16 March 2017
EMA/196601/2017
Veterinary Medicines Division

CVMP assessment report for NEXGARD SPECTRA Type II variation (EMEA/V/C/003842/II/0008)

International non-proprietary name: afoxolaner / milbemycin oxime

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

Rapporteur: J. G. Beechinor
Co-rapporteur: S. Srcic

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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1. Background information on the variation

1.1. Submission of the variation application

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

1.1.1. Scope of the variation

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

The variation is to add new indications for the prevention of angiostrongylosis (reduction of infestation by *Angiostrongylus vasorum*) and spirocercosis (reduction of infestation by *Spirocerca lupi*) with monthly administration, and for the treatment of infestations with the adult hookworm *Ancylostoma ceylanicum.*

Current	**Proposed**
SPC **4.2 Indications for use, specifying the target species** For the treatment of flea and tick infestations in dogs when the concurrent prevention of heartworm disease and/or treatment of gastrointestinal nematode infestations is indicated. Treatment of flea infestations (*Ctenocephalides felis* and *C. canis*) in dogs for 5 weeks. Treatment of tick infestations (*Dermacentor reticulatus*, *Ixodes ricinus*, *Rhipicephalus sanguineus*) in dogs for 4 weeks. Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. Treatment of infestations with adult gastrointestinal nematodes of the following species: roundworms (*Toxocara canis* and *Toxascaris leonina*), hookworms (*Ancylostoma caninum* and *Ancylostoma braziliense*) and whipworm (*Trichuris vulpis*). Prevention of heartworm disease (*Dirofilaria immitis* larvae) with monthly administration.	**SPC** **4.2 Indications for use, specifying the target species** For the treatment of flea and tick infestations in dogs when the concurrent prevention of heartworm disease and/or treatment of gastrointestinal nematode infestations is indicated. Treatment of flea infestations (*Ctenocephalides felis* and *C. canis*) in dogs for 5 weeks. Treatment of tick infestations (*Dermacentor reticulatus*, *Ixodes ricinus*, *Rhipicephalus sanguineus*) in dogs for 4 weeks. Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. Treatment of infestations with adult gastrointestinal nematodes of the following species: roundworms (*Toxocara canis* and *Toxascaris leonina*), hookworms (*Ancylostoma caninum, Ancylostoma braziliense* **and *Ancylostoma ceylanicum***) and whipworm (*Trichuris vulpis*). Prevention of heartworm disease (*Dirofilaria immitis* larvae) with monthly administration.

