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Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for NexGard (EMEA/V/C/002729) and NexGard Spectra (EMEA/V/C/003842) following a worksharing procedure (EMA/VRA/0000245082)

INN: afoxolaner (NexGard); afoxolaner, milbemycin oxime (Nexgard Spectra)

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

Rapporteur: Jeremiah Gabriel Beechinor

Co-Rapporteur: Kim Boerkamp

Table of contents

1. Introduction

1.1. Submission of the variation application

In accordance with Article 65 of Regulation (EU) 2019/6, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 28 March 2025 an application for a group of variations requiring assessment for NexGard and NexGard Spectra, following a worksharing procedure.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Addition of a new therapeutic indication or modification of an approved one
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The grouped variation concerns change(s) to therapeutic indication(s): addition of a new therapeutic indication or modification of an approved one: for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for 28 days and for reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days.

In addition, the applicant has proposed further updates to the product information of both VMPs concerned to:

a)

- align the product information of these products with QRD v.9.1 as no new or additional quality-related data is required for the assessment.
- correct errors (i.e. language of the country where local representative is located outside the country concerned and ISO codes) in section 16. '*Contact details*' of the package leaflet for '*Local representatives and contact details to report suspected adverse events*.'

b)

- reflect the significant improvement of clinical signs observed in correlation with the efficacy for the treatment of demodicosis (caused by *Demodex canis*) in the product information.

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, Part 4.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

NexGard chewable tablets is currently authorised for use in dogs for the treatment of flea and tick infestations and for the treatment of demodicosis, sarcoptic mange and ear mite infestations. It contains the active substance afoxolaner, an insecticide and acaricide belonging to the isoxazoline family. The product should be administered at a dose of 2.7 to 7 mg/kg bodyweight of afoxolaner.

NexGard Spectra chewable tablets is authorised for use in dogs with, or at risk from, mixed infestations by external and internal parasites. The veterinary medicinal product is only indicated when use against ticks, fleas, or mites and one or more of the other target parasites is indicated at the same time. It contains the active substances afoxolaner, an insecticide and acaricide belonging to the isoxazoline family, and milbemycin oxime, an antiparasitic endectocide belonging to the group of macrocyclic lactones. The product should be administered at a dose of 2.50 to 6.94 mg/kg bodyweight of afoxolaner and 0.50 to 1.39 mg/kg bodyweight of milbemycin oxime.

The proposed grouped variation concerns change(s) to therapeutic indication(s): addition of a new therapeutic indication or modification of an approved one to both VMPs: for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for 28 days and for reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days. Additionally, the applicant has proposed an amendment to section 3.9 of the SPC to reflect the improvement of clinical signs observed in correlation with the efficacy for the treatment of demodicosis (caused by *Demodex canis*).

No change to the currently authorised dosing regimen for either VMP is proposed for these indications, i.e. efficacy is expected following administration of single dose (NexGard: 2.7 - 7.0 mg afoxolaner/kg bw; NexGard Spectra: 2.50 - 6.94 mg afoxolaner/kg bw and 0.50 - 1.39 mg milbemycin oxime/kg bw). Treatment may be repeated at 1-month intervals if deemed necessary by the responsible veterinarian.

With the introduction of the proposed changes to therapeutic 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 changes to therapeutic indications will not present an unacceptable risk for the user or the environment. Safety for the target animals is discussed in the sections below.

2.1. Reduction of the risk of infection with Babesia canis via transmission by Dermacentor reticulatus

Babesiosis is an inoculable infectious disease caused by the multiplication of Apicomplexa protozoa, belonging to the genus *Babesia* in various mammals. *Babesia* are strictly intraerythrocytic parasites, infecting the red blood cells (i.e. erythrocytes). These organisms are transmitted by various hard tick species and affect a wide range of mammals, including humans, ruminants, horses and carnivores. Each *Babesia* species is specific to its vector and host, and the geographical distribution and epidemiological characteristics of *Babesia* spp. are linked to the biology of each tick vector.

