6 November 2025
EMADOC-1700519818-2675522
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a grouped variation requiring assessment for Frontpro (EMEA/V/C/005126, EMA/VRA/0000282075)

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 30 June 2025 an application for a group of variations requiring assessment for Frontpro.

1.2. Scope of the variation

Variations requested	
G.I.7.a	Addition of a new therapeutic indication or modification of an approved one
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The grouped variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of tick infestation with *Hyalomma marginatum*, reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days, and reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days. Additionally, the product information is being aligned with version 9.1 of the QRD template.

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

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

Part 1, Part 4.

1.4. Scientific advice

Not applicable.

1.5. Limited market status

Not applicable.

2. Scientific Overview

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/002729/0000).

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. Non-interaction 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.

In September 2021, the CVMP adopted a positive opinion to change the prescription status of Frontpro from 'Prescription-only medicine' to 'Product not subject to prescription'. Notably, at that time, in order to comply with the non-prescription status requested, the applicant omitted those indications included in the previously-approved product information which were considered as requiring prior veterinary diagnosis: use as part of a treatment strategy for the control of flea allergy dermatitis (FAD), treatment of demodicosis (caused by *Demodex canis*), and treatment of sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*).

Frontpro is currently indicated for:

- treatment of flea infestation in dogs (*Ctenocephalides felis* and *C. canis*). One treatment provides immediate and persistent flea killing activity for 5 weeks.
- treatment of tick infestation in dogs (*Dermacentor reticulatus*, *Ixodes ricinus, Ixodes hexagonus, Rhipicephalus sanguineus*). One treatment provides immediate and persistent tick killing activity for one month.

With the current procedure, the applicant proposes to include additional therapeutic indications (efficacy against the tick species *Hyalomma marginatum*, as well as reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days, and reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days).

These variations have already been approved for NexGard (and NexGard Spectra), and the data package presented now is identical to the data packages that were presented for respective variations for NexGard (and NexGard Spectra):

- On 8 December 2022, the CVMP adopted a positive opinion for NexGard (and NexGard Spectra), concerning change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: for the treatment of tick infestations with *Hyalomma marginatum* (EMA/950147/2022).
- On 12 June 2025, the CVMP adopted a positive opinion for NexGard (and NexGard Spectra) concerning change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: for reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days and for reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days (EMADOC-1700519818-2201540).

The applicant further proposes to align the product information of Frontpro with version 9.1 of the QRD template.

No change to the currently authorised dosing regimen for the VMP is proposed for the additional indications, i.e. efficacy is expected following administration of single dose (2.7 - 7.0 mg afoxolaner/kg body weight). Treatment may be repeated at 1-month intervals taking into account the local epidemiological situation and the animal's lifestyle.

During the previous variations, the CVMP noted that 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, in a pivotal study (performed for the authorisation of the indication: treatment of tick infestations with *Hyalomma marginatum*), which was conducted outside Europe, dogs were housed individually for the entire course of the study and 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.

Although it would have been desirable for the studies 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 that the principles of Directive 2010/63/EU should be taken into account, came into force. Consequently, the study was accepted.

2.1. Safety (tolerance, user, environment)

With the introduction of the proposed indications, 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 substances or for a greater frequency than that which has been assessed for the existing indications approved for the product. No change to the impact on the environment is envisaged.

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

2.2. Treatment of tick infestations with Hyalomma marginatum

Frontpro was authorised as an 'informed consent' of NexGard.

Following a variation procedure adopted by the CVMP in December 2022, the treatment of tick infestations with *Hyalomma marginatum* was accepted for NexGard (as well as NexGard Spectra). The applicant hereby presents an identical data package to support amendment of the product information to also allow the use of Frontpro for the treatment of tick infestations with *Hyalomma marginatum*.

Hyalomma marginatum, a hard tick, is a two-host tick that has also been recorded on dogs and is a proven vector for the etiological viral agent of Crimean-Congo haemorrhagic fever. These ticks have been occasionally reported in Central and Western Europe, and have recently been observed in other European countries, such as Germany and Sweden.

