 56 ($P<0.0005$) and on Day 84 ($P<0.0001$) compared to Day 0 values, similar findings being reported for each individual product when analysed separately.

Percent efficacy per animal and group of age (<18 months of age and ⩾18 months of age) were provided in the statistical report. It is noted that in the NexGard treated group, there is an apparent difference between the efficacy observed in the dogs <18 months (99.22%) compared to the dogs ⩾18 months (89.16%). The higher frequency of pododermatitis in dogs aged ≥18 months, which can require prolonged treatment, was considered a likely explanation for the apparent difference in efficacy between the two subgroups.

Protocol deviations were mostly small without impact on the study results; however, they brought to light that when the dosages per kg are calculated, dogs weighing 4.05 kg (and thus receiving a NexGard 28.3 mg tablet) actually receive almost 7 (6.99) mg afoxolaner/kg bodyweight. The applicant agreed to update the SPC to better reflect the correct mg/kg that is administrated in case an animal weighs 4.05 kg.

Four adverse events of vomiting were reported. One animal in the NEXGARD SPECTRA treated group had vomiting a few hours after administration on Day 0 and this was classified as "likely" related to treatment administration. It is noted that vomiting is included in section 4.6 of the SPC of both products.

Notwithstanding the deficiencies highlighted above in terms of the design of this study (absence of a control group), the CVMP is prepared to accept that the results of second dose confirmation and field studies provide sufficient evidence to demonstrate that the administration of NexGard and NEXGARD SPECTRA at their currently recommended treatment doses are safe and efficacious in the treatment of demodicosis (caused by *Demodex canis*) in dogs and consequently, the proposed indication is considered acceptable.

## *2.2. Treatment of sarcoptic mange (caused by Sarcoptes scabiei var. canis)*

The proposed indication against sarcoptic mange is: "Treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*): Monthly administration of the product for two consecutive months".

In support of the above indication, the applicant has provided the results of two field studies.

The first GCP compliant field study was performed to evaluate the efficacy of the final formulation of NexGard in the treatment of sarcoptic mange in naturally infested dogs located in the field in South Africa. This was a randomised, negatively controlled study. Although a phased design approach has been used, it can be accepted that the study methods used in each phase were the same and therefore the phased approach is not considered to have negatively impacted upon the study findings. This study was not blinded (due to the phased approach). The CVMP is willing to accept that the primary endpoint being evaluated is objective rather than subjective in nature (i.e. mite counts) and its reporting is therefore unlikely to have been significantly affected by the absence of blinding.

NexGard was administered at a dose rate of 3.09 to 6.75 mg/kg bodyweight, which falls within the recommended treatment dose of NexGard (2.7–6.9 mg/kg of afoxolaner). However, it is noted that the upper end of the dose range used is higher than the recommended treatment dose of afoxolaner in NEXGARD SPECTRA (2.50–5.36 mg/kg of afoxolaner).

Twenty privately owned mixed breed dogs (6 males and 14 females; ⩾6months; 4.08-18.34 kg bodyweight) were included in the study. The study animals are considered to be representative of the target population.

Infestation with *Sarcoptes scabiei* var. *canis* was confirmed by skin scrapings on Day -1/0 and dogs were allocated to two groups according to a predetermined randomisation list as suitably infested animals were identified. There were 10 animals in each group, which is considered to be a small sample size for a field efficacy study. One of the animals included in the NexGard treated group did not complete the study. The applicant justifies the use of privately owned dogs on account of the unavailability of a reliable model of *Sarcoptes scabiei* var. *canis* infestation and this can be accepted. Dogs were not kept under homogeneous laboratory conditions but instead stayed with their owners under their usual housing conditions for the duration of the study.

Skin scrapings were taken on Days -1/0, 28±2, and 56±2 from five different body areas suspected of being infested. The clinical signs and the extent of the lesions on each dog were assessed on the days during which scrapings were made and coloured photographs were taken of each dog before treatment in order to illustrate the extent and resolution of lesions.

The applicant states that due to the fact that zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution and percentage reduction calculations were based on geometric means rather than arithmetic means. That said, the applicant has presented % efficacy calculations based on both arithmetic and geometric means. Nine out of 10

animals in the negative control group retained their mite infestation up to Day 56±2 and the number of *S. scabiei* var. *canis* mites recorded from these animals ranged from 0 to 743 (92.8 AM or 12.1 GM). The CVMP considers this to represent adequate infestation intensity in the control group for the duration of the study.