In support of the proposed indication for the reduction of the risk of infection with *B. canis* via transmission by *D. reticulatus*, the applicant has provided the results of one pivotal laboratory dose confirmation study (Lab#1), along with supportive evidence from two studies in the published scientific literature (Beugnet et al., 2014a and 2015b).

The pivotal dose confirmation study (Lab#1) was a well-conducted, GCP compliant, study performed in South Africa. Consideration was given to the current CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.4).

The IVP used is the commercial formulation of "NexGard Spectra". It has previously been accepted by CVMP that there is no interaction between the anthelmintic substance milbemycin oxime and afoxolaner. Milbemycin oxime shows no activity against protozoans, including *B. canis*. Therefore, the results obtained with NexGard Spectra are also considered relevant to NexGard (afoxolaner only), and vice versa.

With regard to animal welfare during the study, it is noted that animals were housed individually in cages. While visual and auditory contact with other dogs was accommodated, no physical contact was possible (constituting a deviation from Directive 2010/63/EU). However, the applicant justifies the approach taken on the basis that daily evaluation of potential babesiosis necessitated single housing as urine colour change and diarrhoea are significant signs of *B. canis* and thus individual cage environments were necessary for accurate attribution. Dogs were socialised weekly on days when they did not harbour ticks. At least one toy/chew was made available to each dog (replenished weekly). Otherwise, housing conditions (including cage size, photoperiod, etc.) were in line with the afore-mentioned Directive.

Twenty-four laboratory dogs were included in this study, with a range of ages and bodyweights represented. Dogs were allocated to three groups of eight dogs each (Groups 1 and 2 – untreated controls; Group 3 – treated with NexGard Spectra). To ensure that dogs had not previously been infected with *B. canis*, blood samples were collected from each animal on Day -5 and tested for *B. canis* using Polymerase Chain Reaction (PCR) and Immunofluorescence Assay (IFA). No dog tested positive for *B. canis* by either method prior to study start. All animals were also tested for their ability to carry adequate numbers of *D. reticulatus* ticks prior to the start of the study. On Day -7, all dogs were artificially infested with approximately 50 (±2) unfed adult ticks (not infected with *B. canis*). Subsequently, all dogs (depending on group allocation) were infested with 50 (±2) viable, unfed, adult ticks that had been infected with *B. canis*, on Day 1 (Groups 1 and 3 only) and Day 28 (Groups 2 and 3 only). The *B. canis* infection rate of the ticks used in this study was 23% (confirmed by PCR), which exceeds the prevalence reported in the field. To facilitate tick infestation, dogs were sedated and placed into an infestation chamber for approximately one to two hours following infestation.

Tick count and removal was conducted on Days -5 (all dogs), Day 7 (Groups 1 and 3 only) and Day 34 (Groups 2 and 3 only).

The primary assessment criterion was the number of *B. canis* infected dogs counted in the control and the IVP group on the various assessment days. Dogs were considered infected with *B. canis* if/when they tested positive by both PCR analysis and IFA serology. At least six dogs in the negative control group had to test positive for *B. canis* to demonstrate adequate infection levels. The secondary efficacy variable was the assessment of the effect against ticks (as counted on Days 7 and 34).

Blood samples were collected for PCR and IFA analysis from dogs in Group 1 on Day 21, for dogs in Group 2 on Day 42 and for dogs in Group 3 on Days 21, 28, 42 and 56. Additional blood sampling for

PCR analysis was conducted in dogs from Group 1 (Day 8 and Day 9) and Group 2 (Day 35, Day 36 and Day 37) that were diagnosed positive for babesiosis on a blood smear.

Rectal temperatures were recorded once daily from Day 7-29 for animals in Groups 1 and 3, and from Day 34-56 for animals in Groups 2 and 3. In cases where a diagnosis of *B. canis* infection was suspected (e.g. clinical signs of babesiosis such as lethargy, haematuria or body temperature >39.5 °C), two blood smears were obtained from the animal in question and examined for *Babesia* merozoites.

By Day 9 all dogs in Group 1, and by Day 37 for Group 2 had tested positive for *B. canis* by PCR analysis. This indicated a successful infection challenge.

