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Veterinary Medicines Division

## Committee for Veterinary Medicinal Products (CVMP)

# CVMP assessment report for grouped variation for Frontpro (EMEA/V/C/005126/VRA/0014/G)

INN: afoxolaner

**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 64 of Regulation (EU) 2019/6, the marketing authorisation holder, Boehringer Ingelheim Vetmedica GmbH (the applicant), submitted to the European Medicines Agency (the Agency) on 24 July 2023 an application for a group of variations requiring assessment for Frontpro.

## *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.4 | Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data. |
| 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 a new therapeutic indication for the treatment of tick infestations with *Ixodes hexagonus* and align the wording of the indications for use with applicable CVMP guidelines, to update SPC section 3.7 to allow the use of the product in breeding, pregnant and lactating female dogs, 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

On 20 May 2019, Frontpro, initially named Afoxolaner MERIAL, was authorised as an 'informed consent' of NexGard. A marketing authorisation was granted for NexGard through the centralised procedure on 11 February 2014 (EMEA/V/C/002729).

Frontpro and NexGard contain the active substance afoxolaner, an acaricide and insecticide belonging to the isoxazoline group. The product Nexgard Spectra, a fixed combination product, contains two active substances: afoxolaner and milbemycin oxime. Noninteraction of these two active substances was confirmed

in 2014 (EMEA/V/C/003842/0000).

Frontpro is available in four strengths (11 mg, 28 mg, 68 mg, 136 mg) of chewable tablets for oral administration once a month to dogs and puppies according to their weight. Treatment of puppies less than 8 weeks of age and/or dogs less than 2 kg bodyweight should be based on a benefit-risk assessment by the responsible veterinarian.

Frontpro is currently indicated for:

- treatment of flea infestation in dogs (*Ctenocephalides felis* and *C. canis*) for at least 5 weeks.
- treatment of tick infestation in dogs (*Dermacentor reticulatus*, *Ixodes ricinus*, *Rhipicephalus sanguineus*). One treatment kills ticks for up to one month.

With the current procedure, the applicant proposes to add a new therapeutic indication (*Ixodes hexagonus* ticks) and to allow the use of the product in breeding, pregnant and lactating female dogs. Both variations have already received a positive opinion for NexGard and Nexgard Spectra, and the data package presented now is identical to the data packages that were presented for the respective variations for NexGard and Nexgard Spectra.

The applicant further proposes to align the product information with version 9.0 of the QRD templates, update the product information in line with the current 'Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products' (EMA/CVMP/EWP/170208/2005-Rev.1 Corr.), and also takes the opportunity to propose editorial changes to the product information.

Two pivotal studies are included in the dossier. During the previous variation for NexGard and Nexgard Spectra (EMEA/V/C/WS2280/G), the CVMP had already commented on the observation that in the first (pivotal) study, which was conducted outside Europe, dogs were housed individually for the entire course of the study in cages that were smaller than required by Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes. In the EU individual housing of the test animals is not recommended for the entire study duration (EMEA/CVMP/EWP/005/2000-Rev.4). However, although it would have been desirable for the study to have been conducted in line with European animal welfare legislation (Directive 2010/63/EU), requiring new studies would not be justifiable from an animal welfare perspective. It is also notable that this study was performed before Regulation (EU) 2019/6, which requires compliance with Directive 2010/63/EU, came into force. Consequently, the study was accepted.

## *2.1. Safety (tolerance, user, environment)*

With the introduction of the proposed indication, Frontpro 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 substance 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 indication will not present an unacceptable risk for the user or the environment.

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

Frontpro was authorised as an 'informed consent' of NexGard. Information on potential effects of the active substance on reproduction in laboratory animals has been provided with the original marketing authorisation procedure for NexGard (and Nexgard Spectra): the CVMP then concluded that neither afoxolaner nor milbemycin oxime shows potential for teratogenicity: "*Laboratory studies in rats and rabbits have not produced any evidence of teratogenic effects, or any adverse effect on the reproductive capacity in males and females*".

Following a worksharing variation procedure in December 2022 for NexGard and Nexgard Spectra, the wording of section 4.7 of the SPC ('Use during pregnancy, lactation or lay'), was amended to: "*Can be used in breeding, pregnant and lactating dogs. The safety of the veterinary medicinal product has not been established in breeding males*."

The applicant hereby presents an identical data package to support amendment of the product information to also allow the use of Frontpro in breeding, pregnant and lactating female dogs.

A reproductive safety study has been performed in the target species (Reproductive Safety Study), which was well designed and performed largely in line with VICH GL43 - Guideline on target animal safety for veterinary pharmaceutical products.

