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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for NexGard Combo (EMEA/V/C/005094/VRA/0007/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 62 of Regulation (EU) 2019/6, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 6 January 2023 an application for a group of variations requiring assessment for NexGard Combo.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
G.I.7.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one
G.I.18	One-off alignment of the product information with version 9.0 of the QRD templates i.e. major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicinal products placed on the market in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004

The group of variations is to add two new therapeutic indications for immediate and persistent tick killing activity against *Ixodes hexagonus* and for persistent tick killing activity against *Rhipicephalus sanguineus*, and to align the product information with version 9.0 of the QRD templates.

1.3. Changes to the dossier held by the European Medicines Agency

This application relates to the following sections of the current dossier held by the Agency:

Part 1 and Part 4.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

NexGard Combo is authorised in cats with, or at risk from mixed infections by cestodes, nematodes and ectoparasites and is to be used exclusively when all three groups are targeted at the same time. The active substances are esafoxolaner, eprinomectin and praziquantel. The product is a spot-on solution presented in applicators which deliver 0.3 or 0.9 ml solution.

The proposed variation is to add two new therapeutic indications for immediate and persistent tick killing activity against *Ixodes hexagonus* and for persistent tick killing activity against *Rhipicephalus sanguineus*, and to align the product information with version 9.0 of the QRD templates.

In relation to the addition of the two new therapeutic indications, the applicant has adequately justified the new indications by reasons that cats are possible hosts for *Ixodes hexagonus* and *Rhipicephalus sanguineus*. Additionally, both tick species are endemic in Europe.

As the product 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, no new concerns in terms of target animal safety, user safety or the environment are to be expected.

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

2.1. Addition of a new therapeutic indication - treatment of infestations with Ixodes hexagonus

To support the proposed new indication for the treatment of tick infestations with *Ixodes hexagonus*, the applicant has provided the results of two pre-clinical dose confirmation studies (studies #1 and #2) and the results of a field study that was previously submitted with the initial marketing authorisation application (field trial #1).

Both dose confirmation studies were blinded, randomised, negatively-controlled, GCP-compliant, conducted in Europe (study #2) and South Africa (study #1), and investigated the efficacy of a single topical administration of NexGard Combo against induced infestations of *Ixodes hexagonus* in cats. Both dose confirmation studies were designed and conducted largely in line with the relevant guidelines: 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.3) and Guideline for the demonstration of efficacy of ectoparasiticides (7AE17a).

For each study, 16 cats were assigned randomly or based on pre-study tick counts to treatment or negative control group and infested under sedation with approximately 40 adult female *Ixodes hexagonus* ticks on days -2 and 28 in study #2 and on days -2, 7, 14, 28 and 35 in study #1.

It is noted that, in both studies, cats were housed individually during the entire study duration, i.e. for more than 45 and 37 days, respectively. According to Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes, with the exception of naturally solitary animals, animals shall be housed in stable groups of compatible animals. In cases where individual housing is justified in accordance with article 33(3), the duration of housing shall be limited to the minimum necessary and visual, auditory, olfactory and/or tactile contact shall be maintained. The CVMP considers that the minimum necessary duration of individual housing would have been between tick infestation and tick collection. Between tick collection and a new infestation, group housing would have been possible, especially in studies with longer intervals between infestations, such as study #2 where only two infestation timepoints would have allowed for grouping of animals between counting of ticks on day 2 and infestation on day 28. However, cats were randomly allocated to treatment groups and for group housing, new groups would have had to be formed, which could be considered an additional source of stress for the study animals, in contrast to keeping them individually with visual, auditory and olfactory contact as before. Furthermore, grouping of animals could have led to the transfer of the IVP between the animals by physical contact and grooming resulting in a "common" group exposure to treatment. Consequently, single housing is considered to have been justified.