The primary efficacy endpoint was the percentage reduction in mite count in the NexGard treated group compared to the control group at each assessment day using Abbott's formula. This is considered appropriate. A 100% efficacy (based on AM and GM) was attained in the treated group on both Days 28 and 56, which meets the overall efficacy threshold of 100% for *Sarcoptes scabiei* recommended by guideline 7AE17a. In terms of the secondary efficacy endpoints, dogs treated with NexGard had significantly lower skin lesion scores, lesion extension and pruritus ($P<0.0005$) on Days 28 and 56 compared to Day 0 values.

There were 3 protocol amendments. It is agreed that one of these impacted on the study outcome whereby 5 "negative control" dogs were treated at the end of the study with NexGard on Day 56±2 instead of Advocate. In the follow-up assessments performed 28±2 days after the test product administration, one mite was found among the five dogs. In light of this observation in the extended part of the study, the CVMP agrees with the applicant that these findings suggest that a second treatment is required to eliminate mite infestation (as demonstrated during the main part of the study where no mites were reported at Day 28 following administration of two treatments one month apart).

Regarding safety, two dogs administered NexGard died between Day 0 and 84±2. Due to insufficient information concerning these adverse events, no conclusion can be drawn on an association between effect and treatment. However, it is noted that the product was administered in accordance with the existing posology approved for the product.

Although this study was conducted outside the EU and that the upper end of the dose range used (6.75 mg afoxolaner/kg bodyweight) is higher than the recommended treatment dose of afoxolaner in NEXGARD SPECTRA (2.50–5.36 mg/kg of afoxolaner), taking into account the fact that published literature cited by the applicant indicates genetic homogeneity of *S. scabiei* var. *canis* across different geographical regions (suggesting that difference in susceptibility is not anticipated) and given the results of study CVM 1513 which demonstrated that both NexGard and NEXGARD SPECTRA had approximately 100% efficacy against the *S. scabiei* var. *canis* mites found in dogs under natural conditions within the EU when administered at the recommended treatment dose, the CVMP concludes that further confirmatory data to support efficacy of the product is unnecessary.

In summary, it may be accepted that the results of this study provide supportive evidence that monthly administration of NexGard at the recommended treatment dose for two consecutive months is effective in the treatment of sarcoptic mange, with elimination of live *S. scabiei* var. *canis* mite infestation and reduction in clinical signs.

A second GCP compliant field study evaluated the efficacy and safety of NexGard and NEXGARD SPECTRA using the final formulations at their respective recommended dosages administered at monthly intervals for two consecutive months in the treatment of sarcoptic mange in naturally infested dogs presented as veterinary patients in Europe (Portugal and Germany). The study can be considered representative of the European situation and included more than one geographical area (albeit the majority of study animals were enrolled in Portugal). No control group was used in this study and the pivotal efficacy parameter was percentage reduction in live mite counts compared to pre-treatment counts based on arithmetic mean data. The clinical expert justifies the conduct of the study without the use of a control group on the basis of the recommendations of the guideline 7AE17a which states *"…In exceptional cases, where justified, studies may be performed without the*

*use of control animals (e.g. in the case of animals infected with Sarcoptes scabiei). When treatment of individual animals is intended, more specifically small companion animals, studies without the use of control may be performed if justified."* Due to the potentially debilitating nature of the disease and therefore on ethical grounds, the CVMP accepts the omission of an untreated control group.

Whilst it is acknowledged that guideline 7AE17a suggests that, in exceptional cases, studies without the use of control may be performed if justified, in the opinion of the CVMP, the absence of a control group is nevertheless a significant deficiency in this study's design and, as a consequence, the conclusions that may be reached are considered to be somewhat limited by the absence of a comparator group on the basis that, without a control group, it cannot be concluded that the differences in outcome parameters when compared pre- and post-treatment are solely attributable to the administration of afoxolaner. Furthermore, the absence of a control group has the potential to result in biased assessment of clinical parameters by the study investigators. That said, the CVMP accepts that it is unlikely that spontaneous remission from an infestation with *S. scabiei* var. *canis* is to be expected and the omission of a control group for studies investigating efficacy against *S. scabiei* var. *canis* is foreseen in the relevant guideline.

