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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for NexGard and NexGard Spectra (EMEA/V/C/WS2280/G)

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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 27 June 2022 an application for a group of variations requiring assessment for Nexgard Spectra and NexGard, following a worksharing procedure.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
G.I.4	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.

The group of variations is to add two new therapeutic indications for the treatment of tick infestations with *Hyalomma marginatum* and for the treatment of ear mite infestations (caused by *Otodectes cynotis*), and to amend the product information to allow the use of the product in breeding, pregnant and lactating female dogs. In addition, the applicant takes the opportunity to make an editorial change in section 6.5 of the SPC for both products.

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. Limited market status

Not applicable.

2. Scientific Overview

The product NexGard contains the active substance afoxolaner, an insecticide and acaricide belonging to the isoxazoline family. The product Nexgard Spectra contains two active substances: afoxolaner and milbemycin oxime (MO), an anthelmintic belonging to the group of macrocyclic lactones. Non-interaction of the two active substances has been confirmed for Nexgard Spectra in 2014 (EMEA/V/C/003842/0000).

Both products are currently authorised as chewable tablets for use in dogs.

NexGard is presented in four different strengths of chewable tablet administered at a dose rate of 2.7–7 mg of afoxolaner/kg body weight (bw). Nexgard Spectra is presented in five different strengths of chewable tablet administered at a dose rate of 2.50-5.36 mg of afoxolaner and 0.50-1.07 mg of MO/kg bw. No change to the currently approved dose is proposed with the current variations.

The proposed variations are identical for both products, namely the addition of two new therapeutic indications:

- Treatment of *Hyalomma marginatum* tick infestations. An immediate and persistent effect for up to one month is proposed.
- Treatment of ear mite infestations (caused by *Otodectes cynotis*). A single treatment dose is proposed; however, a further veterinary examination one month after the initial treatment is recommended as some animals may require a second treatment.

In addition, this variation application intends to amend the product information to allow the use of the product in breeding, pregnant and lactating female dogs.

Finally, the applicant takes the opportunity to make an editorial change in section 6.5 of the SPC for both products.

The CVMP notes that in the EU individual housing of the test animals is recommended during the time period(s) of infestation with ectoparasites, i.e. from the day of infestation until the day of ectoparasite counting, and that for the other time periods, housing of animals in groups should be considered with sufficient space according to animal species (EMEA/CVMP/EWP/005/2000-Rev.4). However, in two (pivotal) studies, both conducted outside Europe, dogs were housed individually for the entire course of the study. Also, cages were smaller than required by Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes in one (pivotal) study conducted outside Europe. Although it would have been desirable for the studies to have been conducted in line with European animal welfare legislation (Directive 2010/63/EU), requiring new studies would not be justifiable from an animal welfare perspective. It is also notable that these studies were performed before Regulation (EU) 2019/6, which requires compliance with Directive 2010/63/EU, came into force. Consequently, the studies are accepted.

2.1. Safety (tolerance, user, environment)

With the introduction of the proposed indications, NexGard and Nexgard Spectra 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. As such, 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 product. No change to the impact on the environment is envisaged.

Therefore, no further assessment is deemed necessary in respect of user safety or safety for the environment, and it can be concluded that the introduction of the proposed indications will not present an unacceptable risk for the user or the environment.

2.1.1. Use during pregnancy, lactation or in breeding dogs: Reproductive safety study

Information on potential effects of the two active substances on reproduction in laboratory animals has been provided with the original marketing authorisation procedure for NexGard and Nexgard Spectra. It was then concluded by the CVMP that neither of the two active substances shows potential for

teratogenicity: "*Laboratory studies in rats and rabbits have not produced any evidence of teratogenic effects, or any adverse effect on the reproductive capacity in males and females*".

For both products, the applicant intends to change the current wording of the "Use during pregnancy, lactation or lay" section, from: "*The safety of the veterinary medicinal product has not been established during pregnancy and lactation or in breeding dogs*" to: "*Can be used in breeding, pregnant and lactating dogs. The safety of the veterinary medicinal product has not been established in breeding males*."

To further support the safe use of the product in breeding, pregnant and lactating dogs, a reproductive safety study has been performed in the target species (Reproductive Safety Study), which was well designed and performed largely in line with VICH GL43 - Guideline on target animal safety for veterinary pharmaceutical products.

An appropriate number of twenty healthy, intact, and reproductively-sound adult Beagles (dams) were divided into two groups of 10 dogs each. Group 1 was sham-dosed. Group 2 received monthly administrations of Nexgard Spectra (formulation as currently marketed) by the recommended route, at 3X the maximum recommended treatment dose (15.01-16.16 mg/kg bw for afoxolaner and 3.00-3.23 mg/kg bw for milbemycin oxime). Five healthy adult male Beagle dogs were included for mating but were not treated.