	Prevention of angiostrongylosis (reduction of infestation by *Angiostrongylus vasorum*) with monthly administration. **Prevention of spirocercosis (reduction of infestation by *Spirocerca lupi*) with monthly administration.**
SPC **4.9 Amounts to be administered and administration route**	**SPC** **4.9 Amounts to be administered and administration route**
(…)	(…)
Treatment schedule:	Treatment schedule:
The treatment schedule should be based on veterinary diagnosis and on the local epidemiological situation.	The treatment schedule should be based on veterinary diagnosis and on the local epidemiological situation.
	Treatment of flea and tick infestations and gastrointestinal nematodes:
NEXGARD SPECTRA can be used as part of the seasonal treatment of fleas and ticks (replacing treatment with a monovalent flea and tick product) in dogs with diagnosed concurrent gastrointestinal nematode infestations. A single treatment is effective for the treatment of gastrointestinal nematodes. After treatment of the nematode infestations, further flea and tick treatment should be continued with a monovalent product.	NEXGARD SPECTRA can be used as part of the seasonal treatment of fleas and ticks (replacing treatment with a monovalent flea and tick product) in dogs with diagnosed concurrent gastrointestinal nematode infestations. A single treatment is effective for the treatment of gastrointestinal nematodes. After treatment of the nematode infestations, further flea and tick treatment should be continued with a monovalent product.
Heartworm disease:	**Prevention o***f heartworm disease:*
NEXGARD SPECTRA kills *Dirofilaria immitis* larvae up to one month after their transmission by mosquitoes therefore the product should be administered at regular monthly intervals during the time of the year when vectors are present, starting in the month after the first expected exposure to mosquitoes. Treatment should continue until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month. When replacing another heartworm preventative product in a heartworm prevention programme, the first treatment with NEXGARD SPECTRA should start on the date when the former medication was due to have been administered.	NEXGARD SPECTRA kills *Dirofilaria immitis* larvae up to one month after their transmission by mosquitoes therefore the product should be administered at regular monthly intervals during the time of the year when vectors are present, starting in the month after the first expected exposure to mosquitoes. Treatment should continue until 1 month after the last exposure to mosquitoes. To establish a treatment routine, it is recommended that the same day or date be used each month. When replacing another heartworm preventative product in a heartworm prevention programme, the first treatment with NEXGARD SPECTRA should start on the date when the former medication was due to have been administered.
Dogs living in heartworm endemic areas, or those which have travelled to endemic areas, may be infested with adult heartworms. No therapeutic effect against adult *Dirofilaria immitis* has been established. It is therefore recommended that all dogs 8 months of age or more, living in heartworm endemic areas, should be tested for existing adult heartworm infestation before being	Dogs living in heartworm endemic areas, or those which have travelled to endemic areas, may be infested with adult heartworms. No therapeutic effect against adult *Dirofilaria immitis* has been established. It is therefore recommended that all dogs 8 months of age or more, living in heartworm endemic areas, should be tested for existing adult heartworm infestation before being

treated with the product for heartworm prevention.	treated with the product for heartworm prevention. ***Prevention of angiostrongylosis:* In endemic areas, monthly administration of NEXGARD SPECTRA will reduce the establishment of *Angiostrongylus vasorum*.** ***Prevention of spirocercosis:*** **In endemic areas, monthly administration of NEXGARD SPECTRA will reduce the establishment of *Spirocerca lupi*.**
Package Leaflet **4. Indications** For the treatment of flea and tick infestations in dogs when the concurrent prevention of heartworm disease and/or treatment of gastrointestinal worm infestations is indicated. Treatment of flea infestations (*Ctenocephalides felis* and *C.canis*) in dogs. Treatment of tick infestations (*Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus*) in dogs. Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. Treatment of infestations with adult gastrointestinal nematodes of the following species: roundworms (*Toxocara canis* and *Toxascaris leonina*), hookworms (*Ancylostoma caninum, Ancylostoma braziliense*) and whipworm (*Trichuris vulpis*). Prevention of heartworm disease (*Dirofilaria immitis* larvae) with monthly administration. **8. Dosage for each species , route(s) and method of administration** Treatment schedule: The treatment schedule should be based on veterinary diagnosis and on the local epidemiological situation. NEXGARD SPECTRA can be used as part of the seasonal treatment of fleas and ticks (replacing a	**Package Leaflet** **4. Indications** For the treatment of flea and tick infestations in dogs when the concurrent prevention of heartworm disease and/or treatment of gastrointestinal worm infestations is indicated. Treatment of flea infestations (*Ctenocephalides felis* and *C.canis*) in dogs. Treatment of tick infestations (*Dermacentor reticulatus, Ixodes ricinus, Rhipicephalus sanguineus*) in dogs. Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. Treatment of infestations with adult gastrointestinal nematodes of the following species: roundworms (*Toxocara canis* and *Toxascaris leonina*), hookworms (*Ancylostoma caninum, Ancylostoma braziliense* **and *Ancylostoma ceylanicum*)** and whipworm (*Trichuris vulpis*). Prevention of heartworm disease (*Dirofilaria immitis* larvae) with monthly administration. **Prevention of angiostrongylosis (reduction of infestation by *Angiostrongylus vasorum*) with monthly administration.** **Prevention of spirocercosis (reduction of infestation by *Spirocerca lupi*) with monthly administration.** **8. Dosage for each species , route(s) and method of administration** Treatment schedule: The treatment schedule should be based on veterinary diagnosis and on the local epidemiological situation. **Treatment of flea and tick infestations and gastrointestinal worms:** NEXGARD SPECTRA can be used as part of the seasonal treatment of fleas and ticks (replacing a