In study #1 an *Ixodes hexagonus* isolate originating from the Netherlands in 2015 was used. The guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.4) recommends to enrich laboratory tick isolates with ticks from field isolates about every six years; the in-life phase of this study took place in September-October 2021. The applicant pointed out that the time of study falls within the higher end of the recommended deadline for genetic enrichment. However, given that the infestation rate was adequate, no negative impact on the results is anticipated.

In study #2 a different isolate of *I. hexagonus* originating from the Netherlands, collected in the field in 2018, was used for infestation.

In both studies, mineral oil was applied topically as negative control at day 0; the treatment group received a single topical administration of NexGard Combo at the minimum recommended therapeutic dose of 0.12 ml/kg bodyweight.

Ticks were collected and counted approximately 48 hours after treatment (day 2) and after each infestation, and the numbers of live attached, live free, dead attached and dead free ticks were recorded. Efficacy was based upon a 90% reduction of live attached female ticks for the treated group when compared to the placebo controlled group using arithmetic mean counts.

Sufficient effectiveness of NexGard Combo compared to the untreated control group was demonstrated in study #2, with a percentage efficacy of 93.6% and 100% at days 2 and 30, respectively, as well as in study #1, where a percentage efficacy of 96.5%, 98.7%, 99.2%, 100% and 100% was recorded at days 9, 16, 23, 30 and 37, respectively. For all these time points, the results were statistically significant.

However, an insufficient efficacy of only 60.5% when compared with the control group was observed on study day 2 in study #1, where three cats harboured more than 30 live attached female ticks on day 2.

The applicant hypothesises that the design of study #1 may have had an artificial negative impact on the performance of the product on Day 2: whereas for study #2, cats were fitted with Elizabethan collars prior to tick infestation at Day -2 and the collars were removed before treatment on Day 0, for study #1 the Elizabethan collars were fitted to the animals during the period Day -2 to Day 2 and that this may have had a significant impact on the distribution/resorption of the compound in the initial two days after treatment and this may have thus resulted in the reduced efficacy at Day 2.

It is noted that the study report states that the Elizabethan collars were non-absorbent. No data that Elizabethan collars impact the distribution of the active substance are available.

Therefore, the applicant's explanation can currently only be considered as a hypothesis and no data to verify this hypothesis are available. Although the difference in study design is acknowledged, this cannot erase insufficient results on the one hand and does not confirm immediate efficacy on the other hand. In addition, if the hypothesis that the Elizabethan collars have impacted the distribution of the active substance would be further supported with data, a review of the pharmacokinetics and the efficacy of the product also at later timepoints of the study would be expected, considering also the potential impact on the proposed length of persistent efficacy.

In conclusion, immediate efficacy of the veterinary medicinal product against ticks of the species *Ixodes hexagonus* has not been demonstrated.

In order to confirm successful treatment administration in study #1, plasma blood levels for esafoxolaner were measured on day 9, which confirmed that all treated cats had measurable plasma levels for esafoxolaner. The applicant further noted that two of the treated cats with more than 30 ticks on day 2 had the lowest esafoxolaner blood levels (50.3 ng/ml and 34.7 ng/ml); the third one had 78.5 ng/ml, which was above the average esafoxolaner blood levels in this study (70.8 ng/ml). It is hypothesised in the critical expert report, that "in view of the pharmacokinetic profile of esafoxolaner applied within NexGard Combo and especially the T_{max} of 7 ± 3 days, these 3 cats belonged to the 'slower absorbers' and needed some extra time to be cleared of their existing ticks". This explanation can only be partly followed: comparing the aforementioned plasma levels with the plasma levels measured in study #2, where plasma levels where measured weekly, also as a surrogate for assuming efficacy, it is noted that the arithmetic mean plasma levels throughout the study were quite consistent, i.e. 40.7 ng/ml, 43.6 ng/ml, 42.5 ng/ml, 41.5 ng/ml and 42.4 ng/ml for days 2, 7, 14, 21 and 28, respectively. Furthermore, it is noted that on days 2 and 7, the plasma concentrations in study #2 were between 22.7 and 89.7 ng/ml and between 25.9 and 82.0 ng/ml,

respectively, with sufficient efficacy for all treated cats. However, the applicant explained that manual body search for ticks as well as the application of Elizabethan collars might have contributed to differences in the distribution of the compounds of the medicinal product in comparison to classical pharmacokinetic study setups. Consequently, the applicant considers that no meaningful comparison of the different datasets of plasma values is possible. The applicant's reasons for not comparing the plasma levels are noted and the issue is not pursued further.