The treatment dose was considered adequate to assess reproductive safety of both NexGard as well as Nexgard Spectra, as the principles stated in VICH GL43 were generally followed and no significant difference in reproductive safety is expected to occur between a 2.2X and 3X dose regimen. Also, it is acknowledged that no interaction between the two active substances of Nexgard Spectra exists. As such, the results of this study can also be extrapolated to NexGard.

Animals were treated at appropriate 4-week intervals, with at least two doses administered pre-mating (therefore ensuring that, for afoxolaner, a steady state was reached). Dosing continued until weaning at Day 49 after parturition. All dams that whelped received 6 to 11 total treatments per female. Animals were therefore adequately dosed prior to breeding (covering the follicular phase until conception), throughout the gestation period (including embryonic phase, foetal phase, and natal phase), and after parturition for an appropriate duration of time, adequately covering all key periods of the gestation. For the purpose of investigating negative effects on reproductive parameters in breeding, pregnant or lactating dams, the study design and the range of reproductive parameters measured are considered appropriate and sufficient.

Ultimately, 8 control dams and 10 dams that were dosed regularly with Nexgard Spectra whelped and completed the study. There were 41 puppies born in the control group (40 live born; 38 puppies were ultimately weaned) and 60 puppies born in the Nexgard Spectra group (58 live born; 52 puppies were ultimately weaned). Ultimately, more puppies were therefore born in the treatment group.

Study results showed that Nexgard Spectra was well tolerated by the treated dams up to 3 times the maximum recommended dose at monthly intervals. In these females, the main adverse effects observed were emesis and diarrhoea, both of which are specified in the "Adverse events" section of the SPC.

The reproduction performance parameters evaluated (most importantly, the number of live and stillborn puppies, puppies with abnormalities, mortality and body weight of the pups) can be considered adequate to support the safety statements proposed in the "Use during pregnancy, lactation or lay" section of the SPC. Overall, parameters evaluated were very similar between treatment and control groups and lacked statistically significant difference. Results did not suggest an

impact of Nexgard Spectra on the female reproductive performance when administered before and during the gestation.

Regarding health abnormalities in the puppies, the following observations were considered of importance: in litters from the treated dams, 3 puppies showed hepatic abnormalities (hepatocellular vacuolation or congenital hepatic fibrosis), versus 1 in the control group. One puppy showed concurrent hepatic fibrosis and hydrocephalus/open fontanelle, one puppy showed neurological signs, and in one puppy of this group, 'transitory' morphological findings ('flat chest') were observed. No puppy of the control group showed neurological signs, hydrocephalus/open fontanelle or flat chest.

Though the absence of a treatment-related effect can never be fully excluded, as however there appears no common pattern for the observed abnormalities, all abnormalities have been described as congenital birth defects known to occur in the beagle, and as most distinct abnormalities occurred only in a single animal and therefore appear not to exceed incidences of birth defects as described in public literature, these observations do not necessarily indicate a treatment related effect, and could be considered incidental.

Reproductive safety in males was not assessed in this study. This is however appropriately reflected in the proposed SPC ("*The safety of the veterinary medicinal product has not been established in breeding males*" and: "*In breeding males, use only according to the benefit-risk assessment by the responsible veterinarian*").

Overall conclusion:

This reproductive target animal safety study supports the safe use of NexGard and Nexgard Spectra in breeding, pregnant and lactating dogs. It can be concluded that the benefit of treatment in breeding female dogs and during pregnancy and lactation outweighs the risks in these dogs; therefore, this variation can be accepted.

The proposed wording in the "Use during pregnancy, lactation or lay" section of the SPC and corresponding section of the package leaflet is considered appropriate for both products.

2.2. Efficacy

2.2.1. Treatment of tick infestations with *Hyalomma marginatum*

Hyalomma marginatum, a hard tick, is a two-host tick that has also been recorded on dogs and is a proven vector for the etiological viral agent of Crimean-Congo haemorrhagic fever. These ticks have been occasionally reported in Central and Western Europe, and have recently been observed in other European countries, such as Germany and Sweden.

The claimed efficacy for *Hyalomma marginatum* is based on a single, pre-clinical, dose confirmation study (*Hyalomma marginatum* Study). The omission of an additional clinical trial in support of the claim is considered acceptable by the CVMP for the following reasons: in multiple clinical and pre-clinical studies, both NexGard as well as Nexgard Spectra have been demonstrated to be highly effective against various different tick species, amongst of which *Ixodes hexagonus* and *Ixodes ricinus*. Similar to these two tick species, *Hyalomma marginatum* also belongs to the family of *Ixodidae*. The outcome of the dose confirmation study currently presented supports that treatment with afoxolaner is also highly effective (>97%) against *Hyalomma marginatum.* Finally, *Hyalomma marginatum* is currently considered to be a non-autochthonous tick species in Europe, for which deviations from the recommendations set out in available guidelines may be acceptable. In light of the above, the omission of additional studies in support of the indication against *H. marginatum* is considered acceptable.