product authorised for the treatment of fleas/ticks only) in dogs with diagnosed concurrent gastrointestinal worm infestations. A single treatment is effective for gastrointestinal worms. Efficacy of the treatment against flea and tick infestations lasts for one month. Further treatments may be indicated throughout the flea and/or tick season. Ask your veterinarian how to continue flea and tick treatment. Heartworm disease: (…) Dogs living in heartworm endemic areas (where heartworm disease is present), or those which have travelled to endemic areas, may be infested with adult heartworms. No therapeutic effect against adult Dirofilaria immitis has been established. It is therefore recommended that all dogs 8 months of age or more, living in heartworm endemic areas, should be tested for existing adult heartworm infestation before being treated with the product for heartworm prevention. **15 Other Information** (…) Milbemycin oxime is an antiparasitic endectocide belonging to the group of macrocyclic lactones. It is active against several gastrointestinal worms (such as: *Toxocara canis, Toxascaris leonina*, *Ancylostoma braziliense, Ancylostoma ceylanicum*, *Trichuris vulpis* and *Dirofilaria immitis* larvae.	product authorised for the treatment of fleas/ticks only) in dogs with diagnosed concurrent gastrointestinal worm infestations. A single treatment is effective for gastrointestinal worms. Efficacy of the treatment against flea and tick infestations lasts for one month. Further treatments may be indicated throughout the flea and/or tick season. Ask your veterinarian how to continue flea and tick treatment. **Prevention of** heartworm disease: (…) Dogs living in heartworm endemic areas (where heartworm disease is present), or those which have travelled to endemic areas, may be infested with adult heartworms. No therapeutic effect against adult *Dirofilaria immitis* has been established. It is therefore recommended that all dogs 8 months of age or more, living in heartworm endemic areas, should be tested for existing adult heartworm infestation before being treated with the product for heartworm prevention. ***Prevention of Angiostrongylosis:*** **In endemic areas, monthly administration of NEXGARD SPECTRA will reduce the establishment of *Angiostrongylus vasorum*.** ***Prevention of spirocercosis:*** **In endemic areas, monthly administration of NEXGARD SPECTRA will reduce the establishment of *Spirocerca lupi*.** **15 Other Information** (…) Milbemycin oxime is an antiparasitic endectocide belonging to the group of macrocyclic lactones. It is active against several gastrointestinal worms (such as: *Toxocara canis, Toxascaris leonina*, *Ancylostoma caninum*, *Ancylostoma braziliense,* ***Ancylostoma ceylanicum***, *Trichuris vulpis,* ***Angiostrongylus vasorum*, *Spirocerca lupi***) and *Dirofilaria immitis* larvae.

2. Scientific discussion

The product Nexgard Spectra includes afoxolaner and milbemycin oxime as active substances and is currently authorised for the treatment of flea (*C. felis* and *C. canis*) and tick (*D. reticulatus*, *I. ricinus*, *R. sanguineus*) infestations in dogs when the concurrent prevention of heartworm disease and/or treatment of gastrointestinal nematode (roundworms: *T. canis* and *T. leonina*; hookworms: *A. caninum* and *A. braziliense*; whipworm: *T. vulpis*) infestations is indicated.

