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Veterinary Medicines Division

Committee for Veterinary Medicinal Products

CVMP assessment report for a type II variation for NexGard Combo (EMEA/V/C/005094/II/0002/G)

INN: esafoxolaner / eprinomectin / praziquantel

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 7 of Commission Regulation (EC) No 1234/2008, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 30 March 2021 an application for a grouped type II variations for NexGard Combo.

1.2. Scope of the variation

Variations requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

To add two new therapeutic indications: for the treatment of notoedric mange (*Notoedres cati*); and the treatment of infections with *Aelurostrongylus abstrusus* (adults) and prevention of aelurostrongylosis; and to support the safe use of the product in breeding, pregnant and lactating queens.

The marketing authorisation holder also took the opportunity to implement minor changes 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 3 and Part 4

1.4. Scientific advice

The applicant received scientific advice from the CVMP on 15/06/2017 (EMA/CVMP/SAWP/178051/2017). The scientific advice pertained to the efficacy/clinical development of the dossier.

Scientific advice EMA/CVMP/SAWP/178051/2017 mainly addresses eprinomectin and praziquantel dose determination, product equivalence as per VICH GL7, and clinical demonstration of the efficacy in endoparasites, but also the data package required to be submitted in support of the indication against notoedric mange (*Notoedres cati*) and against *Aelurostrongylus abstrusus*. The applicant followed CVMP's scientific advice.

The applicant also received scientific advice from the CVMP on 16/02/2018 (EMA/CVMP/SAWP/157138/2018) as follow-up advice on the protocol of the reproductive target animal safety study. This was followed in principle to support safe use of the product in breeding, pregnant

and lactating queens. Details and conclusions are presented in the respective section of this assessment report.

1.5. MUMS/limited market status

The applicant requested classification of "treatment of notoedric mange (*Notoedres cati*)" of this application as MUMS/limited market by the CVMP, and the Committee confirmed that, where appropriate, the data requirements in the relevant CVMP guideline(s) on minor use minor species (MUMS) data requirements would be applied when assessing the application. MUMS/limited market status was granted as the indication for the treatment of notoedric mange in cats is considered a minor use.

2. Scientific Overview

The variation EMEA/V/C/005094/II/0002/G is related to the following changes:

- Addition of new therapeutic indications:
  - Treatment of notoedric mange (*Notoedres cati*)
  - Treatment of infections with feline lungworms (adults of *Aelurostrongylus abstrusus*) and prevention of aelurostrongylosis (by reduction of the level of infection with L3, L4 larvae of *Aelurostrongylus abstrusus*)
- To support the safe use of the product in breeding, pregnant and lactating queens.

2.1. Treatment of notoedric mange *(*caused by *Notoedres cati)*

To demonstrate that one single treatment of NexGard Combo is adequate for the treatment of notoedric mange caused by *Notoedres cati* mites in cats, the applicant provided the results of one pivotal dose confirmation study in accordance with VICH Guideline on good clinical practice (CVMP/VICH/595/98-FINAL) and EMA guideline on the demonstration of efficacy (7AE17a).

Four naturally infested donor cats originating from a European country were co-housed with 23 naïve cats in four rooms of 6-7 cats, with the objective of obtaining an adequate number of *N. cati* infested cats for the study. An adequate infestation was confirmed in 10 out of 23 cats by detection of at least five motile mites after deep skin scrapings (D-7/D-3, D+14, D+27/D+28, D+42, D+56) of each cat. Deep skin scrapings were taken from the edge of active lesions until a small amount of blood was visible. The study was performed in three phases (depending on the time point when cats became adequately infested) including four, eight and two cats, respectively. The study was conducted with the four naturally infested donor cats and the 10 cats infested by co-mingling. The 14 included cats (9 females, 5 males, healthy European shorthair cats aged 1 to 3 years) were randomly allocated (based on pre-treatment live mite counts) into one of two groups (control and investigational veterinary product (IVP)).

Efficacy was demonstrated for the primary endpoint by comparison of live mite counts between the control group and the treatment group. The efficacy was consistently 100% at each time point tested in the IVP group based on mite counts ($p=0.0082$).

In order to evaluate the clinical success rate, skin lesions were assessed, and bodyweight monitored on D+14, D+27/D+28, D+46 and D+56 as secondary endpoints. From D+42 to the end of the study the success rate was 100% in treated animals and significantly different compared to the control

group. The bodyweight gain was statistical significantly higher in the IVP compared to the control group at the end of the study.