The study was a pivotal, well-designed dose confirmation study that was performed largely taking into consideration the 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.4) (though some deviations from this guideline were noted and will be discussed) and the Guideline on the demonstration of efficacy of ectoparasiticides (7AE17A). The study was performed in accordance with GCP. According to the above-mentioned GLs, this can be accepted.

This was a single-site, negatively controlled, appropriately blinded, randomized, laboratory study. The study investigated the efficacy of a single treatment of NexGard (at the recommended clinical dose) against *Hyalomma marginatum* ticks in dogs for up to 39 days (i.e. >1 month).

The study covered the entire period of the claimed effect of treatment. Study duration is therefore considered appropriate. The use of an untreated control group is also considered appropriate for this type of study. A study protocol, study report and the statistical results have been provided.

The study was conducted in Morocco. Whilst the study was conducted outside the EU, given the design of this laboratory study, this is not of concern. The tick strain used was a recent strain that derived from Morocco. However, as this tick species is currently not endemic in Europe, the use of a Moroccan tick strain is considered acceptable.

An acceptable number of healthy, adult Beagle dogs were included and divided in groups of 8 dogs each. Study population is considered to be sufficiently representative for the target population. On Day 0, one group was left untreated, one group received treatment with NexGard.

It is noted that Nexgard Spectra was not assessed in this study. As non-interaction of the active substances has been confirmed for Nexgard Spectra (EMEA/V/C/003842/0000), the outcome of this study is also considered relevant for Nexgard Spectra. It is however noted that the afoxolaner dose as authorised for both products differs (for NexGard: 2.7–7 mg afoxolaner/kg bw; for Nexgard Spectra: 2.50–5.36 mg/kg bw of afoxolaner).

In this study, the animals received treatment at a dose range of 2.9 to 6.7 mg/kg of afoxolaner (mean dose of afoxolaner was 5 mg/kg bw). Although the minimum dose rate approved for NexGard (2.7 mg/kg) was not administered in this study, the dose range administered can be accepted as falling sufficiently within the lower end of the dose range currently approved for NexGard, with only 1 animal being dosed at 6.7 mg/kg bw, and the remainder dosed at 5.9 mg/kg bw or below. For Nexgard Spectra (for which a slightly lower minimum dose rate of afoxolaner is approved (2.5 mg/kg bw)), it can be accepted that whilst the minimum dose was not administered in this study, a number of animals were administered doses close to the minimum recommended dose rate and the mean dose (5 mg/kg bw), falls within the authorised dose range for the product and can therefore be considered generally representative of the intended field use of the product. Furthermore, and as highlighted by the applicant, initial developmental studies were conducted with a dose of 2.5 mg/kg bw of afoxolaner, and these had been highly successful in demonstrating efficacy for other members of the *Ixodidae* family for which Nexgard Spectra is currently approved. Also, the applicant considered that the high level of efficacy that was observed in the study should be taken into account.

To evaluate susceptibility of the animals, dogs were sedated and challenged at Days -14 and -7. Due to the initial low tick attachment, the study was extended, and an additional infestation was conducted on Day -7, which is considered acceptable.

To assess both immediate as well as persistent efficacy, dogs were challenged at Days -2, 7, 28 and 36. Ticks were then thumb-counted on Days 2, 9, 30 and 38 (48 ± 2 h after product administration or

infestation) and removed and counted on Days 3, 10, 31 and 39 (72 ± 2 h after product administration or infestation).

Challenges were performed with approximately 30 (15 females and 15 males) viable, adult, unfed *H. marginatum* ticks. The number of challenges and the method of challenge are considered appropriate; however, it is noted that only 30 ticks were used for each challenge, whilst the 'Guideline for the testing antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats' states that approximately 50 unfed adult ticks should be used for a challenge. No justification is provided for use of a lower number of ticks. It is however noted that the treatment effect was high and all control animals were adequately infested (even more control animals than required according to the guideline – 8 versus 6 – were used); in addition, for the control group attached tick counts ranged from 8-29 across days 3, 10, 31 and 39 with at least 6 control animals exhibiting tick counts >14 at each timepoint. In this regard, the infestation rate can be considered adequate, given that the aforementioned guideline specifies that 12-25 ticks should attach to each animal at each time point. Considering the above, the method of challenge is considered adequate for this study.