The product is presented in five different strengths of chewable tablet with afoxolaner and milbemycin

oxime administered at a dose rate of 2.5-5.36 mg/kg and 0.5-1.07 mg/kg, respectively. The frequency of repeat administration is dependent upon the target parasite being treated and the local epidemiological situation. According to the currently approved SPC for Nexgard Spectra, repeated monthly administration of the product is foreseen when the product is to be administered to animals with concurrent infestations of nematodes and fleas/ticks or for the purpose of preventing heartworm disease caused by *Dirofilaria immitis*.

The variation is to add new indications:
- Prevention of angiostrongylosis (reduction of infestation by *Angiostrongylus vasorum*)
- Prevention of spirocercosis (reduction of infestation by *Spirocerca lupi*),
- Treatment of infestations with the adult hookworm *Ancylostoma ceylanicum.*

For all three newly proposed indications, the product is to be administered at the same dose rate as currently authorised. For two indications (prevention of angiostrongylosis and/or spirocercosis), repeated monthly administration is proposed which is the same treatment frequency authorised for the existing treatment indication against fleas/ticks and the prevention of heartworm disease.

Safety (tolerance, user, environment)

Given that the posology for the newly proposed indications does not differ to that which has been already accepted for the existing target parasites, it can be accepted that no concerns in terms of target animal tolerance/safety are considered to arise.

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

No change to the impact on the environment is envisaged.

Justification of combination

The justification of the applicant justified the additional indications on the basis of the severity of resulting clinical conditions, the prevalence of the infection and/or the zoonotic potential. A succinct summary of the life-cycle of each of the newly proposed target parasites was provided along with information on their prevalence and significance in terms of both canine and human exposure:

- Broadening of the activity spectrum of this combination product was justified, since the canine infection with *Angiostrongylus vasorum* is endemic throughout Europe, and concurrent infection is possible with one or more of the other target parasites for which the product is currently indicated.
- Although the target helminth *Ancylostoma ceylanicum* is not known to occur in the geographical region where the product may be marketed (Europe) (canine infection with *Ancylostoma ceylanicum* predominantly occurs in Asia, Australia and South Africa as well as some other regions), the potential for spread of *A. ceylanicum* to Europe and the existence of the parasite in European overseas territories were highlighted in support of the proposed indication. Information regarding the geographical distribution of *A. ceylanicum* and situations in which treatment may be required, has been included in section 4.4 of the SPC.

Overall, the CVMP considered the rationale for these two proposed new indications as acceptable and to be in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).

S. lupi is present in wild carnivores in Europe and has been reported in hunting dogs in Greece; the relevance of *S. lupi* for the European region can therefore be accepted. However, the proposed indication was considered to have been inadequately supported by data and has not been accepted. The guideline "efficacy of anthelmintics: specific recommendations for canines" (VICH GL19) requires two dose confirmatory studies in order to grant a claim. In the absence of a second dose confirmatory study (or acceptable justification for its omission) that suitably demonstrates an acceptable level of efficacy of the product against *S. lupi*, an indication for the treatment of *S. lupi* is considered to have been inadequately supported. Therefore the proposed indication for *S. lupi* has not been accepted by the CVMP.

Prevention of angiostrongylosis (Angiostrongylus vasorum)

Following a scientific advice providing guidance on the appropriateness of the proposed data package, results of three dose confirmatory studies were provided in support of the proposed indication against the lungworm *A. vasorum*. All studies were performed under laboratory conditions, using artificially infected dogs.

A GCP-compliant study was conducted in France, to evaluate the efficacy of Nexgard Spectra, when administered once or twice orally to prevent the establishment of *Angiostrongylus vasorum* in dogs. On Day -11, 40 (20 female and 20 male) Beagle dogs aged between 9–11 months and in the bodyweight range 8–14 kg were randomised by bodyweight. On D-7, all dogs were intra-gastrically inoculated with approximately 300 *A. vasorum* L_3 stage larvae collected from Denmark. The inoculation schedule was designed so that *A. vasorum* were expected to be migrating larvae on Day 0, migrating/intra-arterial larvae on Day 7, intra-arterial immature adult nematodes on Day 21 and adults on Day 49. The product was administered at as close a dose to the minimum recommended treatment dose, given the available tablet strengths. A suitable number of animals were included in the study and at least six of the untreated control animals harboured a minimum of 25 adult *A. vasorum* worms, confirming adequacy of infection. Dogs were allocated to five treatment groups (control; treated once on Day 0; once on Day 7, once on Day 21; or twice on Day 21 and Day 49 post-infection). No adverse effects attributable to treatment were reported in this study.