Considerable differences between cats in dermal absorption affecting both T_{max} and total systemic bioavailability are expected for topically applied products. Efficacy against already established ticks may be more sensitive to these variations than efficacy against new infestation at later time points. Consequently, the lack of immediate efficacy against *I. hexagonus* may be a true biological observation and not just an artefact in the particular experiment.

In conclusion, although it can be accepted that the product kills *Ixodes hexagonus* ticks within 48 (± 2) hours after new infestations, the efficacy concerning *I. hexagonus* ticks present on the animal prior to treatment administration is not accepted and the applicant agreed to remove any mentioning of "immediate" efficacy for *Ixodes hexagonus* ticks that are present on the animal before treatment administration.

2.2. Addition of a new therapeutic indication - treatment of infestations with Rhipicephalus sanguineus

To support the proposed new indication for the treatment of tick infestations with *Rhipicephalus sanguineus*, the applicant provided the results of four pre-clinical dose confirmation studies (studies #3, #4, #5 and #6) and the results of a field study that was previously submitted with the initial marketing authorisation application (field trial #1).

All dose confirmation studies were blinded, randomised, negatively-controlled, GCP-compliant, conducted in Europe or South Africa, and investigated the efficacy of a single topical administration of NexGard Combo against induced infestations of *Rhipicephalus sanguineus* in cats. All four dose confirmation studies were designed and conducted in line with the relevant guidelines: 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.3) and Guideline for the demonstration of efficacy of ectoparasiticides (7AE17a).

For each study, twenty cats were assigned based on pre-study tick counts to treatment or control groups and were infested with approximately 50 adult unfed *R. sanguineus* ticks in a 1:1 sex ratio.

Study #3 and study #4 were pivotal studies, both conducted in South Africa over a study duration of 60 and 44 days, respectively. In these studies, the infestations took place on days -2, 7, 14, 21, 30, 37, 44, 53 and 58 (study #3) and on days -7, -2, 7, 14, 21, 28, 35 and 42 (study #4).

For study #3, a *Rhipicephalus sanguineus* isolate originating from the US acquired in 2014 without genetic enrichment before the animal phase of the study was used. However, since the isolate was not older than 6 years and the tick infestation was adequate, this can be accepted.

For study #4, a *Rhipicephalus sanguineus* isolate originating from Europe acquired in 2007 from France with regular genetic enrichments with ticks collected from the field (last enrichment: 2017, Greece) was used. Since the enrichment was not older than 6 years without record of being resistant to ectoparasiticides, the isolate used is considered adequate.

For all studies technical oil or mineral oil was administered topically in a dose of 0.12 ml/kg bodyweight as negative control at day 0; the treatment group received a single topical administration of NexGard Combo at the minimum recommended therapeutic dose of 0.12 ml/kg bodyweight.

For infestation, cats were sedated with medetomidine and fitted with Elizabethan collars. Ticks were then placed on the lateral side (study #3) or at the back (study #4) of the cats to avoid contact to the treatment application site. For a maximum of 4 hours the cats were placed in infestation crates and afterwards returned back into individual cages. Remaining ticks in the crates were placed back on the animal.

Ticks were collected and counted approximately 48 hours after treatment (day 2) and after each infestation, and the numbers of live attached, live free, dead attached and dead free ticks were recorded. Efficacy was based upon a 90% reduction of live attached female ticks for the treated group when compared to the placebo controlled group using arithmetic mean counts.