The claimed efficacy for *Hyalomma marginatum* is based on a single, pre-clinical, dose confirmation study (Lab 1). The omission of an additional clinical trial in support of the claim is considered acceptable by the CVMP for the following reasons: in multiple clinical and pre-clinical studies, both NexGard as well as NexGard Spectra have been demonstrated to be highly effective against various different tick species, amongst of which *Ixodes hexagonus* and *Ixodes ricinus*. Similar to these two tick species, *Hyalomma marginatum* also belongs to the family of *Ixodidae*. The outcome of the dose confirmation study currently presented supports that treatment with afoxolaner is also highly effective (>97%) against *Hyalomma marginatum.* Finally, *Hyalomma marginatum* is currently considered to be a non-autochthonous tick species in Europe, for which deviations from the recommendations set out in available guidelines may be acceptable. In light of the above, the omission of additional studies in support of the indication against *H. marginatum* is considered acceptable.

The study (Lab 1) was a pivotal, well-designed dose confirmation study that was performed largely taking into consideration 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) (though some deviations from this guideline were noted and will be discussed) and the Guideline on the demonstration of efficacy of ectoparasiticides (7AE17A). The study was performed in accordance with GCP. According to the above-mentioned GLs, this can be accepted.

This was a single-site, negatively controlled, appropriately blinded, randomized, laboratory study. The study investigated the efficacy of a single treatment of NexGard and a spot-on product (at the recommended clinical dose) against *Hyalomma marginatum* ticks in dogs for up to 39 days (i.e. >1 month).

The study covered the entire period of the claimed effect of treatment. Study duration is therefore considered appropriate. The use of an untreated control group is also considered appropriate for this type of study. A study protocol, study report and the statistical results have been provided.

The study was conducted in South Africa. Whilst the study was conducted outside the EU, given the design of this laboratory study, this is not of concern. The tick strain used was a recent strain that derived from Morocco. However, as this tick species is currently not endemic in Europe, the use of a Moroccan tick strain is considered acceptable.

An acceptable number of 24 healthy, adult Beagle dogs were included and divided in three groups of 8 dogs each. Study population is considered to be sufficiently representative for the target population. On Day 0, one group was left untreated, one group received treatment with NexGard, and one group received a spot-on product. As this spot-on product is not relevant for this variation, this data will not be discussed.

In this study, the animals received treatment at a dose range of 2.9 to 6.7 mg/kg bw of afoxolaner (mean dose of afoxolaner was 5 mg/kg bw). Although the minimum dose rate approved for NexGard (2.7 mg/kg) was not administered in this study, the dose range administered can be accepted as falling sufficiently within the lower end of the dose range currently approved for NexGard, with only 1 animal being dosed at 6.7 mg/kg bw, and the remainder dosed at 5.9 mg/kg bw or below. Furthermore, and as highlighted by the applicant, initial developmental studies were conducted with a dose of 2.5 mg/kg bw of afoxolaner, and these had been highly successful in demonstrating efficacy for other members of the *Ixodidae* family. Also, the applicant considered that the high level of efficacy that was observed in laboratory study 1 should be taken into account.

To evaluate susceptibility of the animals, dogs were sedated and challenged at Day -14. Due to the initial low tick attachment, the study was extended, and an additional infestation was conducted on Day -7, which is considered acceptable.

To assess both immediate as well as persistent efficacy, dogs were challenged at Days -2, 7, 28 and 36. Ticks were then thumb-counted on Days 2, 9, 30 and 38 (48 ± 2 h after product administration or infestation) and removed and counted on Days 3, 10, 31 and 39 (72 ± 2 h after product administration or infestation).