Faecal samples were collected on study Days 35, 42, 50 and 56 for examination of *A. vasorum* L_1 larvae. All animals were necropsied on study Days 62–65 and parasites were enumerated. Percent efficacy was calculated using the Abbott formula based on geometric mean intra-arterial adult *A. vasorum* worm counts. Larvae were present in the faeces of all groups from Day 50/51. Worms were recovered from seven of the eight untreated dogs, with six harbouring at least 25 worms (geometric mean=24.6). A majority of the treated dogs harboured worms and the mean worm counts of the treated groups were not statistically significantly different from the untreated control group. While a higher efficacy of 88.1% was seen after two treatments on day 21 and 49 after infection compared to a single treatment, the minimum required efficacy threshold of 90 % was not achieved, and a statistically significant difference in worm counts between the treatment group and the untreated control group was not found. In conclusion, the results of this study failed to demonstrate an acceptable level of efficacy of the product following artificial infection with L_3 *A. vasorum* larvae.

A second GCP-compliant study was performed in France to evaluate the efficacy of oral treatment administered monthly, two or three times, to prevent the establishment of *A. vasorum* in dogs following induced infestation. The study was partially blinded with a parallel, negative controlled

randomised block design.

Thirty Beagle dogs aged between 8–10 months and in the bodyweight range 7.1–20.6 kg, were randomly allocated to one of three groups of ten dogs each (untreated group; treated on days 0 and 28, treated on days 0, 28 and 56). Actual doses administered ranged between 2.57–4.81 mg afoxolaner/kg and 0.51–0.96 mg milbemycin oxime/kg bodyweight.

On study Day–28, all dogs were orally inoculated with approximately 364 larvae *of A. vasorum* L3 stage. Compared to the previous study, inoculation of infective L3 larvae was performed 3 weeks earlier so that inoculated L3 larvae were anticipated to be intra-arterial immature adult nematodes on Day 0 and mature adults by Day 28. The infective larvae originated from Denmark.

No health abnormalities related to treatment were observed apart from transient diarrhoea or loose faeces during the first 4 hours post-treatment in two animals of the group treated on study Days 0, 28 and 56. No vomiting of the product was observed. One dog was removed from efficacy calculations as it had probably been overdosed on study day 56.

Faecal samples were collected on study Days 20, 28, 42, 56, 70 and 77/79 for examination of *A. vasorum* L1 larvae. Larvae were present in the faeces of all groups from 56 days post-infection.

A reduction in larval counts was observed in both treatment groups until study Day 42 when an increase in counts was observed. Whilst L1 larval counts at the Day 77/70 count were the lowest in the group treated three times at 28 day intervals, they were higher at earlier time points (study Days 28 and 56) compared to the group treated twice 28 days apart.

At necropsy on day 85–87, a minimum of 59 worms were recovered from thoracic contents of all ten untreated dogs (geometric mean=181.3; range=59–365) confirming the adequacy of infection. Despite a statistically significant difference between the geometric mean in adult worm counts of the treated groups and the untreated control group, the reduction in worm count for both treatment groups failed to reach the accepted efficacy threshold of 90% (88.7% for the group treated on three consecutive monthly occasions, and 80.95 % for the group treated on two consecutive monthly occasions).

The pivotal, third study, conducted in 2016 in France, used a trickle infection technique (artificial infection every 2 weeks) in order to more accurately reproduce the likely exposure pressure under natural conditions. Prior to the conduct of the study, CVMP had provided scientific advice on the study design, and the applicant followed this advice.