No adverse events were observed in either group during the study.

In the scientific advice (EMA/CVMP/SAWP/178051/2017) the CVMP agreed, that for this MUMS product one dose confirmation study is sufficient to assess the efficacy and to justify a treatment claim of the product against natural infestations with *Notoedres cati* in cats. In line with the scientific advice and based on the binding sites of eprinomectin and esafoxolaner at the ligand-gated chloride channels possible interaction and additive activity against mites was sufficiently discussed by the applicant. Relevant information has been added in section 5.1 of the SPC.

In summary, the new indication "Treatment of notoedric mange (caused by *Notoedres cati*) can be accepted.

2.2. Treatment of infections with feline lungworms and prevention of aelurostrongylosis

To demonstrate both the preventive activities of NexGard Combo against the developmental stages of *Aelurostrongylus abstrusus* (L3, L4 larvae, immature adults), and also the treatment properties of NexGard Combo against the adult stages of *Aelurostrongylus abstrusus* in cats, the applicant provided the results of one dose confirmation study performed in accordance with VICH GL7 "Efficacy requirements for anthelmintics: Overall guidelines" (CVMP/VICH/832/99-corr), VICH GL20 "Efficacy of anthelmintics: Specific recommendations for feline" (CVMP/VICH/545/00-FINAL) and the W.A.A.V.P guideline for evaluating the efficacy of anthelmintics for dogs and cats (Jacobs et al., 1994).

Forty healthy European shorthair cats (21 m and 19 f, aged from 8 to 11 months), tested negative for lungworms by faecal examinations on D–7 or D-6, were enrolled in the study. The study was conducted in two phases with 20 cats each in phase 1 (blocks 1-4) and phase 2 (blocks 5-8). Within the blocks, cats were randomly allocated to five groups. All cats were artificially infected orally with approximately 225 infective L3 larvae of *A. abstrusus* on D-4. The *A. abstrusus* strain used for inoculation was recently isolated from a naturally infected cat and maintained since then under laboratory conditions. The inoculation schedule was designed so that *A. abstrusus* were expected to be 3rd stage larvae on treatment D0 (group 2), 4th stage larvae on treatment D+3 (group 3), immature adults on treatment D+10 (group 4) and adult lungworms on treatment D+37 (group 5). Group 1 served as control treated with mineral oil at D0, whereas the cats of groups 2, 3, 4, and 5 received a product identical to the marketed formulation on D0, D+3, D+10 and D+37, respectively, topically in the midline of the neck. Each individual dose corresponded to the minimum recommended dose of 1.44 mg esafoxolaner, 0.48 mg eprinomectin and 10 mg praziquantel per kg bw.

After treatment, faecal samples were collected from all cats on D+28, D+35, D+42, D+49, D+56 and D+63. The samples were examined and counted for L1 lungworm larvae using the Baermann-Wetzel funnel method. Adequacy of infection was confirmed throughout the entire study period by counting more than five L1 larvae in at least 6 cats of the control group.

In the group treated on D0 (targeting L3) reduction of larval shedding based on geometric mean was 100% up to D+49 and declined to 97.3% on D+ 63. In the group treated on D+3 (targeting L4 larvae), reduction of larval shedding was 100% up to D+35 and decreased to 95.4% on D+63. In cats treated on D+10 (targeting immature adults), reduction of larval shedding was 100% up to D+35 and declined to 97.2% on D+63. In the group treated on D+37, targeting adult lungworms (patent infection), no reduction of larval shedding was found on D+ 42 (5 days after treatment), whereas 97.9% efficacy was calculated on D+49, 99.6% on D+56 and 99.5% at the end of the study period

(D+63). Following treatment, there were significantly less L1 larvae in the faeces in all treated groups, compared to the control group ($p \leq 0.0149$), except in the group targeting adult worms on D+42, 5 days after treatment.

Over the course of the study, all cats treated with NexGard Combo on D0 (Group 2), D+3 (Group 3), and D+10 (Group 4) had significantly lower cumulative counts than the control cats ($p \leq 0.0004$). Reduction of larval shedding based on geometric mean was 99.8, 99.5, and 99.8%, respectively. In conclusion, this study demonstrated that a single administration of NexGard Combo is highly effective against L3, L4 larvae, immature adults and adults of *A. abstrusus*.