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

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

Animals were treated at appropriate 4-week intervals, with at least two doses administered pre-mating (therefore ensuring that, for afoxolaner, a steady state was reached). Dosing continued until weaning at Day 49 after parturition. All dams that whelped received 6 to 11 total treatments per female.

Animals were therefore adequately dosed prior to breeding (covering the follicular phase until conception), throughout the gestation period (including embryonic phase, foetal phase, and natal phase), and after parturition for an appropriate duration of time, adequately covering all key periods of the gestation. For the purpose of investigating negative effects on reproductive parameters in breeding, pregnant or lactating dams, the study design and the range of reproductive parameters measured are considered appropriate and sufficient.

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

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

The reproduction performance parameters evaluated (most importantly, the number of live and stillborn

puppies, puppies with abnormalities, mortality and body weight of the pups) can be considered adequate to support the safety statements proposed for the section of the SPC concerning ”Use during pregnancy, lactation or lay”. Overall, parameters evaluated were very similar between treatment and control groups and lacked statistically significant difference. Results did not suggest an impact of afoxolaner on the female reproductive performance when administered before and during the gestation.

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

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

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

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

The proposed wording of the section concerning ”Use during pregnancy, lactation or lay” of the SPC and corresponding section of the package leaflet is considered appropriate.

## *2.2. Efficacy*

### 2.2.1. Addition of a new therapeutic indication - treatment of tick infestations with *Ixodes hexagonus*

In 2019, Frontpro was authorised as an 'informed consent' of NexGard.

Following a worksharing variation procedure in July 2019 for NexGard and Nexgard Spectra, a positive opinion was received for the addition of a new therapeutic indication: treatment of tick infestations with *Ixodes hexagonus*. Also, similar to NexGard, for this newly proposed indication Frontpro is to be administered at the same dose rates as currently authorised, namely 2.7-7.0 mg afoxolaner/kg bodyweight, monthly.

In support of the addition of an identical indication for Frontpro, the applicant hereby presents a similar data package as the one presented for the abovementioned worksharing procedure for NexGard and Nexgard Spectra. This data package includes the results of a single dose confirmation study and reference to the results of a field trial that was previously submitted for the initial marketing authorisation for Nexgard Spectra. Though Nexgard Spectra is a fixed combination product that contains two active substances, afoxolaner and milbemycin oxime, acaricidal activity against *Ixodes hexagonus* ticks is related to afoxolaner only and the absence of interaction between afoxolaner and milbemycin oxime has been previously confirmed.

The GCP-compliant dose confirmation study investigated the efficacy of a single oral administration of afoxolaner alone (NexGard) or in combination with milbemycin oxime (Nexgard Spectra) against induced infestations of *Ixodes hexagonus* on dogs. This was a blinded, randomised, negatively-controlled study conducted in Europe and live attached tick counts were used to calculate efficacy. Twenty-four dogs were randomly assigned into three groups and infested with approximately 50 ticks on Days -2, 7 and 28. Group 1 was the control group and did not receive treatment. Groups 2 and 3 were given a single oral dose of NexGard and Nexgard Spectra respectively on Day 0. Tick counts were recorded on Days 2, 9 and 30 with the numbers of live attached, live free, dead attached and dead free ticks recorded. Efficacy was based upon a threshold of 90% reduction in tick counts for Groups 2 and 3 when compared to Group 1 using arithmetic mean counts.

The percent efficacy using arithmetic means of NexGard (Group 2) and Nexgard Spectra (Group 3) compared to the untreated control group was 100% at all post-treatment counts (Days 2, 9 and 30), apart from 96.7% for NexGard on Day 30. There were statistically significant differences of the arithmetic mean counts between each treated group and control group for all time points ($p<0.0001$). The overall efficacy for afoxolaner was 100% on Days 2 and 9 and 98.1% on Day 30.

Based upon the findings from this study, it can be accepted that under laboratory conditions, both NexGard (and thus also Frontpro) and Nexgard Spectra administered at the recommended treatment dose demonstrated an acceptable level of efficacy (>90%) against the tick species *Ixodes hexagonus*.

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. In addition to the dose confirmation study described above, reference has been made to the results of a field trial provided with the original marketing authorisation application for Nexgard Spectra. Although only 6 dogs in that study were identified as being infested with *I. hexagonus* ticks (four treated with Nexgard Spectra and two with the positive control product), also taking into consideration the '3Rs', this is considered acceptable. It can be accepted that the findings of that clinical trial provide supporting evidence for efficacy of all three afoxolaner-containing products (including Frontpro) against *I. hexagonus* ticks under field conditions of use.