In terms of efficacy, the primary efficacy criterion was the percentage of tick efficacy in the IVP group compared to the control group at each assessment time point. Efficacy was calculated using Abbott's formula, and efficacy calculations were based on arithmetic mean values, which is considered appropriate. Live free ticks were not considered for efficacy evaluations, which is also considered acceptable for a systemically acting acaricide.

Results showed that infestation in the control dogs was adequate. Efficacy based on arithmetic means exceeded 90% (97.1 to 100%) from 48 hours after treatment up to Day 39, successfully demonstrating both an immediate as well as a persistent efficacy of the product against *Hyalomma marginatum* ticks. Results met the recommended efficacy threshold of 90% as defined in the aforementioned guideline.

No adverse events directly attributable to NexGard were reported in this study.

Overall conclusion:

In summary, the indication against tick infestations with *Hyalomma marginatum* in dogs can be accepted for both NexGard and Nexgard Spectra.

In terms of safety, no issues were observed during the study, confirming safety of the products when used according to label.

2.2.2. Treatment of ear mite infestations (caused by *Otodectes cynotis*)

The ear mite *Otodectes cynotis*, a species of the genus *Otodectes* (*Acari: Psoroptidae*), is the causative organism for otodectic mange.

In support of the proposed indication 'Treatment of ear mite infestations (caused by *Otodectes cynotis*)", the applicant has provided the results of two dose confirmation studies (Lab 1, Lab 2), and two clinical trials (Field 1, Field 2) assessing effectiveness of treatment in dogs with naturally acquired *Otodectes cynotis* infestations.

Dose confirmation studies

The first dose confirmation study (Lab 1) was a blinded, single site, GCP compliant, dose confirmatory laboratory study performed using experimentally-infested animals. Animals were infested with a strain of mites that derived 'from donor animals coming from a region where the use of acaricides was uncommon'. As however *Otodectes cynotis* is a worldwide distributed parasite, and peer-

reviewed literature supported that significant phenotypical differences are unlikely to occur between strains, representativeness of the strain used in this study for the European situation was considered justified.

The aim of the study was to assess the efficacy of a single 2.5 mg/kg bw dose of afoxolaner against existing *Otodectes cynotis* infestations.

The (two-phase) study was conducted in two well balanced groups of eight healthy dogs each. One group was left untreated, the other group received NexGard chewable tablets for dogs.

The animals were mongrel dogs, 9 males and 7 females, 15.4 kg to 22.0 kg bw. The number of study animals is considered adequate (8 animals per group), and the phased approach is not considered to have negatively impacted upon the study findings. It is noted that the animals needed to be ≥6 months upon inclusion, whilst the product is authorised for dogs over 8 weeks. As the inclusion criteria of the two additional studies presented in the dossier did allow inclusion of animals from 8 weeks of age, this issue was not pursued further.

On Study Day -2, the success of the artificial infestation was confirmed via otoscopic examination by the presence of >10 mites in at least one ear of each dog. Given that 15/16 ears in the control group and 13/16 ears in the treatment group had ≥10 live mites, it is agreed that there was an acceptable level of infestation prior to treatment.

At Day 0, the IVP was administered as a single dose, using the formulation currently marketed at the recommended treatment dose. The actual dose range was 2.57-2.80 mg/kg bw of afoxolaner. The dose range administered can therefore be accepted as being appropriately representative for both products, falling within the lower end of the dose range currently approved for Nexgard Spectra (2.5 mg/kg bw), as well as NexGard (for which the currently approved lowest end of the dose range is slightly higher - 2.7 mg/kg bw).

The primary effectiveness criterion was the number of live mites collected from the treated group on Day 28 compared to that of the control group. Efficacy was calculated in line with the guideline 7AE17a 'Demonstration of efficacy of ectoparasiticides', which requires an overall efficacy of more than 90% for mange mites other than *Sarcoptes scabiei*. Both arithmetic as well as geometric means were calculated, which can be accepted as being in line with 7AE17a.

On Days 14 and 28, an otoscopic assessment was performed to assess the qualitative score of live mites. On Day 28, the final, quantitative assessment of live mites was performed, by sedating the animals, flushing the ears and examining the earwax under an optical microscope for the count of live mites.

At Day 28, in the control group, the quantitative assessment of live mites showed a large variation in numbers of live mites (range: 0-447 mites; arithmetic mean: 109.9; geometric mean: 22.3). However, as 7/8 animals in this group retained an infestation of live mites, this was considered indicative of an adequate established infestation. In the NexGard group, at Day 28, two animals harboured one and four live mites, respectively (arithmetic mean: 0.6; geometric mean: 0.3). Efficacy was therefore significant: 98.5% (p-value 0.0041) by geometric means and 99.4% (p-value 0.0084) by arithmetic means.