Twenty Beagle dogs (aged 8.6–9.4 months and in the bodyweight range 10–16.4 kg, randomised to two groups of ten animals) received Nexgard Spectra at a the lower milbemycin oxime dose rate (0.6 mg /kg) that falls within the dose range recommended in the SPC (0.5–1.07 mg milbemycin oxime/kg). This was considered to be sufficiently representative of a 'worst case' in terms of dose rate. The product was given monthly, by manual administration into the back of the mouth on day 0, 28, 56 and 84. On study Days -7, 7, 21, 35, 49, 63 and 77, all dogs were orally inoculated with approximately 32–43 *A. vasorum* L3 stage larvae. The infective larvae originated from Denmark. Faecal samples were collected on study Days -7/-6, 35, 49, 63, 77 and 90 for examination of *A. vasorum* L1 larvae. Specific health observations were performed every 4 weeks and included heart rate, respiratory rate, lung, mucous membranes. No health abnormalities related to treatment were reported. All animals were euthanised on study days 90–92 and thoracic contents was examined for worm enumeration. Gross macroscopical differences in appearance of the lung surface between treatment groups were reported (assumed to be directly attributable to the difference in *A. vasorum* worm burden between treatment groups).

No larvae were detected in the faeces until study Day 49 in the control group. A statistically significant

reduction in faecal L1 larval counts was observed in the treated group compared with the control group from study Day 63 onwards. Total worm counts included both adult and immature adult stages. Based on total worm counts, an acceptable level of efficacy was demonstrated (94.9%), and a statistically significant difference in geometric mean worm counts between treatment and control groups was shown. Results of this study are considered to support the proposed indication for a reduction of infestation by *A. vasorum*.

The CVMP recognised that based on current guidance (VICH GL Topic 7 and VICH GL Topic 19), two dose confirmation studies would typically be required; however, the CVMP in a scientific advice given to the applicant prior to submission of the dossier, confirmed that a single confirmatory study could be accepted taking into consideration that adequate infection was established in the control group; the reduction in total worm burden in the treatment group exceeded the standard efficacy threshold of 90% (relative to the untreated control group); the difference in total worm count between the treatment and control group is statistically significant ($p<0.05$), and that there were no concerns about the conduct of the study that would call into question the validity of the test results.

Based upon the totality of data provided (three dose confirmatory studies — one demonstrating an acceptable level of efficacy and two achieving marginally less than the efficacy threshold), the CVMP accepted that the data package is adequate to support the indication "Prevention of angiostrongylosis (by reduction of the level of infection with immature adult (L_5) and adult stages of *Angiostrongylus vasorum*) with monthly administration".

Prevention of spirocercosis (Spirocerca lupi)

A single dose GCP-compliant study was performed to determine the efficacy of monthly oral administration to prevent the establishment of *Spirocerca lupi* in experimentally infected dogs. The proposed indication against the oesophageal worm *S. lupi* was "Prevention of spirocercosis (reduction of infestation by *Spirocerca lupi*) with monthly administration".

The study was conducted in South Africa, i.e. outside the EU. It was a blinded, negative controlled and randomised parallel group designed single centre study, conducted in three phases. The aim was to evaluate the efficacy against the establishment of adult worms associated with nodule formation in the oesophagus in experimentally infected dogs given 6 consecutive monthly treatments i.e. preventative efficacy against adult stages.

Sixteen mixed breed dogs (aged less than 12 months and in the bodyweight range 9.67-15.62 kg) were randomly allocated to two groups of eight animals). Dogs were treated with a non-macrocyclic lactone anthelmintic at least 20 days prior to the study and were individually housed during the study. They were administered Nexgard Spectra monthly at a dose rate (0.6 mg/kg) as close to the minimum recommended treatment dose of milbemycin oxime (0.5 mg/kg) as possible. This is considered to be sufficiently representative of a 'worst case' in terms of dose rate. The dogs were treated on days 0, 28, 56, 84, 112 and 140 of the study. On study days -28, -14 and -2, animals were orally inoculated with approximately 15 *S. lupi* L3 stage larvae.