None of the dogs in Group 3 tested positive for *B. canis* by PCR at any timepoints, demonstrating that single oral administration of NexGard Spectra was 100% effective at blocking the transmission of *B. canis* for 28 days post-administration. However, the possibility that some treated dogs were PCR positive at the timepoints when animals in the control group were positive cannot be excluded. Nonetheless, it is accepted that none of the dogs in the treated group developed clinical infection and/or seroconverted based on IFA results. Following rescue treatment, all animals in Group 1 and Group 2 tested negative at the next relevant PCR timepoint.

With regard to the secondary efficacy endpoint (efficacy against *D. reticulatus*), the IVP provided 100% reduction at 7 days post-administration (6 days after infestation on Day 1) as well as at 34 days post-administration (6 days after infestation on Day 28). At each of these timepoints, control animals had more live attached ticks than those treated with the IVP (Group 3). The differences between the live attached tick counts of the dogs in the negative control groups and the IVP treated group were statistically significant ($p \leq 0.0001$).

The strain of *D. reticulatus* used in this dose confirmation study was of EU origin (Ireland) and had been enriched with ticks obtained from the Netherlands in 2009, 2012, 2014 and 2017. While it is noted that the efficacy of afoxolaner against *D. reticulatus* is the primary aim in terms of reducing the risk of infection with *B. canis*, it is acknowledged that the strain of *B. canis* used in this study also originated from within the EU (Netherlands). Therefore, it can be accepted that the parasite strains used in this study were suitably representative of EU field conditions. Furthermore, although female ticks are the major vector of *Babesia*, it is noted that efficacy against male ticks was also evaluated in this pivotal study (sex ratio 1:1). Therefore, the results indicate adequate efficacy against the transmission of *B. canis* by both female and male ticks.

With regard to safety, the IVP appears generally to have been well-tolerated, and no adverse events were observed during the study period which were considered to be treatment related. Clinical observations noted in study animals (mainly untreated controls) included lethargy, dark urine, diarrhoea, vomiting and excessive salivation. These findings were deemed by the applicant to have been a result of infection with *B. canis*, or adverse events associated with rescue treatments (diminazene and imidocarb). On this basis, the product information pertaining to safe use in the target species is considered adequate in its current state.

The first supportive GCP-compliant study for reduction of transmission of *B. canis* by *D. reticulatus* (Beugnet et. al, 2014a) was conducted in South Africa. However, the strains of both *D. reticulatus* and *B. canis* used in the experimental model originated in the EU.

The IVP used in the study was the commercial formulation of "NexGard", containing 2.27% w/w afoxolaner; dogs were administered the 3 g chew size containing 68 mg afoxolaner (as appropriate for the weight range). This equated to an actual achieved dose rate of 3.17-5.68 mg afoxolaner/kg

bodyweight for dogs in the IVP group (i.e. within the range currently recommended in the NexGard SPC; 2.7-7.0 mg/kg bw).

The study had a controlled, blinded, randomised block design. Sixteen healthy mongrel dogs (male and female), weighing from 11.97 to 21.43 kg and older than 2 months were included. Study animals were confirmed free of both tick infestation and *B. canis* infection prior to inclusion. Dogs were randomly allocated (based on bodyweight blocking) to two groups of n=8 animals each.

Dogs were infested with 50 viable, unfed, adult (balanced male:female ratio) *D. reticulatus* ticks on Days 7, 14, 21 and 28. The *B. canis* infection rate of the ticks was confirmed by PCR and ranged from 8-10%. Tick counts were conducted in situ on Days 9, 16 and 23, with ticks being removed and counted on Day 30 (or earlier if a dog was diagnosed positive for *B. canis*).

The arithmetic mean tick counts recorded for the untreated control group was 15.0 at Day 9 and 41.1 on Day 16, indicating a vigorous tick challenge. This approach is in line with the recommendations of the CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMA/CVMP/EWP/5/2000-Rev.4) and is therefore considered acceptable.

The primary assessment criterion was the blocking efficacy of NexGard on *B. canis* transmission. Animals were defined as positive for *B. canis* when confirmed positive by IFA or PCR or by blood smear.