Challenges were performed with approximately 30 (15 females and 15 males) viable, adult, unfed *H. marginatum* ticks. The number of challenges and the method of challenge are considered appropriate; however, it is noted that only 30 ticks were used for each challenge, whilst the 'Guideline for the testing antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats' states that approximately 50 unfed adult ticks should be used for a challenge. No justification is provided for use of a lower number of ticks. It is however noted that the treatment effect was high and all control animals were adequately infested (even more control animals than required according to the guideline – 8 versus 6 – were used); in addition, for the control group attached tick counts ranged from 8-29 across days 3, 10, 31 and 39 with at least 6 control animals exhibiting tick counts >14 at each timepoint. In this regard, the infestation rate can be considered adequate, given that the aforementioned guideline specifies that 12-25 ticks should attach to each animal at each time point. Considering the above, the method of challenge is considered adequate for this study.

In terms of efficacy, the primary efficacy criterion was the percentage of efficacy against ticks recorded in the IVP group compared to the control group at each assessment time point. Efficacy was calculated using Abbott's formula, and efficacy calculations were based on arithmetic mean values, which is considered appropriate. Live free ticks were not considered for efficacy evaluations, which is also considered acceptable for a systemically acting acaricide.

Results showed that infestation in the control dogs was adequate. Efficacy based on arithmetic means exceeded 90% (97.1 to 100%) from 48 hours after treatment up to Day 39, successfully demonstrating both an immediate as well as a persistent efficacy of the product against *Hyalomma marginatum* ticks. Results met the recommended efficacy threshold of 90% as defined in the aforementioned guideline.

No adverse events directly attributable to NexGard were reported in this study.

Overall conclusion:

In summary, based upon the findings from this study, it can be accepted that under laboratory conditions, NexGard (and thus also Frontpro) administered at the recommended treatment dose demonstrated an acceptable level of efficacy (>90%) against *Hyalomma marginatum* ticks.

In terms of safety, no issues were observed during the study, confirming safety of NexGard (and thus also Fronpro) when used according to label.

2.3. Reduction of the risk of infection with Babesia canis canis via transmission by Dermacentor reticulatus for 28 days and reduction of the risk of infection with Dipylidium caninum via transmission by Ctenocephalides felis for 30 days

Following a variation procedure for NexGard (as well as NexGard Spectra) adopted by the CVMP in June 2025, reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days and reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days were accepted as additional indications. The applicant hereby presents an identical data package to support amendment of the product information to also allow the use of Frontpro (authorised as an 'informed consent' of NexGard) for these indications.

For each of the two proposed indications, the applicant has conducted one well-designed pivotal laboratory study covering the entire period of reduction of the risk of disease transmission, in line with the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015).

In addition, reference is made to studies from published scientific literature. It is noted that these studies were conducted prior to the introduction of the above-mentioned CVMP guidance document. As a result, the applicant has highlighted that the cited studies may not fully conform with guideline recommendations.

All studies submitted (pivotal and supportive) were GCP-compliant and were performed with the final formulation of NexGard or NexGard Spectra. The studies are summarised below, under the respective headings for each indication.

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

Babesiosis is an inoculable infectious disease caused by the multiplication of Apicomplexa protozoa, belonging to the genus *Babesia* in various mammals. *Babesia* are strictly intraerythrocytic parasites,

infecting the red blood cells (i.e. erythrocytes). These organisms are transmitted by various hard tick species and affect a wide range of mammals, including humans, ruminants, horses and carnivores. Each *Babesia* species is specific to its vector and host, and the geographical distribution and epidemiological characteristics of *Babesia* spp. are linked to the biology of each tick vector.

In support of the proposed indication for reduction of the risk of infection with *B. canis canis* via transmission by *D. reticulatus*, the applicant has provided the results of one pivotal laboratory dose confirmation study (Lab 2), along with supportive evidence from two studies in the published scientific literature (Beugnet et al., 2014a and 2015b).

The pivotal dose confirmation study (Lab 2) was a well-conducted, GCP compliant, study performed in South Africa. Consideration was given to the current CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000-Rev.4).