Efficacy both in terms of geometric as well as arithmetic means was therefore adequate, meeting the efficacy threshold of more than 90% for mange mites other than *Sarcoptes scabiei*, as recommended by guideline 7AE17a.

In terms of debris and cerumen (secondary effectiveness criterion), a moderate improvement regarding the debris/cerumen compared to the control group was observed at Day 28. This may be

expected as reactions to mites do not resolve immediately once mites die.

All recorded adverse events (n=3) were considered to be most likely not related to the administration of the IVP.

In summary, it can be accepted that the results of this study provide supportive evidence that NexGard, administered as a single dose at the currently approved dose, demonstrated an acceptable level of efficacy against an experimental infestation with *Otodectes cynotis* mites. Further, given that the dose of afoxolaner administered in this study is close to the minimum dose recommended for Nexgard Spectra (2.50 – 5.36 mg afoxolaner/kg bw), the data derived from this study may also be considered supportive of efficacy for Nexgard Spectra, which is also subject of this variation.

The second dose confirmation study (Lab 2) was a blinded, single site, GCP compliant laboratory study performed using naturally infested animals. This is in line with guideline 7AE17a, which states that at least one dose confirmation study should be performed using naturally infested animals. Though the study was performed outside of Europe, as *Otodectes cynotis* is a worldwide distributed parasite and peer-reviewed literature supported that significant phenotypical differences are unlikely to occur between strains, representativeness for the European situation is considered adequately justified.

The aim of the study was to assess the efficacy of a dose of afoxolaner of at least 2.5 mg/kg bw (NexGard and Nexgard Spectra) for the treatment of naturally acquired *Otodectes cynotis* infestation in dogs.

Enrolment was based on diagnostics. Ultimately, an appropriate number of 18 healthy beagle dogs were included that were all positive for *O. cynotis* in both ears. Animals were allocated into three treatment groups. One group received treatment with NexGard, one group received treatment with Nexgard Spectra, and one group was left untreated.

Efficacy evaluation was primarily based upon the number of live mite counts in all animals of each group. Efficacy was calculated per each treatment group in line with the guideline 7AE17a, which requires an overall efficacy of more than 90% for mange mites other than *Sarcoptes scabiei*.

At Day 0, both IVPs were administered as a single dose, using the formulation currently marketed, at the recommended treatment dose. It is noted that none of the treated animals received treatment at the lowest possible dose as authorised (2.5 mg of afoxolaner/kg bw).

On Days 3, 7, 14, 21 and 30, an otoscopic assessment was performed to assess the qualitative score of live mites. On Day 30, also a quantitative assessment of live mites was performed, by means of sedating the animals, flushing the ears and examining the earwax under an optical microscope for the count of live mites.

Both arithmetic as well as geometric means were calculated for each treatment group, which can be accepted as being in line with guideline 7AE17a.

At Day -1, mean otoscopic scores were identical (2.42) in the 3 groups.

All animals in the negative control group retained a mite infestation up to the quantitative assessment of live mites at Day 30.

In Group 2 (NexGard), no live mites were identified from Day 7 until Day 30, resulting in an acaricidal efficacy of 100% (for both arithmetic and geometric means).

In Group 3 (Nexgard Spectra), however, 4/6 dogs remained infested at Day 30. Two animals presented no live mites after ear flush, one animal presented live mites only in the right ear, and 3 animals presented live mite counts in both ears. The acaricidal efficacy for arithmetic and geometric

means, respectively, was determined at 89.19% and 92.90%. As in this study the number of parasites was expected to be highly variable and unknown at Day 0, geometric means instead of arithmetic means was used to assess effectiveness. It can be concluded that efficacy in terms of geometric means was adequate, meeting the efficacy threshold of more than 90% for mange mites (other than *Sarcoptes scabiei*), as recommended by guideline 7AE17a.

On adverse events, two animals had one episode of diarrhoea observed in the first hour post-treatment (pasty bloody stools). Diarrhoea is already mentioned as an adverse event under section 4.6 of the SPC for both products.

Based upon the presented results, it can be accepted that this dose confirmation study supports that NexGard and Nexgard Spectra, administered once at the currently approved dose, demonstrated an acceptable level of efficacy (100% and 92.90%, respectively, by geometric means) against a natural infestation with *Otodectes mites*.

Supplementary study

The applicant presented a GCP compliant, supplementary clinical trial (Field 2). The aim of the study was to determine the efficacy of afoxolaner (as both NexGard and Nexgard Spectra) against naturally acquired *Otodectes cynotis* infestations in dogs under field conditions, following one administration (Nexgard) or two monthly administrations (NexGard and Nexgard Spectra) at doses targeting the minimum label dose.

This was a parallel group designed, blinded, randomised, multicentric, negatively controlled, efficacy study conducted in Europe. Dogs included were 'privately owned by study sites/kennels'.