During the study, dogs underwent daily clinical examinations to detect any signs of canine babesiosis. Blood smears were taken for any animal exhibiting a high temperature including body temperature (>39.4 °C) or clinical signs of *B. canis* infection. Blood samples were collected for IFA and PCR analysis from all dogs once on Day -7 (prior to treatment to ensure animals were negative for *B. canis*), and on Days 14/15, 21, 28, 42, 49 and 56. Additional Day 86 and Day 93 post-study samples were taken on all dogs to check the maintenance of the serological status.

All dogs in the untreated control group tested positive for babesiosis based on blood smear and PCR analysis on Day 14/15. Seven out of the eight control dogs became serologically positive (IFA) on Day 21. However, none of the NexGard treated animals tested positive for *B. canis* by blood smear, PCR or IFA, indicating that NexGard was 100% effective at preventing the transmission of *B. canis* by infected *D. reticulatus* ticks for 28 days post-administration.

In terms of target animal safety, NexGard was well-tolerated by all dogs with no adverse events reported. *Babesia canis* was transmitted by *D. reticulatus* to all untreated control dogs, confirmed following demonstration of hyperthermia, detection of *B. canis* parasites in blood smears and PCR assay from blood and serology. Dogs with a confirmed diagnosis of *B. canis* infection were subsequently treated with imidocarb and diminazene, and NexGard treated dogs remained negative based on all criteria until study end (Day 56). These findings support the claim that oral treatment of dogs with NexGard can prevent transmission of *B. canis* and development of clinical babesiosis through its effect on *D. reticulatus* for 28 days.

A second laboratory study (Beugnet et. al, 2015b) assessed the speed of kill and efficacy of NexGard against *D. reticulatus*, and was provided as supportive information for the claimed indication. The study also included a group treated with fluralaner to evaluate comparative efficacy between the two isoxazolines. Dogs were also infested with *Rhipicephalus sanguineus* ticks for comparative purposes. However, in the context of the current variation, only information relating to NexGard and *D. reticulatus* was considered.

A parallel group, randomised, single centre, blinded and controlled study design was implemented. Twenty-four mixed breed dogs (male and female), weighing from 12 to 27.7 kg and older than 6 months were included. Eight animals were included in each group.

Dogs assigned to the IVP group were treated with NexGard on Days 0, 28 and 56 as per label instructions. Dogs assigned to control group were not treated and served as negative controls. Dogs were infested with 50 viable, unfed, adult (male:female ratio of 1:1) *D. reticulatus* ticks (originating from Europe) on Days 28, 35, 42, 49, 56, 63, 70, 77 and 84. Ticks were directly deposited on the mid-line of the dogs. On Days 28 and 56, NexGard treatment was administered at the time of tick challenge. Speed of kill was investigated at 24 hours post-infestation. The arithmetic mean tick counts for the negative control group ranged from 19.5 to 39.8, indicating vigorous tick challenges on all assessment days. This approach is considered to be appropriately in line with the recommendations of the CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.4).

The primary endpoint in this study was the percentage reduction in arithmetic mean tick count (live attached and live free) compared to the control. Abbott's formula was used to calculate the percentage reduction between the treated and control animals, and the resulting percentage reductions at 24 hours against new tick infestations were 99.4, 99.1, 94.1, 95.5, 99.6, 99.0, 96.0, 94.4, and 85.2% on days 29, 36, 43, 49, 57, 64, 71, 78 and 85, respectively. It is noted that the efficacy against *D. reticulatus* reported for day 85 fell slightly short (85.2%) of the expected level (90%) recommended in the aforementioned CVMP guideline. However, given the proximity to guideline requirements, and considering the body of original and complementary evidence provided by the applicant regarding efficacy against *D. reticulatus*, it can be accepted that Nexgard and NexGard Spectra are expected to have adequate efficacy in the treatment and prevention of *D. reticulatus* under field conditions. The NexGard treated groups had statistically significantly ($p < 0.05$) less *D. reticulatus* ticks compared to the untreated control group at all timepoints.

No adverse events related to the oral administration of NexGard were observed.

The recommended dose rates for NexGard and NexGard Spectra will remain unchanged as a result of this variation, and appropriate guidance is given in relation to reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for 28 days in the proposed SPC.