The infective L3 larvae of *S. lupi* were sourced from an area endemic for spirocercosis but which is outside the EU. Insufficient information/data has been provided to permit concluding whether the isolate used may be considered sufficiently representative of the susceptibility (or otherwise) of European isolates of *S. lupi* to milbemycin oxime.

Faecal *S. lupi* egg counts were performed on study Days 112, 140 and 168. No *S. lupi* eggs were detected in the faeces of treated animals, and a statistically significant difference in faecal egg counts was observed between treated and control groups on study Days 140 and 168 resulting in a 100% of

reduction of faecal egg output (as compared to the control group).

All dogs were endoscopically examined on study Days 112 and 140. However, it is noted that due to the nature of the oesophageal mucosa, small ridges could have been mistaken for nodules (due to spirocercal infection) that were not yet completely resolved. Results of endoscopy were therefore only considered supportive of necropsy findings. Study animals were necropsied on study day 168 and parasites were enumerated, and lesions caused by *S. lupi* were quantified. At necropsy, nodules and damage to the aorta and oesophagus were described and considered as supportive to the evaluation of effectiveness. Lesions were assessed by number and size (oesophagus and aorta) and severity (aorta only). Based on the extent of lesions, it seems that milbemycin oxime acts on immature stages reaching the oesophagus, after their migration along the aorta.

The efficacy was 92.3% (based on geometric adult mean counts), and the difference in worm counts between groups was reported to be statistically significant. The results of this study support the proposed indication for a reduction of infestation by *S. lupi*. No statistically significant differences between treated and untreated animals were reported in terms of the frequency of occurrence of oesophageal and aortic lesions, or in the size and severity of aortic lesions.

No health abnormalities related to treatment were reported. Vomiting was observed post-inoculation on a few occasions, however, no larvae were observed and so no re-inoculation of larvae was necessary.

According to the VICH GL19 guideline, two dose confirmatory studies are required in order to grant a claim. As a second dose confirmatory study or acceptable justification for its omission was not provided, an indication for the treatment of *S. lupi* was not accepted.

Treatment of infestation with Ancylostoma ceylanicum

The proposed new indication against the hookworm *A. ceylanicum* is "Treatment of infestations of adult gastrointestinal nematodes of the following species: hookworms (*Ancylostoma ceylanicum*)"

Nexgard Spectra has already been approved for the treatment of the hookworms *Ancylostoma braziliense* and *Ancylostoma caninum* in the original application.

In support of the proposed indication, a GCP-compliant, a randomised, blinded, negative controlled, parallel group design dose confirmatory study, conducted in France, was provided. Sixteen Beagle dogs aged 6–7 months and in the bodyweight range 10.2–16.6 kg were allocated to two groups (untreated and controls). Eight dogs were treated with Nexgard Spectra chewable tablets on study Day 0, by placing the tablet(s) directly into the back of the mouth. Actual doses administered ranged from 2.5–3.1 mg afoxolaner/kg bodyweight and 0.5–0.6 mg milbemycin oxime/kg bodyweight, which corresponds to the lower dose range of Nexgard Spectra. On study Days -17, animals were orally inoculated with approximately 500 *A. ceylanicum* L3 stage larvae. Infective L3 larvae of *A. ceylanicum* were sourced from an infected dog in Thailand and subsequently maintained in donor cats in Germany. Given the current absence of documented infestation with *A. ceylanicum* in Europe, the approach used by the applicant (study conducted within the EU but isolate used to induce artificial infestation sourced from outside the EU) was considered to be in line with guideline recommendations. All eight animals in the untreated control group individually harboured at least 210 *A. ceylanicum* worms indicating an adequate level of experimental infection in the study population in line with VICH guideline GL19 (Efficacy of anthemintics: specific recommendations for canines) which recommends a range of 100-300 infective *Ancylostoma caninum* and *Ancylostoma braziliense* larvae.