32 dogs of various breeds were ultimately included. Overall, although the animals were site owned dogs, the study population is considered sufficiently representative for the population in the field that will ultimately be treated.

Using a randomised block design, animals were divided in four groups of 8 dogs each: Group 1: negative control; Group 2: NexGard (Day 0); Group 3 NexGard (Day 0 and 30); Group 4: Nexgard Spectra (Day 0 and 30). Animals in Groups 3 and 4 therefore received two consecutive treatments. The number of animals that were included per treatment group is considered adequate.

Both products were administered at a dose close to the minimum label dose (NexGard: 2.69 - 2.99 mg/kg bw of afoxolaner, average dose: 2.82 mg/kg bw; Nexgard Spectra: 2.58 - 2.86 mg/kg bw of afoxolaner, average dose: 2.73 mg/kg bw), ensuring the assessment of effectiveness at the lower end of the dose range currently approved for these products, which is considered appropriate.

Efficacy evaluation was primarily based on the quantitative assessment of the total number of live mite counts (right and left ear and sum of adults, nymphs and larvae; sum of both ears were used for efficacy calculations) assessed during ear flushing, counting and classifying. Quantitative assessment was performed in all animals around Day 45. Efficacy calculations were primarily based on geometric means, but arithmetic means were also reported, which is considered appropriate and in line with guideline 7AE17a. The level of significance of the formal tests was at 5%, all tests were two sided.

The secondary efficacy criterion was semi-quantitative otoscopic assessment (that also included scoring of inflammation (debris/cerumen)). For otoscopic assessments, the presence or absence of visible live ear mites were recorded according to the following parameters: 'Negative'; + (low infestation); ++ (medium infestation), and +++ (high infestation). Otoscopic assessments were performed at Day -8, 0, 15, 30 and 45.

Similar to Study Lab 2, inclusion criterion was the presence of (naturally acquired) *O. cynotis* infestations in both ears as determined by otoscopic examination. Included animals had 'low to high'

infestations at Day 0. Even though some of the included animals primarily suffered from a 'low infestation', as it is acknowledged that the severity of a natural infection is expected to be lower than in a laboratory setting, the infestation upon initial presentation is considered to adequately represent the situation in the field.

Results demonstrated that at Day 45, based on geometric means, efficacy in all treated groups (Groups 2, 3, and 4) was 99.9% (p=0.0006), whilst no treatment effect was observed in the negative control group (Group 1). Based on arithmetic means, Group 3 showed an efficacy of 99.9%, while for Groups 2 and 4, efficacy was 99.8%.

Regarding the secondary criterion, otoscopic scores showed that in the treated groups, after D15, no animals scored ++ or above. Though it is noted that whilst all treated groups demonstrated a marked improvement, four animals maintained a 'low' ear mite score at Day 45. No explanation is provided for this observation, but as the quantitative assessment of the mites is considered to be a more accurate assessment for the evaluation of the presence of (live) mites and marked improvement was considered demonstrated, this issue is not pursued further.

Regarding debris/cerumen, most dogs had a negative or 'low' score on Day 30, and further improvement was observed on Day 45. It is considered that the follow-up period was not sufficient to evaluate complete resolution of all clinical signs, which may be expected as reactions to mites do not resolve immediately once mites die.

Overall, there was no significant effect of the number of treatment(s).

In conclusion, this study (performed with dogs that were naturally infested) demonstrated that both NexGard and Nexgard Spectra, administered as a single dose (NexGard) or as two doses (NexGard and Nexgard Spectra) at close to the minimum label dose, had an acceptable level of efficacy (99%) against natural infestation with *O. cynotis* mites.

Clinical trial

The applicant presented one clinical trial (Field 1). Instead of a study report, the applicant presented the scientific publication of the research (Panarese, 2021), a summary provided by the consulted expert as well as a study protocol. These documents were assessed in conjunction.

The data presented describe a very small (non-GCP compliant) field study. The aim of the study was to determine the efficacy of afoxolaner (NexGard) when administered twice at a monthly interval to dogs for the treatment of naturally acquired *Otodectes cynotis* infestation under field conditions. Animals were dosed according to label (3.33-4.86 mg afoxolaner/kg bw), which can be accepted in a clinical trial.

The study was a multi-site, negative control, blinded, clinical efficacy field trial conducted on pet-dogs in Italy. The study was performed using a randomized block design based on order of inclusion, and enrolment was based on diagnostics.

The study was performed in a single European region (Apulia region, Italy) and twenty dogs were included (of which ten were treated with the IVP). No justification for this number of animals was presented; however, it is noted that Guideline 7AE17a does not refer to a minimum number of animals that need to be included in order for a field study to be representative. Although this study was performed only in a single European region, as *Otodectes cynotis* is a worldwide distributed parasite and peer-reviewed literature supported that significant phenotypical differences are unlikely to occur between strains, representativeness of this study for the European situation was considered justified. In addition, an additional study (Field 2) also provided support for effectiveness of the product in dogs naturally infested with field strains from Europe (Greece).