It is noted that the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015) stipulates that at least one laboratory study and one clinical trial is needed for each claimed vector-borne pathogen, unless otherwise justified. However, it is accepted that a high level of efficacy against *D. reticulatus* (and consequently transmission of the vector-borne pathogen (VBP) *B. canis*) was demonstrated in the presented laboratory dose confirmation studies.

The VBP infection rate in the vectors used in the dose confirmation study Lab#1 was also much higher than that reported in the field according to published literature. In this study, the *B. canis* infection rate of *D. reticulatus* ticks used for artificial infestations was 23%. All animals were also repeatedly infested, which served to mimic a high and prolonged infection pressure.

Additionally, it is noted that a number of the referenced GCP-compliant studies, including the pivotal laboratory dose confirmation study Lab#1, were conducted using EU strains of *D. reticulatus* and *B. canis*. *Dermacentor reticulatus* ticks originating from Europe (Ireland) and enriched with ticks obtained from the Netherlands were used in the cited study. The *Babesia canis* parasite used in the study originated from Europe (Netherlands). Furthermore, it is acknowledged that regular use of isoxazolines

in Europe, representing the vast majority of ectoparasiticides sold by veterinarians, has reduced the prevalence of canine babesiosis (Solano-Gallego et al., 2016). On this basis, the applicant's argumentation regarding difficulties in running clinical trials to evaluate *Babesia* transmission is accepted.

Based on the totality of evidence presented with the original and current application, it is considered that the omission of further clinical trials has been adequately justified by the applicant.

In conclusion, based on the data presented, it is accepted that NexGard and NexGard Spectra, when administered on a single occasion at the recommended therapeutic dose, achieved an adequate level of efficacy to support an indication for the reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for 28 days after treatment. For accuracy purposes, the protozoan agent has been referred to as *Babesia canis* *canis* in the product information in order to differentiate from other *Babesia canis* subspecies which can be transmitted by other tick species.

Given the above, the corresponding G.I.7.a variation is considered to be approvable.

2.2. Reduction of the risk of infection with Dipylidium caninum via transmission by Ctenocephalides felis

Dipylidiasis is caused by the heteroxenous cestode *Dipylidium caninum* through ingestion of the intermediate host (fleas) by the definitive host (carnivores). *D. caninum* is also a zoonotic pathogen, although human infections are rare. Children seem the most vulnerable due to their playing habits and close proximity to pets.

To support the second proposed additional treatment claim, one laboratory dose confirmation study (Lab#2) and one published study (Beugnet et al., 2017) were presented.

The pivotal dose confirmation study (Lab#2) was conducted in South Africa using the commercial formulation of NexGard, in accordance with VICH GCP standards. While not performed within the EU, the study was designed considering the relevant CVMP and VICH guidelines for efficacy of ectoparasiticides, anthelmintics, and data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats.

The study was performed in accordance with the CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestations in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.4) and the requirements provided in VICH GL19: Efficacy of anthelmintics: specific recommendations for canines (EMA/CVMP/VICH/835/1999).

The study used US strains of *C. felis* and *D. caninum*. Given that efficacy of afoxolaner against flea isolates from the EU and USA was similar in the original studies submitted with the marketing authorisation applications for NexGard (EMEA/V/C/002729/0000) and NexGard Spectra (EMEA/V/C/003842/0000), it can be accepted that the results of this study are also relevant for the EU field situation. Although the strain of *D. caninum* used in this dose confirmation study was also of US origin, no differences for EU strains are anticipated as it has been shown that the distinct genotypes of the *D. caninum* population are related to host origin (dogs or cats), irrespective of their geographical origin (Labuschagne et al. 2018). Moreover, the effect of both NexGard and NexGard Spectra is against the flea vector rather than the tapeworm, which renders the specific strain of *D. caninum* of lesser importance for the reduction claim sought for the VMP.