Results comparing the pharmacokinetic behaviour of the products NexGard Combo and Broadline indicate a high inter-individual variability of the pk parameters (C_{max}, T_{max} and AUC_{last}) without statistical significance. It appears, however, that there are no relevant differences in the pharmacokinetic behaviour of eprinomectin and praziquantel when administered in NexGard Combo compared to Broadline. The CVMP consequently concluded that the efficacy data submitted for Broadline can be accepted to support the nematocidal/cestocidal efficacy of NexGard Combo. (EMA/640861/2020: CVMP assessment report for NexGard Combo, EMEA/V/C/005094/0000).

Hence, the application relies also on three studies previously submitted and assessed for Broadline in the context of a type II variation procedure in 2015 (EMEA/V/C/002700/II/0001) in order to justify a treatment claim for *A. abstrusus* (L3, L4, immature adults and mature adults) at that time. These pre-clinical studies are included in the dossier as well. One clinical field study performed with Broadline has also been submitted. In relation to these studies, the acceptable results obtained with Broadline in experimental dose confirmation studies and the overall efficacy of 90.5 % against *A. abstrusus* in the field do further support the claim for *A. abstrusus* for NexGard Combo.

This is in line with the scientific advice provided in 2017 (EMA/CVMP/SAWP/178051/2017), where the CVMP agreed that the efficacy of the new triple combination against the lungworm *A. abstrusus* can be demonstrated in one dose confirmation study.

There is a lag period of larval shedding due to the transit of the larvae from the lungs through the digestive tract. In this period the larvae might be unaffected by treatment. Therefore, no or little effect on the L1 larval release can be expected within approximately 2 weeks after any treatment and a check of effectiveness is only advisable thereafter.

Thus, a corresponding advice, addressing these characteristics has been added to the section 4.9 Special warnings for each target species of the SPC:

"Lungworm treatment: No or little effect on the L1 larvae release of *A. abstrusus* in the faeces can be expected within approximately 2 weeks after treatment due to the transit period of L1 larvae from the lungs through the digestive tract. Any faecal larval count to control effectiveness (and the decision if a second treatment with a narrow spectrum product is necessary) should, therefore, only be made two weeks after treatment at the earliest."

2.3. Use in breeding, pregnant and lactating queens

The applicant applied for a change of the current wording of section 4.7 of the SPC from: "The safety of the veterinary medicinal product has not been established during pregnancy and lactation. Since foetotoxic and teratogenic effects are described in laboratory animals after significant daily exposure to glycerol formal, use only according to the benefit-risk assessment by the prescribing veterinarian" to: "Can be used in breeding, pregnant and lactating queens."

Information on potential effects on reproduction of the three active substances in laboratory species has been provided during the initial marketing authorisation procedure. It was concluded by CVMP that none of the substances show potential for teratogenicity. Reproductive toxicity studies conducted with afoxolaner revealed NO(A)ELs of at least 5 mg/kg bw/day depending on the study. For praziquantel, fertility and reproductive performance were unaffected in a reproductive toxicity study, no embryotoxic or foetotoxic effects were noted. For eprinomectin, reduced reproductive performance, body tremors in the litter and increased pup mortality, decreased litter weight and pup growth were observed with a NOAEL of 1 mg/kg bw/day following oral administration. For the excipient glycerol formal, foetotoxic and teratogenic effects are described in laboratory animals after significant daily exposure.

Data on effects on reproductive organs in the target species are available from the pivotal TAS study presented with the original dossier, including organ weights, macroscopical and histopathological examination, and have been assessed in context of the marketing authorisation procedure. No test article related changes on reproductive organs were noted with up to 5 times the maximum recommended dose in healthy kittens initially aged 8 to 9 weeks and treated up to 6 times at 4-week intervals.

To further support the safe use of the product in pregnant and lactating queens, an overall well-designed, randomised, negative controlled, blinded, target animal reproductive safety study, performed mostly according to the requirements described in GL VICH 43, target animal safety for veterinary pharmaceutical products, chapter 3.3, reproductive safety studies, was conducted with monthly administrations of 1x and 3x the maximum recommended treatment dose by the recommended route prior to mating until weaning of offspring. A statistically significant greater litter size and lower pup weight in the verum groups compared to the placebo group was observed; as other parameters did not differ between treatment groups and in view of the high weaning index (with a higher proportion of kittens weaned in the 3x group to controls), these observations are not of concern. No apparent treatment related effects were noted. One kitten with hydrocephalus/cranial fontanelle not closed was the only obvious congenital birth defect in the study. Although it occurred in the high dose group (3x) it does not necessarily indicate a treatment related effect but could be incidental.