According to the guideline recommendations, an infestation was considered adequate if at least six animals in the control group harboured at least 25% (n=13) live attached ticks, which was confirmed for all observation time points in study #3. However, in study #4, on the first observation time point (D2) only one cat and on the last observation time point (D44) only 2 cats of the control group were adequately infested. Consequently, percentage efficacy could only be calculated from D9 to D37 in this study.

In summary, sufficient effectiveness of NexGard Combo compared to the untreated control group was demonstrated, with a percentage efficacy of 89.8% (rounded up to 90%), 100%, 100%, 100%, 99%, 96.8% and 96.1% on study days 2, 9, 16, 23, 32, 39 and 46 in one study (#3), as well as 99.5%, 97.8%, 94.2%, 96.9% and 89.8% (rounded up to 90%) on study days 9, 16, 23, 30 and 37 in the other study (#4). For all these time points, the results were statistically significant. Although it is noted that 89.8% efficacy is below the required 90%, the actual difference is considered negligible and also based on the method of efficacy calculation. However, an insufficient efficacy of only 88.2% and 62.7% when compared with the control group was observed on study days 55 and 60 in study #3.

As an additional parameter, the number of dead ticks 24-48 hours post infestation was observed. The p-values for the comparison of the log-counts of dead ticks for the Nexgard Combo treated group versus negative control group were significantly different at all time-points (p-values < 0.0001–0.007) in study #3; dead tick counts were at all timepoints higher in the treated group compared to the negative control group. However, no statistical analysis was performed in study #4. In both studies, the single treatment was well tolerated and no treatment related adverse events occurred.

Based on these two pivotal dose confirmation studies, it can be concluded that a single treatment of cats with NexGard Combo at the minimum recommended dose was well tolerated and showed a persistent efficacy of ≥ 90% against *Rhipicephalus sanguineus* tick infestations from one week until 37 days after treatment.

It is noted that all cats were housed individually during the entire study, i.e. for more than 60 and 44 days, respectively. Similar as for the *I. hexagonus* studies above, for group housing, new groups would have had to be formed, which could be considered an additional source of stress for the study animals, in contrast to keeping them individually with visual, auditory and olfactory contact as before. Furthermore, grouping of animals could have led to the transfer of the IVP between the animals by physical contact and grooming resulting in a "common" group exposure to treatment. Consequently, single housing is considered to have been justified.

Studies #5 and #6 are considered non-pivotal, both conducted in Germany over a study duration of four days. These studies were performed to verify the immediate and sustained efficacy in the first week post treatment. In these studies, the infestations took place on days -5, -2 and 2 (study #5) and on days -4, -2 and 2 (study #6).

NexGard Combo was administered at day 0 to animals in the treatment group at the minimum recommended therapeutic dose of 0.12 ml/kg bw, while animals in the negative control group received mineral oil.

For study #5, a *Rhipicephalus sanguineus* isolate originating from Europe was used; the isolate was

maintained under laboratory conditions in Germany since 2018. For study #6, a *Rhipicephalus sanguineus* isolate also originating from Europe was used; the isolate was maintained under laboratory conditions in Ireland for three years. However, both studies failed as the control animals were not adequately infested at both observation time points (D2 and D4) (study #5) or at the first timepoint (D2) (study #6), respectively. Although in the latter study the control group was adequately infested on D4, the percentage efficacy in the treated group was only 69.5%. From a statistical point of view, a valid and successfully performed study cannot compensate a valid but unsuccessful study in particular with regard to efficacy demonstration of a product. However, it is acknowledged that the applicant only claims efficacy against *R. sanguineus* from day 7 and has not claimed immediate efficacy.