In relation to animal welfare during the study, it is noted that animals were housed individually in cages. Visual and auditory contact with other dogs was accommodated, but no physical contact was possible. While this represents a deviation from Directive 2010/63/EU, the applicant has justified the

approach taken on the basis that individual housing was necessary to identify the origin of any *D. caninum* proglottid(s) found in the cage environment. At least one toy/chew was made available to each dog (replenished weekly). Otherwise, housing conditions (including cage size, photoperiod, etc.) were in line with the afore-mentioned Directive. This argumentation can be accepted.

The study followed a parallel group, blinded, randomised, single centre, negative controlled, design. Fourteen Beagle and mongrel dogs (10 male and 4 female), weighing from 13.30 - 19.05 kg, and aged 12 - 110 months were included. All dogs were confirmed healthy and free of both flea infestation and *D. caninum* infection prior to inclusion. Dogs were randomly allocated to two groups, based on flea counts following pre-treatment infestation with non-infected *C. felis*.

On Day 0, all IVP dogs were treated with NexGard. Afoxolaner was administered at a target dose of 2.5 mg/kg bw (actual range 2.54 to 2.80 mg/kg bw). However, the currently authorised minimum RTD for NexGard is slightly higher, at 2.7 mg afoxolaner/kg bw. Nonetheless, the approach taken can be accepted on the basis that the lower dose of 2.5 mg/kg bw reflects that recommended for NexGard Spectra. No interaction has been identified between afoxolaner and milbemycin oxime (as included in the fixed combination VMP NexGard Spectra). Therefore, if efficacy can be demonstrated at 2.5 mg/kg bw for the mono-active NexGard, then it is logical that efficacy should also be anticipated at the authorised dose range of 2.7-7.0 mg afoxolaner/kg bodyweight.

Dogs were infested with 100 unfed, adult (balanced male:female ratio), *C. felis* fleas infected with a recent field isolate (< 10 years old) of *D. caninum* on Days 1, 7, 14, 21 and 30. Fleas were removed and counted only on Day 35. On Day 35, the arithmetic mean flea count was 58.1 in the control group, and 0 in the treated group. Although not the primary objective of the study, this confirms 100% efficacy of NexGard against *C. felis*.

By extension, the results also support that the reduction of transmission of *D. caninum* is directly related to the sustained insecticidal activity. The infection rate of the batch of fleas used each week to infest the dogs ranged from 13% to 37% (confirmed by microscopic examination of a sample of at least 30 fleas at each infestation timepoint to determine the prevalence of infection with *D. caninum* cysticercoids). This is a significantly higher infection rate compared to that reported in published literature; Beugnet et al. (2014b) collected and analysed fleas in Europe (2701 *C. felis* and 2828 *C. canis*) and found that 2.23% of *C. felis* fleas were infected with *D. caninum*. The assessment criterion was the number of dogs that became infected with *D. caninum*, through macroscopic faecal examination (including inspection of cages and sleeping areas) and visual inspection of the perianal region of the dogs for the presence of proglottids. Previous studies had demonstrated that this method was sensitive enough to recover all infected animals. Macroscopic faecal examinations (including inspection of cages and sleeping areas) and visual inspection of the perianal region of the dogs for the presence of proglottids were carried out from Days 28 to 70, to confirm *D. caninum* infections.

All 7 dogs in the negative control group were found positive for *D. caninum*, with infections first confirmed on Day 30. In the experimental design, infesting dogs with a high rate of *D. caninum* infected fleas resulted in a high level of infection in control dogs which overcome the difficulty to diagnose infection under field conditions. In the present study design, a large number of proglottids were shed in faeces by the dogs.

None of the NexGard-treated animals was confirmed positive for *D. caninum* by macroscopic faecal examination, indicating that NexGard was 100% effective at blocking the transmission of *D. caninum* for 30 days post-administration. The difference in infection rate between the negative control group and IVP treated group was statistically significant ($p = 0.0006$).

NexGard was well-tolerated by all animals in the IVP group.

A second GCP-compliant laboratory study (Beugnet et al., 2017), also conducted in South Africa, was cited by the applicant from published literature in support of the *C. felis*/*D. caninum* claim. While it is not clear from the publication itself, the applicant states that the cestode (*D. caninum*) originated from South Africa and the vector (*C. felis*) originated from Europe.