At each visit (Days 0, 28, and 56), *Sarcoptes scabiei* var. *canis* mites were counted in five skin scrapings per dog and the dogs were scored for the presence/extent of specific clinical signs (pruritus, papules and crusts, alopecia). Skin scrapings of 106 dogs presenting signs suspicious of sarcoptic mange were screened to confirm the infestation and to establish *S. scabiei* var. *canis* mite counts. 91 dogs were initially included and treated on Day 0 with NexGard (n=47) or NEXGARD SPECTRA (n=44). Twenty six dogs were excluded from the efficacy analysis for various reasons. Sixty five dogs (38 dogs in the NexGard treated group and 27 dogs in the NEXGARD SPECTRA treated group) which completed the study as per study protocol were included in the analysis of the efficacy of the treatments. The sample size is considered adequate. These study animals (64 privately owned dogs and 1 shelter dog, aged from 2 months to 11.4 years old and weighting 2.1 to 56.3 kg) in the Per Protocol dataset can be considered sufficiently representative of the target population. Dogs were kept at home, under their usual housing conditions and were allocated to treatment groups according to the randomization schedule to be treated twice, four weeks apart (Days 0 and 28), with either NexGard or NEXGARD SPECTRA at their respective recommended treatment doses.

The applicant states that due to the fact that zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution and percentage reduction calculations were based on geometric means. That said, the applicant presented % efficacy based on both arithmetic and geometric means. At Day 0, all 65 dogs included in the analysis of the efficacy had ⩾5 *Sarcoptes scabies* var. *canis* mites present. It can therefore be accepted that infestation of study animals was adequate prior to treatment.

The primary efficacy endpoint was the live mites count of the test product group at Days 26-30 (Day 28) and 55-61 (Day 56) compared to the live mites count in the same treatment group at baseline (Day 0 – prior to treatment). The guideline 7AE17a recommends an overall efficacy of approximately 100% for *Sarcoptes scabiei*. Compared to baseline, reduction of live *S. scabiei* var. *canis* mite counts was 95.83% AM (or 98.91% GM) on Day 28 and 99.58% AM (or 99.69% GM) on Day 56 for the NexGard treated group. For the NEXGARD SPECTRA treated group, efficacy of 99.39% AM (or 99.56% GM) on Day 28 and 100% (both AM and GM) on Day 56 was reported.

In terms of the secondary efficacy endpoints, 37/38 (97.37%) of dogs were mite-free on Day 28 and Day 56 in the NexGard treated group. 26/27 (96.30%) of dogs were mite-free on Day 28 and 100% of dogs on Day 56 in the NEXGARD SPECTRA treated group. In addition, over the course of

the study, there was an improvement in clinical signs (pruritus, papules and crusts, and alopecia) in all dogs compared to baseline (p=0.0001, at both Day 28 and Day 56). In terms of owner satisfaction, the majority of owners of dogs in both the NexGard and the NEXGARD SPECTRA group were either "very satisfied" or "satisfied" with the performance of the treatment and one owner was "not satisfied" due to difficulties in acceptance of the tablet by the dog.

Two dogs administered NEXGARD SPECTRA on Day 0 were reported to experience an adverse event during the study. One animal died within 24 hours of administration of the product. Due to insufficient information, no conclusion could be drawn on an association between effect and treatment. The other animal was removed from the study at Day 28 due to enlarged lymph nodes. Lymphomegaly is inconsistent with the known pharmacological and toxicological profiles of NEXGARD SPECTRA and this adverse event is considered unlikely to be associated with product administration.

Based upon the data provided and notwithstanding the deficiency highlighted above in terms of the study design (absence of a control group), the CVMP accepts that this study demonstrates that both NexGard and NEXGARD SPECTRA have been shown to have an acceptable level of efficacy (approximately 100%) for the treatment of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis* in dogs under natural conditions when administered at the recommended treatment dose for two consecutive months. However, given that one animal in the NexGard-treated group was not considered to be mite free on study Day 56 (after two monthly treatments), the applicant agreed with the view of the CVMP that the recommendation should be based upon results of clinical examination and skin scrapings rather than limit treatment duration to two administrations a month apart. The CVMP has proposed amended wording in section of 4.9 of the SPC to clarify this aspect: "Treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*): Monthly administration of the product for two consecutive months. Further monthly administration of the product may be required based on clinical assessment and skin scrapings."