Inclusion criterion was the presence of ≥1 live mite in at least one ear. It is noted that the inclusion criterion applied differs from that of the laboratory studies (Lab 1: presence of >10 mites in at least one ear; Lab 2: both ears should be positive for *O. cynotis*). As this was a field study performed in pet dogs, it however is acknowledged that the severity of an infection can be expected to be lower than in a laboratory setting and is considered representative for the population that will ultimately be treated. At D0, the total count of ear mites for each dog ranged from 1 to 21 and 1 to 24 for the control and treated group, respectively. The infestation of the animals prior to treatment is considered adequate.

NexGard was administered to the treatment group at the recommended treatment dose at Day 0 and Day 30 ±2. It is therefore noted that animals received two consecutive treatments. Treatment was administered to animals of several breeds (pointer, Breton, Segugio, Barboncino), aged 3 months to 11 years and weighing 2.3 to 19 kg. All animals harboured ≥1 live *Otodectes cynotis* mite upon inclusion, and were otherwise healthy.

Eight out of the ten animals in the negative control group retained mite infestation up to Day 42. It can therefore be accepted that the infestation intensity in the control group remained adequate.

Efficacy evaluation was primarily based on the number of live (motile) ear mite counts in animals on Day 42, thus, following two treatments. Arithmetic means for each group was calculated, which can be accepted as being an appropriate outcome parameter for demonstrating efficacy in line with guideline 7AE17a.

The clinical signs, semi-quantitative ear mite counts at Day 30 and the bacterial and fungal populations were also assessed on Day 0, 30 and 42.

At D30, before the re-administration of the IVP, all dogs in the IVP group were negative for the presence of ear mites at the otoscopic examination and deep swab method. Although ultimately the animals received two treatments, as treated dogs were negative for the presence of ear mites at Day 30, this study is considered to support that a single dose is sufficient for the treatment of *O. cynotis* infestation. A parasitological cure (100% efficacy based on arithmetic means) was again observed at Day 42 in all dogs in the IVP group, again meeting the overall efficacy threshold of more than 90% for mange mites other than *Sarcoptes scabiei*, as recommended by guideline 7AE17a.

It is noted that the clinical signs and symptoms associated with *O. cynotis* infestation reduced over the study period; however, the follow up period was not sufficient to evaluate complete resolution of all clinical signs. This may be expected as reactions to mites do not resolve immediately once mites die.

Based upon the findings from this small study performed under field conditions, it is accepted that in this small group of animals, NexGard administered once at the currently approved dose rate demonstrated an acceptable level of efficacy (100%) against natural infestation with *O. cynotis* mites in dogs.

No adverse events related to the administration of NexGard were observed in this study.

Overall conclusion:

In summary, based on the presented data, both NexGard and Nexgard Spectra demonstrated an acceptable level of efficacy against *O. cynotis* mite infestations after a single administration, also when administered at the minimum label dose.

The indication against ear mite infestations *(*caused by *Otodectes cynotis)* in dogs can therefore be accepted.

To ensure that a reinfestation is treated appropriately, the following text has been included under the

"Amounts to be administered and administration route" section of the SPC: "*A further veterinary examination one month after the initial treatment is recommended as some animals may require a second treatment*". This is considered appropriate.

In terms of safety, the CVMP accepts that both NexGard chewable tablets and Nexgard Spectra chewable tablets can be considered safe in the treatment of ear mite infestations *(*caused by *Otodectes cynotis)* in dogs, as shown in the four studies presented above.

3. Benefit-risk assessment of the proposed change

NexGard is authorised as chewable tablets for the treatment of flea (*Ctenocephalides felis* and *C. canis*) and tick (*Dermacentor reticulatus, Ixodes ricinus, Ixodes hexagonus, Rhipicephalus sanguineus*) infestations and for the treatment of demodicosis (caused by *Demodex canis*) and sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*) in dogs; the product can also be used as part of a treatment strategy for the control of flea allergy dermatitis. The active substance is afoxolaner, an insecticide and acaricide belonging to the isoxazoline family, which is administered at a dose of 2.7–7 mg/kg bodyweight.