The IVP used in the study was the commercial formulation of "NexGard Spectra".

The study followed a parallel group, blind, randomised, negative control design. Twenty healthy mixed breed dogs (males and non-pregnant females) were included. Dogs had not been treated with a long-acting topical or systemic acaricide/insecticide in the 12 weeks preceding Day 0. Dogs were randomly allocated (based on bodyweight blocking) to two groups (IVP-treated and negative control) of n=10 animals each.

On Day 0, dogs in the IVP group were treated with NexGard Spectra at a dose rate ranging from 2.92 to 3.02 mg/kg bw. All dogs were infested with 100 infected *C. felis* fleas on Days 7, 14, 21 and 28. The *D. caninum* infection rate of the fleas used to infest dogs was assessed by dissecting 30 fleas before each weekly infestation; the rate of infection ranged from 10 to 33%.

An arithmetic mean of 47.7 fleas were recovered from the untreated control dogs, whereas no fleas were recovered from the treated group on Day 35, corresponding to 100% efficacy against fleas at Day 35. This indicated an adequate level infestation, in line with the CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMA/CVMP/EWP/5/2000-Rev.4), which states that approx. 50% of the fleas used for artificial infestation present on each control animal at each time point following infestation.

The primary efficacy criterion was based on the collection of *D. caninum* proglottids, either in dog's faeces or on cage floors. This approach has been previously demonstrated in studies conducted by the same author to be sensitive enough to identify all *D. caninum*-infected animals (Beugnet et al., 2013 and 2014). This method was selected over microscopic coproscopy or faecal PCR due to limitations in the sensitivity of the latter techniques. Based on the daily collection of *D. caninum* proglottids excreted by dogs during the 70 days of the study, 70% (7/10) of the control dogs and 0% (0/10) of the treated dogs were infected with *D. caninum*; this difference was statistically significant ($p < 0.0031$). The author concluded that, under the conditions of this study, a single treatment with orally administered NexGard Spectra was 100% effective in preventing infection with *D. caninum* tapeworms in dogs, after four weekly infestations with 100 fleas from a population infected by *D. caninum*.

NexGard Spectra was generally well-tolerated by treated dogs. On Day 35, one dog from the treated group had mild erythema on the abdomen and inguinal area, which resolved without requiring therapy. A second dog in the IVP group displayed bilateral hair loss on the flanks on Day 43; following topical treatment with an essential oil the skin condition improved. It is noted that erythema is already captured as an adverse event in the product information for NexGard Spectra with a frequency descriptor of "Very rare". However, limited discussion is provided regarding the potential causes of hair loss in the second animal. Nonetheless, considering the delay between IVP administration and onset of clinical signs, and also the known pharmacokinetic properties of afoxolaner and milbemycin oxime (T1/2 of 2 weeks and 3.3±1.4 days, respectively) it could be accepted that this finding was unlikely to have been treatment related. Therefore, no updates to section 3.6 of the SPC or corresponding sections of the package leaflet are considered necessary at this time.

It is agreed that the findings of this published study support the claim that oral treatment of dogs with afoxolaner can prevent transmission of *D. caninum* through its effect on *C. felis* for one month.

The recommended dose rates for NexGard and NexGard Spectra will remain unchanged as a result of this variation, and appropriate guidance is given in relation to reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days in the proposed SPC.

It is noted that the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015) stipulates that at least one laboratory study and one clinical trial is needed for each claimed vector-borne pathogen, unless otherwise justified. However, it is accepted that a high level of efficacy against *C. felis* (and consequently transmission of the VBP *D. caninum*) was demonstrated in the presented laboratory dose confirmation studies.

The VBP infection rate in the vectors used in the dose confirmation study Lab#2 was also much higher than that reported in the field according to published literature. In this study, the *D. caninum* infection rate of the batch of fleas used each week to infest the dogs ranged from 13% to 37%, compared to a reported 2.23% prevalence in *C. felis* in Europe (Beugnet, 2014b). All animals were also repeatedly infested, which served to mimic a high and prolonged infection pressure.

Based on the totality of evidence presented with the original and current application, it is considered that the omission of further clinical trials has been adequately justified by the applicant.