Whilst the isolates met the required conditions for laboratory organisms with regard to origin, enrichment and had not previously been challenged with ectoparasitics, there was in consequence no experience available on the suitability of the isolates to confirm a generally adequate infestation rate in cats. It is known that *R. sanguineus* primarily infests dogs, but in the field it can infest other host species like cats. However, the argumentation of the applicant's expert that for successful collection, the field environment where *R. sanguineus* are searched is, to variable extent, populated by dogs (e.g. shelter), and consequently some collected ticks may have lost ability to infest cats, is noted.

According to guideline EMEA/CVMP/EWP/005/2000-Rev.3, at least two dose confirmation studies should demonstrate efficacy over the entire claimed duration of efficacy. As the applicant proposes a claim for "Persistent tick killing activity from 7 days to five weeks after treatment against *Rhipicephalus sanguineus*", the divergent results obtained in studies #5 and #6 do not hamper the proposed claim and both studies with observation time points on D2 and D4 serve only as supporting information.

While in both studies the single treatment was well tolerated and no treatment related adverse events occurred, in study #5 one cat of the treatment group died during D2 sedation for tick counting. However, the argumentation of the applicant that, due to the observed pathologic signs of cardiomyopathy and endocardial fibrosis with chronic congestion to the lungs, cardiovascular failure is the cause of death and a relation to treatment is unlikely, can be accepted.

2.3. Clinical field trial

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) recommends that for the demonstration of efficacy of ectoparasiticides two types of studies should be performed, pre-clinical studies and clinical trials. For the current variation application, the marketing authorisation holder submitted the results of the clinical trial that was conducted to support the initial marketing authorisation of NexGard Combo (field trial #1).

This GCP-compliant clinical field trial was conducted in accordance with the CVMP guideline EMEA/CVMP/EWP/005/2000-Rev.3. The study was conducted in six European countries (Bulgaria, France, Germany, Hungary, Portugal, Romania). A total of 146 clients-owned cats met the inclusion criteria for tick infestation and were allocated either to a NexGard Combo (IVP) group (n=94), or to a Frontline Combo Spot-on Cats (CP) comparator group (n=52). Cats were treated once on Day 0 at label dose with their respective product. The percent tick efficacy results (inclusive of all tick species) for the IVP group were 98.3%, 98.1%, 98.6% and 98.1% and for the CP group were 98.8%, 95.8%, 94.6% and 85.8%, for assessments on Days 7, 14, 21 and 28, respectively.

Five different tick species were identified, including *Rhipicephalus sanguineus* and *Ixodes hexagonus* and, as part of this variation, the applicant newly provided tables with individual cats counts for both *I. hexagonus* and *R. sanguineus* ticks in the beginning of the study.

The applicant summarised that 10.2% (n=15) and 6.2% (n=9) of the included cats harboured *I. hexagonus* and *R. sanguineus* ticks, respectively, and further lines out that none of the cats harbouring *I. hexagonus* and *R. sanguineus* ticks in the beginning of the study, harboured any ticks at all timepoints later during the study.

The final study report also indicates that some of the cats included in the trial harboured *I. hexagonus* and *R. sanguineus* ticks during the study period.

The following, which is written in the EPAR of the initial marketing authorisation procedure for NexGard Combo, also applies to this variation procedure:

"Due to the manual removal of ticks after each visit, and in conjunction with the high percentage of cats with only one tick at a single time point, a relevant infestation pressure cannot be extrapolated over the entire study period.

Therefore, the placebo cure rate could be quite high. Since no negative-controlled group was included, efficacy in comparison to placebo could not be evaluated. Hence, it is not evident that the control product is more effective than placebo under this study design.

Due to questions on the study design and the statistical analysis, no clear conclusion regarding the efficacy of the NexGard Combo in regard to efficacy against ticks could be drawn from this study."

Notwithstanding the above, it is acknowledged that the incidence of these tick species is rare, and that a new dedicated clinical trial would not be feasible as it would imply the enrolment of an unrealistic high number of animals; therefore, no new study is requested. In summary, given that adequate (persistent) efficacy of NexGard Combo against the claimed tick species *Ixodes hexagonus* and *Rhipicephalus sanguineus* has been shown in the respective dose-confirmation studies, this clinical trial can be considered to support the persistent efficacy against the newly proposed tick species *Ixodes hexagonus* and *Rhipicephalus sanguineus*.