Overall, it can be concluded that the benefit of treatment during pregnancy and lactation outweighs the risks in cats with, or at risk from, mixed infections by cestodes, nematodes and ectoparasites in which all three groups are targeted at the same time.

The males included in the study were not treated and thus, the effect of the product on male reproductive safety cannot be assessed. Information on the use of the product in male breeding cats is provided in the product information in line with scientific advice (EMA/CVMP/SAWP/157138/2018): "The safety of the veterinary medicinal product has not been established in breeding male cats. Laboratory studies in rats and rabbits have not produced any evidence of adverse effects of the active substances on the reproductive capacity in males. In breeding males, use only according to the benefit-risk assessment by the prescribing veterinarian."

3. Benefit-risk assessment of the proposed change

NexGard Combo is authorised for the treatment of cats with, or at risk from mixed infections by cestodes, nematodes and ectoparasites. The veterinary medicinal product is exclusively indicated when all three groups are targeted at the same time. It contains a fixed combination of esafoxolaner / eprinomectin / praziquantel as active substances.

The proposed variation is to add two new therapeutic indications: for the treatment of notoedric mange (*Notoedres cati*); and the treatment of infections with *Aelurostrongylus abstrusus* (adults) and prevention of aelurostrongylosis; and to support the safe use of the product in breeding, pregnant and lactating queens. The marketing authorisation holder also took the opportunity to implement minor changes in the product information.

The indication for the treatment of notoedric mange (caused by *Notoedres cati*) has been classified as MUMS/limited market and therefore reduced data requirements apply for this indication, which have been considered in the assessment.

3.1. Benefit assessment

Direct therapeutic benefit

The proposed benefit of NexGard Combo is its efficacy in the "Treatment of notoedric mange (caused by *Notoedres cati*)" and "Treatment of infections with L3, L4 larvae and adults of *Aelurostrongylus abstrusus* and prevention of aelurostrongylosis (by reduction of the level of infection with L3, L4 larvae of *Aelurostrongylus abstrusus*)". This was demonstrated in two well designed dose confirmation studies (one study to confirm the efficacy of NexGard combo against *N. cati* and another one to confirm efficacy against *A. abstrusus*), both conducted to an acceptable standard. Additionally, three dose confirmation studies and one field study carried out with Broadline were considered to support the new indication against lungworms, based on the demonstration of product comparability between NexGard combo and Broadline.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation

Safety:

Risks for the target animal:

Administration of NexGard Combo in accordance with SPC recommendations is generally well tolerated. Information that the safety of the veterinary medicinal product has not been established in breeding male cats is given in the product information.

Risk for the user:

Risk for the user remains unaffected by this variation.

Risk for the environment:

Risk for the environment remains unaffected by this variation

Special risks:

Risk of resistance remains unaffected by this variation, but a slight revision of the general advice on parasite resistance given in section 4.4 has been conducted, as this is a fixed triple combination not a mono product.

Risk management or mitigation measures:

Appropriate information has been included in the SPC and other product information to inform on the potential risks of this product relevant to the user, environment and to provide advice on how to prevent or reduce these risks.

3.3. Evaluation of the benefit-risk balance

No change to the benefit-risk balance of the product is envisaged on the following aspects: quality, user safety, environmental safety, consumer safety.

Based on the data presented, the overall benefit-risk is deemed positive.

4. Conclusion

Based on the original and complementary data presented on safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the variation to the terms of the marketing authorisation for NexGard Combo can be approved, since the data satisfy the requirements as set out in the legislation (Commission Regulation (EC) No. 1234/2008), as follows:

The following new therapeutic indications can be accepted: treatment of Notoedric mange (caused by *Notoedres cati*); treatment of infections with feline lungworms (L3, L4 larvae and adults of *Aelurostrongylus abstrusus*) and prevention of aelurostrongylosis (by reduction of the level of infection with L3, L4 larvae of *Aelurostrongylus abstrusus*). Furthermore, the safe use of the product in breeding, pregnant and lactating queens has been confirmed.

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 product.

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

I, IIIA and IIIB

Please refer to the separate product information showing the tracked changes.

As a consequence of this variation, sections 4.2, 4.4, 4.5, 4.7, 4.9, 5. and 5.1 of the SPC are updated. The corresponding sections of the Package Leaflet are updated accordingly.