In conclusion, based on the data presented, it is accepted that NexGard and NexGard Spectra, when administered on a single occasion at the recommended therapeutic dose, achieved an adequate level of efficacy to support an indication for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days after treatment.

Consequently, the corresponding G.I.7.a variation is considered to be approvable.

Additional changes to the product information

The proposed amendment to section 3.9 of the SPC regarding the improvement of clinical signs observed in correlation with the efficacy for the treatment of demodicosis (*Demodex canis*) is not fully acceptable. While the applicant's reference to the 2018 "CVMP assessment for worksharing grouped type II variation for NexGard and NexGard Spectra (EMEA/V/C/WS1338/G)" is noted, from a disease management perspective, effective treatment will logically lead to a reduction in clinical signs and an improvement in the condition of the treated animal. Given that treatment of demodicosis has already been accepted and included as an indication in section 3.2 of the SPC, efficacy for this claim is to be expected. The CVMP nonetheless acknowledges that information relating to the improvement in clinical signs associated with treatment against *D. canis* is mentioned in the product information for a number of similar products. On this basis, the CVMP can agree to include such information. However, in order to ensure consistency with the wording previously accepted by the CVMP for other similar products, the applicant amended the additionally proposed wording in section 3.9 of the SPC for NexGard and NexGard Spectra accordingly.

The applicant has also taken the opportunity to align the product information for both products – NexGard and NexGard Spectra - with version 9.1 of the QRD template. This is considered acceptable.

3. Benefit-risk assessment of the proposed change

NexGard chewable tablets is authorised for use in dogs for the treatment of flea and tick infestations and for the treatment of demodicosis, sarcoptic mange and ear mite infestations. It contains the active substance afoxolaner, an insecticide and acaricide belonging to the isoxazoline family. The product should be administered at a dose of 2.7 to 7 mg/kg bodyweight of afoxolaner.

NexGard Spectra chewable tablets is authorised for use in dogs with, or at risk from, mixed infestations by external and internal parasites. The veterinary medicinal product is only indicated when use against ticks, fleas, or mites and one or more of the other target parasites is indicated at the same time. It contains the active substances afoxolaner, an insecticide and acaricide belonging to the isoxazoline family, and milbemycin oxime, an antiparasitic endectocide belonging to the group of macrocyclic lactones. The product should be administered at a dose of 2.50 to 6.94 mg/kg bodyweight of afoxolaner and 0.50 to 1.39 mg/kg bodyweight of milbemycin oxime.

The proposed variation concerns change(s) to therapeutic indication(s): addition of a new therapeutic indication or modification of an approved one: for reduction of the risk of infection with *Babesia canis* via transmission by *Dermacentor reticulatus* for 28 days and for reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days. The product information has also been aligned with version 9.1 of the QRD template.

3.1. Benefit assessment

Direct therapeutic benefit

The benefit of NexGard and NexGard Spectra is their efficacy in the reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days and the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days. Efficacy for these indications was established in one GCP-compliant laboratory dose confirmation study for each of these claims, and is further supported by evidence from published scientific literature.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

Safety (user, environmental, target animal) remains unaffected by this variation.

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal:

Administration of NexGard and NexGard Spectra in accordance with SPC recommendations is generally well tolerated.

Risk for the user:

The CVMP previously concluded that user safety for these veterinary medicinal products is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

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. Standard advice on waste disposal is included in the SPC.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

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 the 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, safety, user safety, environmental safety, target animal safety.

The products have been shown to be efficacious for the reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days and the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days.

The products are well tolerated by the target animals and present an acceptable risk for users and the environment when used as recommended.

Appropriate precautionary measures have been included in the SPC and other product information.

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original data presented on efficacy, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for NexGard and NexGard Spectra can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows: change(s) to therapeutic indication(s): addition of a new therapeutic indication or modification of an approved one: for reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days and for reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days. The product information for both products – NexGard and NexGard Spectra – has also been aligned with version 9.1 of the QRD template; in addition, information concerning the treatment of demodicosis has been updated.

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, sections 3.2 and 3.9 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.