Nexgard Spectra is authorised as chewable tablets for the treatment of flea (*Ctenocephalides felis* and *C. canis*) and tick (*Dermacentor reticulatus, Ixodes ricinus, Ixodes hexagonus, Rhipicephalus sanguineus*) infestations in dogs when the concurrent prevention of heartworm disease (*Dirofilaria immitis* larvae), angiostrongylosis (reduction in level of immature adults (L5) and adults of *Angiostrongylus vasorum*), thelaziosis (adult *Thelazia callipaeda*) 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 authorised for the treatment of demodicosis (caused by *Demodex canis*) and sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), and it can also be used as part of a treatment strategy for the control of flea allergy dermatitis. The active substances are afoxolaner, an insecticide and acaricide of the isoxazoline family, and milbemycin oxime, an antiparasitic endectocide belonging to the group of macrocyclic lactones, which are administered at a dose of 2.50–5.36 mg/kg bodyweight and 0.50–1.07 mg/kg bodyweight, respectively.

The proposed grouped variation is to add two new therapeutic indications for the treatment of tick infestations with *Hyalomma marginatum* and for the treatment of ear mite infestations (caused by *Otodectes cynotis*), and to amend the product information to allow the use of the product in breeding, pregnant and lactating female dogs. In addition, the applicant takes the opportunity to make an editorial change in the "Nature and Composition of immediate packaging" sections of the SPCs for both products.

3.1. Benefit assessment

Direct therapeutic benefit

As this is a variation to introduce two additional indications to existing presentations of the products NexGard and Nexgard Spectra chewable tablets for dogs, the direct benefits would arise from the inclusion of these new indications.

The proposed benefit of NexGard and Nexgard Spectra is their efficacy in the treatment of ear mite infestations (caused by *Otodectes cynotis*). This was successfully demonstrated in two laboratory

studies, a trial performed under field-like conditions and a clinical field trial.

In addition, the products were claimed to provide immediate and persistent tick killing activity for a new tick species, *Hyalomma marginatum*, for up to one month. Efficacy against this non-autochthonous tick was assessed in a laboratory study using the product NexGard. Although efficacy of Nexgard Spectra against this tick species was not specifically evaluated in a laboratory study, based upon the high level of efficacy observed for NexGard in the study conducted, the previously demonstrated absence of interaction between the active substances in Nexgard Spectra, the dose range evaluated and the accepted efficacy of Nexgard Spectra against other tick species from the family *Ixodidae*, a similar level of efficacy can be accepted for both products.

Finally, it was demonstrated that NexGard and Nexgard Spectra can safely be used in breeding, pregnant and lactating dogs.

Additional benefits

Hyalomma marginatum ticks are known vectors for Crimean-Congo haemorrhagic fever virus, a virus that may infect the target species, dogs, without causing overt signs, but has been described to cause haemorrhagic fever in humans.

No further additional benefits are foreseen.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation

Safety:

Risks for the target animal:

Administration of NexGard and Nexgard Spectra in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions are appropriately included in the SPCs and no new adverse reactions arise from the studies performed in support of the proposed new indications.

No increased frequency of treatment administration is proposed. Consequently, no additional risk for the target species is foreseen.

Information that the safety of the veterinary medicinal product has not been established in breeding male dogs is adequately communicated in the product information.

Risk for the user:

The CVMP previously concluded that user safety for these products is acceptable when used according to the SPC recommendations. The frequency of treatment does not change due to the addition of the new indications. Therefore, no additional risk for the user arises.

Risk for the environment:

NexGard and Nexgard Spectra are not expected to pose a risk for the environment when used according to the SPC recommendations.

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 products relevant to the target animal, user, and environment and to provide advice on how to prevent or reduce these risks.

3.4. Evaluation of the benefit-risk balance

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

The proposed benefit of NexGard and Nexgard Spectra is their efficacy in the treatment of ear mite infestations (caused by *Otodectes cynotis*). In addition, NexGard and Nexgard Spectra can be accepted as providing immediate and persistent tick killing activity for a new tick species, *Hyalomma marginatum*, for up to one month.

The products are well tolerated by the target animals and present an acceptable risk for users and the environment, when used as recommended. The products can safely be used in breeding, pregnant and lactating dogs. Appropriate precautionary measures are included in the SPCs and other product information.

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary data presented on efficacy and target animal safety, the Committee for Veterinary Medicinal Products (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 (Regulation (EU) 2019/6), as follows: to add two new therapeutic indications for the treatment of tick infestations with *Hyalomma marginatum* and for the treatment of ear mite infestations (caused by *Otodectes cynotis*), and to amend the product information to allow the use of the product in breeding, pregnant and lactating female dogs. In addition, the applicant takes the opportunity to make an editorial change in the "Nature and Composition of immediate packaging" section of the SPC for both products.

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 these variations, the "Indication for use", "Use during pregnancy, lactation or lay", "Amounts to be administered and administration route", "Pharmacodynamic properties" and "Nature and Composition of immediate packaging" sections of the SPCs are updated. The corresponding sections of the package leaflets are updated accordingly.