CVMP guidelines recommend that two dose confirmation studies are provided for each claim. Given that both NexGard/Frontpro and Nexgard Spectra are already indicated for the treatment of *I. ricinus* ticks, and that the applicant has provided data indicating that *I. ricinus* and *I. hexagonus* have similar susceptibility to afoxolaner, the single dose confirmation study provided with this application and the clinical trial previously provided with the application for initial marketing authorisation for Nexgard Spectra are considered adequate for the purpose of supporting the proposed indication against *I. hexagonus* ticks.

In conclusion, the data package provided in support of this variation is considered appropriate and therefore the indication for the treatment of tick infestations with *Ixodes hexagonus* can be accepted.

## *2.3. Alignment of the product information with version 9.0 of the QRD templates*

In order to align the product information of Frontpro 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 Corr.),

i.e. standard text as recommended by this guideline has been introduced in the SPC and corresponding sections of the package leaflet. In addition, the wording of the indications for use has been amended to describe both the immediate and persistent efficacy against fleas and ticks, in line with applicable CVMP guidelines.

# 3. Benefit-risk assessment of the proposed change

Frontpro is authorised for the treatment of flea (*Ctenocephalides felis* and *C. canis*) and tick (*Dermacentor reticulatus*, *Ixodes ricinus*, *Rhipicephalus sanguineus*) infestations in dogs. The active substance is afoxolaner, an insecticide and acaricide belonging to the isoxazoline family. The product is presented as chewable tablets of 4 different strengths and is administered at a dose of 2.7–7.0 mg afoxolaner/kg body weight.

The proposed grouped variation is to add a new therapeutic indication for the treatment of tick infestations with *Ixodes hexagonus* and align the wording of the indications for use with applicable CVMP guidelines, to update the section of the SPC concerning "Use during pregnancy, lactation or lay" to allow the use of the product in breeding, pregnant and lactating female dogs, and to align the product information with version 9.0 of the QRD templates.

## *3.1. Benefit assessment*

### Direct therapeutic benefit

As this is a variation to introduce an additional indication to an existing product, the benefit will arise from the inclusion of the new indication. The indication against *Ixodes hexagonus* is considered as being of benefit for the user/prescriber as efficacy of the product is extended to cover another tick species.

In addition, it was demonstrated that Frontpro can safely be used in breeding, pregnant and lactating dogs.

### Additional benefits

No further additional benefits are foreseen.

## *3.2. Risk assessment*

### Quality:

Quality remains unaffected by this variation.

### Safety:

*Risks for the target animal*:

Administration of Frontpro in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions are appropriately included in the SPC and no new adverse reactions arise from the studies performed in support of the proposed new indication, nor from the study performed in support of the use in breeding, pregnant and lactating female dogs.

Information that the safety of the veterinary medicinal product has not been established in breeding male

dogs is adequately communicated in the product information.

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

*Risk for the user*:

The CVMP previously concluded that user safety for Frontpro is acceptable when used according to the SPC recommendations. The frequency of treatment is not expected to change due to the addition of the new indication, nor from the use in breeding, pregnant and lactating dogs. Therefore, no additional risk for the user arises.

*Risk for the environment*:

Frontpro is not expected to pose a risk for the environment when used according to the SPC recommendations.

### *3.3. Risk management or mitigation measures*

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

No additional risk management or mitigation measures are considered necessary.

### *3.4. Evaluation of the benefit-risk balance*

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

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

The product has been shown to be efficacious for the treatment of tick infestations (*Ixodes hexagonus*). Given that it is not expected that any new risk will result from the inclusion of this additional indication, it can be accepted that there should be an increased benefit from the use of the product for the treatment of tick infestations with *Ixodes hexagonus* in dogs.

The benefit-risk balance remains unchanged.

## 4. Conclusion

Based on the original and complementary data presented on efficacy and target animal safety, the Committee for Veterinary Medicinal Products (CVMP) concluded that the application for variation to the terms of the marketing authorisation for Frontpro 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 the treatment of tick infestations with *Ixodes hexagonus* and align the wording of the indications for use with applicable CVMP guidelines, to update the SPC section concerning ”Use during pregnancy, lactation or lay” to allow the use of the product in breeding, pregnant and lactating female dogs, and 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 Community marketing authorisation:

I, II, IIIA and IIIB.

As a consequence of these variations, sections ”Qualitative and quantitative composition”, ”Clinical information”, ”Pharmacological information”, ”Pharmaceutical particulars”, ”Name of the marketing authorisation holder”, and “Classification of the veterinary medicinal products” of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.