No health abnormalities related to treatment were reported, apart from one animal in the treated group observed to have vomited 2 hours post-treatment. However, no vomiting of the product was

observed. Loose stools or diarrhoea with or without blood was observed in animals from both the treated and untreated groups and was not considered treatment related but instead more likely to be associated with the *A. ceylanicum* infection, given that these signs appeared to resolve following administration of Nexgard Spectra.

A statistically significant difference in faecal egg counts was observed between treatment groups on study Day 7 with percent efficacy in reducing egg counts (compared to the control group) calculated to be 100%.

Study animals were necropsied on study day 7 and parasites were subsequently enumerated. The interval between treatment and worm enumeration (7 days) and the interval between artificial infection and worm enumeration (24 days) are both in line with the VICH GL19 and are appropriate to support a claim for efficacy against adult stages of *A. ceylanicum*. A statistically significant difference in total worm counts recovered at necropsy, was observed between treatment groups at necropsy with percent efficacy calculated to be 99.9%.

According to the VICH GL19 guideline, two dose confirmatory studies are required in order to grant a claim. However, given that this dose confirmatory study demonstrated an efficacy above 99% against an experimentally induced infection with *A. ceylanicum* and the product has already been shown to be sufficiently efficacious against two other hookworms (*A. caninum* and *A. braziliense*) from the same genus, the CVMP accepted that a second dose confirmatory study would not be required.

3. Benefit-risk assessment

3.1. Benefit assessment

As this is a variation to introduce additional indications to an existing product, the benefit will arise from the inclusion of new indications.

Indications against canine lungworms (*A. vasorum)* and oesophageal worms (*S. lupi)* are considered as being of benefit for the target animals, as they provide new treatment options. However, the data package for *S. lupi* was considered to be inadequate to support the proposed indication.

The benefit of including an indication against the hookworm *A. ceylanicum* was accepted based on the potential zoonotic risk posed by *A. ceylanicum*, the potential for spread of *A. ceylanicum* to Europe and the existence of the parasite in European overseas territories.

3.2. Risk assessment

As this is a variation to introduce additional indications to an existing product, the risk assessment focuses on potential risks arising from the introduction of the newly proposed indications. The proposed indications as written could not be accepted but revised wording was subsequently accepted for some but not all of the proposed indications.

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

3.3. Evaluation of the benefit-risk balance

The benefit of including additional indications for prevention of angiostrongylosis (by reduction of the

level of infection with immature adult (L_5) and adult stages of *Angiostrongylus vasorum*) and for the treatment of *Ancylostoma ceylanicum* was considered to be beneficial without increasing the risk. Insufficient data is considered to have been provided to support the proposed indication against *Spirocerca lupi.*

4. Overall conclusions of the evaluation and recommendations

This variation, accompanied by the submitted documentation which demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met, can be approved for some but not all of the newly-proposed indications.

The proposed amendments to the existing subheadings in section 4.9 of the SPC (and corresponding section of the package leaflet) are considered to be acceptable.

The following proposed new claims have been accepted:

- Prevention of angiostrongylosis (by reduction of the level of infection with immature adult (L_5) and adult stages of *Angiostrongylus vasorum*) with monthly administration.
- Treatment of *Ancylostoma ceylanicum*.

However, the following proposed new claim has not sufficiently been supported by efficacy data and therefore not been accepted:

- Prevention of spirocercosis (reduction of infestation by *Spirocerca lupi*).

4.1. Changes to the Community marketing authorisation

Changes are required in Annexes I and IIIB to the Community marketing authorisation.