In conclusion, given the totality of data presented with this variation application, the CVMP can accept the addition of therapeutic indications against the two new tick species (persistent efficacy), as follows:

- Persistent tick killing activity from 7 days to five weeks after treatment against *Rhipicephalus sanguineus*;
- Persistent tick killing activity from 7 days to four weeks after treatment against *Ixodes hexagonus*.

2.4. Alignment of the product information with version 9.0 of the QRD templates

In order to align the product information of Nexgard Combo with version 9.0 of the QRD templates, the information has been largely transcribed directly from the relevant sections of the previously approved product information for the product to the relevant sections of the newly proposed product information presented with this application. Relevant subheadings have been introduced as appropriate. A number of minor amendments, mostly editorial, have also been made, and can be accepted.

Furthermore, the product information has been updated based on the 'Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products' (EMA/CVMP/EWP/170208/2005-Rev.1), i.e. standard text as recommended by this guideline has been introduced in the SPC and corresponding sections of the package leaflet.

3. Benefit-risk assessment of the proposed change

NexGard Combo is authorised in cats with, or at risk from mixed infections by cestodes, nematodes and ectoparasites and is to be used exclusively when all three groups are targeted at the same time. The active substances are esafoxolaner, eprinomectin and praziquantel. The product is a spot-on solution presented in

applicators which deliver 0.3 or 0.9 ml solution.

The proposed variation is to add two new therapeutic indications for immediate and persistent tick killing activity against *Ixodes hexagonus* and for persistent tick killing activity against *Rhipicephalus sanguineus*, and to align the product information with version 9.0 of the QRD templates.

3.1. Benefit assessment

Direct therapeutic benefit

The proposed benefit of the variation to the marketing authorisation of NexGard Combo is its efficacy for the proposed indications, which was investigated in a number of well-designed laboratory studies conducted to an acceptable standard.

The therapeutic benefit for the animal is the addition of the proposed ticks to the list of indications.

At the time of submission of the application, the marketing authorisation holder applied for the following indications: for immediate and persistent tick killing activity against *Ixodes hexagonus* for one month and for persistent tick killing activity from 7 days to five weeks after treatment against *Rhipicephalus sanguineus*.

Following the assessment of the dossier, the CVMP concluded that the immediate efficacy against *Ixodes hexagonus* ticks was not demonstrated. Thus, the following indications were accepted: for persistent tick killing activity from 7 days to four weeks after treatment against *Ixodes hexagonus* and for persistent tick killing activity from 7 days to five weeks after treatment against *Rhipicephalus sanguineus*.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

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

3.3. Risk management or mitigation measures

Appropriate information is already included in the SPC and other product information to inform on the potential risks of this product relevant to the target animal, user, 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 product is envisaged on the following aspects: quality, safety, user safety, environmental safety, target animal safety.

The product has been shown to be efficacious against infestations with *Ixodes hexagonus* and *Rhipicephalus sanguineus* from 7 days to 4 or 5 weeks after treatment, respectively.

The product is well tolerated by the target animals and presents an acceptable risk for users and the environment, when used as recommended.

The benefit-risk balance remains unchanged.

4. Conclusion

Based on the original and complementary 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 Combo can be approved, since the data satisfy the requirements as set out in the legislation (Regulation (EU) 2019/6), as follows:

- to add a new therapeutic indication for persistent tick killing activity from 7 days to four weeks after treatment against *Ixodes hexagonus*;
- to add a new therapeutic indication for persistent tick killing activity from 7 days to five weeks after treatment against *Rhipicephalus sanguineus*;
- to align the product information with version 9.0 of the QRD templates.

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 Union marketing authorisation:

I, II, IIIA and IIIB.

As a consequence of these variations, all sections of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.