According to guideline 7AE17a, at least two controlled dose confirmation studies in addition to EU clinical field trials should be provided to demonstrate efficacy. Although no laboratory study has been provided, the applicant has provided two clinical field trials and the CVMP accepts that data from these studies suitably demonstrate effectiveness of the products under conditions of field use. Based on the data provided, the CVMP is willing to accept the claim that monthly administration of NexGard or NEXGARD SPECTRA at the recommended treatment dose for two consecutive months (noting that further monthly treatment(s) may be required depending on clinical examination and skin scrapings) is effective in the treatment of sarcoptic mange in dogs under field conditions and that a reduction in clinical signs of *S. scabiei* var. *canis* infestation has been shown. Given that 100% efficacy was demonstrated at Day 56 in the first field study for NexGard and that >99% and 100% efficacies were demonstrated for NexGard and NEXGARD SPECTRA, respectively in the second field study, the CVMP is of the opinion that additional study data from a dose confirmatory study is unnecessary in this instance.

In terms of safety, although a number of adverse events were observed in treated animals in both studies and due to insufficient information no conclusion can be drawn on an association between effect and treatment, the CVMP is willing to accept that, overall, both NexGard and NEXGARD SPECTRA can be considered safe in the treatment of sarcoptic mange caused by *Sarcoptes scabiei* var. *canis.*

In conclusion, the CVMP accepts that NexGard and NEXGARD SPECTRA, when administered monthly for two consecutive months (or longer if recommended based upon clinical examination and skin scrapings), are safe and effective in the treatment of sarcoptic mange (caused by *S. scabiei* var.

*canis*).

## *2.3. Treatment of ear mite infestation (Otodectes cynotis)*

The proposed indication against otodectic mange is: "Treatment of ear mite infestation (*Otodectes cynotis*): Single administration of the product, a second administration one month after the initial treatment may be recommended based on clinical assessment."

In support of the above indication, the applicant has provided the results of one dose confirmation study.

A study was conducted to evaluate the efficacy of a single dose of NexGard using the final formulation against *Otodectes cynotis* in experimentally infested dogs in South Africa. This was a GCP compliant, blinded, negatively controlled laboratory study. Although a phased design approach has been used, it can be accepted that the study methods used in each phase were the same and therefore the phased approach is not considered to have negatively impacted upon the study findings. NexGard was administered at the recommended treatment dose and the actual dose of afoxolaner ranged between 2.57 to 3.32 mg/kg bodyweight, which can be accepted as falling within the lower end of the dose range currently approved for the products (2.7-6.9 mg afoxolaner/kg bodyweight for NexGard and 2.50-5.36 mg afoxolaner/kg bodyweight for NEXGARD SPECTRA). Given that the CVMP has previously accepted that the pharmacokinetic profile of afoxolaner is unchanged by the concomitant administration of milbemycin oxime in NEXGARD SPECTRA, the CVMP accepts that the results of this study conducted using NexGard can be extrapolated to NEXGARD SPECTRA.

Sixteen mixed breed dogs (9 males and 7 females, ⩾6 months, 15.4 to 22 kg at Day -1) were sourced from a colony and housed individually. The number of study animals is considered adequate (8 animals per group). The study animals were experimentally infested with a strain of *O. cynotis* mites originating from donor animals coming from a region where the use of acaricides was uncommon. A total of >10 mites in at least one ear and the evidence of live mites in the other ear confirmed through otoscopic examination on Days -7 and -2 was used to validate appropriate infestation and animal inclusion. On Day -2, dogs were ranked within sex according to individual live mite count scores (0 = 0 live mites; 1 = 1 to 4 live mites; 2 = 5 to 10 live mites, and 3 = >10 live mites) and debris/cerumen in the ears scores (0 = no debris/cerumen, 1 = slight debris/cerumen, 2 = moderate debris/cerumen, and 3 = severe debris/cerumen). Otoscopic assessments were also performed on Days 14 and 28. Ear flushing under sedation and mite counts were performed to assess efficacy on Day 28.

The applicant states that due to the fact that zero mite counts could be recorded, it was expected that the mite counts would not follow a normal distribution and percentage reduction calculations were based on geometric means rather than arithmetic means. That said, the applicant also presented % efficacy based on arithmetic mean count data. The applicant argues that the mite count in animals in the control group ranged from 0 to 477 (109.9 AM) on Day 28, supporting the fact that the infestations were well established and that even though one dog in the control group did not harbour mites on Day 28, there were a sufficient number of dogs (seven) infested with mites. However, no information relating to the method of experimental infestation, timing of infestation or the number of mites with which donor animals were infested were provided. The applicant was requested to provide further information on the method of experimental infestation used, including the number and source of *O. cynotis* mites and to justify how the mites used in this study may be considered suitably representative of those found in dogs within the EU (in terms of both geographical representativeness and susceptibility). In addition, the applicant was requested to

justify how the challenge can be considered adequate considering that 4/8 of the control animals harboured ⩽4 mites (3; 3; 0 and 4 mite counts) on Day 28.

The primary efficacy endpoint was the percentage reduction in mite count in the NexGard treated group compared to the control group at each assessment day using Abbott's formula. Guideline 7AE17a recommends an overall efficacy of >90% for mange mites other than *Sarcoptes scabiei*. The results from this study indicate a statistically significant difference ($p<0.05$ using GM and AM) in the number of visible live mites at Days 14 and 28 between the treatment and control group, with an efficacy of 99.4% (AM) or 98.5% (GM) attained in the treatment group at Day 28. However, it is noted that two of the animals from the NexGard treated group still harboured one and four live mites respectively on Day 28. In terms of debris and cerumen, the difference between the NexGard treated group when compared to the control group was less obvious. The applicant suggests that this may be expected as reactions to mites do not resolve immediately once mites die. No adverse effects attributable to treatment were reported in this study.

Given the guideline requirements for two dose-confirmation studies and supportive field data, it was unclear to the CVMP as to how the data requirements for the proposed indication have been met. The applicant was requested to justify how the data provided can be accepted as meeting guideline requirements. In the absence of acceptable justification and/or suitable data, the proposed indication is not considered to have been adequately supported and should be omitted.

In response to the concerns raised, the applicant decided to withdraw the proposed claim for the treatment of ear mite infestation (*Otodectes cynotis*).

# 3. Benefit-risk assessment of the proposed change

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 *C. canis*) and tick (*Dermacentor reticulatus, Ixodes ricinus* and *Rhipicephalus sanguineus*) infestation, as well as part of a treatment strategy for the control of flea allergy dermatitis (FAD). NexGard is presented in four different strengths of chewable tablet with afoxolaner administered at a dose of 2.7–6.9 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.

NEXGARD SPECTRA contains a fixed combination of afoxolaner 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 *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*, *Ancylostoma braziliense* and *Ancylostoma ceylanicum*) and whipworm (*Trichuris vulpis*)) is indicated. 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 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 three new therapeutic indications: for the treatment of demodicosis (caused by *Demodex canis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*) and ear mite infestation (*Otodectes cynotis*). With this procedure, product information of NexGard is aligned with

the latest QRD template.

### *3.1. Benefit assessment*

As this is a variation to introduce additional indications to existing products, the benefit will arise from the inclusion of new indications. The indications against *D. canis, S. scabiei* var. *canis* and *O. cynotis* are considered as being of benefit for the user/prescriber. However, the proposed indication for treatment of ear mites (*O. cynotis*) was withdrawn in response to a number of concerns having been raised in respect of the adequacy of the data provided.

### *3.2. Risk assessment*

As this is a variation to introduce additional indications to existing products, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indications. 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 has been 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 two additional indications considered approvable, it can be accepted that there should be an increased benefit from the use of the product for the treatment of demodicosis (caused by *Demodex canis*) and sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*) in dogs.

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

The benefit-risk balance remains positive.

## 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 and NexGard 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 new therapeutic indications: for the treatment of demodicosis (caused by *Demodex canis*) and sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*).

However, the proposed indication for treatment of ear mites (*Otodectes cynotis*) is considered to have been inadequately supported and this claim has been withdrawn by the applicant during the assessment.

Taking into account the two accepted claims, 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