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

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

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

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

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

Blood samples were collected for PCR and IFA analysis from dogs in Group 1 on Day 21, for dogs in Group 2 on Day 42 and for dogs in Group 3 on Days 21, 28, 42 and 56. Additional blood sampling for PCR analysis was conducted in dogs from Group 1 (Day 8 and Day 9) and Group 2 (Day 35, Day 36 and Day 37) that were diagnosed positive for babesiosis on a blood smear.

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

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

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

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

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

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

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

The IVP used in the study was the commercial formulation of NexGard, containing 2.27% w/w afoxolaner; dogs were administered the 3 g chew size containing 68 mg afoxolaner (as appropriate for

the weight range). This equated to an actual achieved dose rate of 3.17-5.68 mg afoxolaner/kg bodyweight for dogs in the IVP group (i.e. within the range currently recommended in the NexGard and Frontpro SPCs; 2.7-7.0 mg/kg bw).

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

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

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

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

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

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

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

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

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

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

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

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

The recommended dose rate for Frontpro, which was authorised as an informed consent of NexGard, will remain unchanged as a result of this variation.

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

The VBP infection rate in the vectors used in the dose confirmation study (Lab 2) was also much higher than that reported in the field according to published literature. In this study, the *B. canis* infection rate of *D. reticulatus* ticks used for artificial infestations was 23%. All animals were also repeatedly infested, which served to mimic a high and prolonged infection pressure.

Additionally, it is noted that a number of the referenced GCP-compliant studies, including the pivotal laboratory dose confirmation study (Lab 2), were conducted using EU strains of *D. reticulatus* and *B. canis*. *Dermacentor reticulatus* ticks originating from Europe (Ireland) and enriched with ticks obtained from the Netherlands were used in the cited study. The *Babesia canis* parasite used in the study originated from Europe (Netherlands). Furthermore, it is acknowledged that regular use of isoxazolines in Europe, representing the vast majority of ectoparasiticides sold by veterinarians, has reduced the

prevalence of canine babesiosis (Solano-Gallego et al., 2016). On this basis, the applicant's argumentation regarding difficulties in running clinical trials to evaluate *Babesia* transmission is accepted.

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

Overall conclusion:

In conclusion, based on the data presented, it is accepted that NexGard (and thus also Frontpro) and NexGard Spectra, when administered on a single occasion at the recommended therapeutic dose, achieved an adequate level of efficacy to support an indication for the reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days after treatment.

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

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

To support the proposed treatment claim, one laboratory dose confirmation study (Lab 3) and one published study (Beugnet et al., 2017) were presented.

The pivotal dose confirmation study (Lab 3) was conducted in South Africa using the commercial formulation of NexGard, in accordance with VICH GCP standards. While not performed within the EU, the study was designed considering the relevant CVMP and VICH guidelines for efficacy of ectoparasiticides, anthelmintics, and data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats.

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

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

In relation to animal welfare during the study, it is noted that animals were housed individually in cages. Visual and auditory contact with other dogs was accommodated, but no physical contact was possible. While this represents a deviation from Directive 2010/63/EU, the applicant has justified the approach taken on the basis that individual housing was necessary to identify the origin of any *D. caninum* proglottid(s) found in the cage environment. At least one toy/chew was made available to

each dog (replenished weekly). Otherwise, housing conditions (including cage size, photoperiod, etc.) were in line with the afore-mentioned Directive. This argumentation can be accepted.

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

On Day 0, all IVP dogs were treated with NexGard. Afoxolaner was administered at a target dose of 2.5 mg/kg bw (actual range 2.54 to 2.80 mg/kg bw). However, the currently authorised minimum RTD for NexGard is slightly higher, at 2.7 mg afoxolaner/kg bw. Nonetheless, the approach taken can be accepted considering that, if efficacy can be demonstrated at 2.5 mg/kg bw, then it is logical that efficacy should also be anticipated at the authorised dose range of 2.7-7.0 mg afoxolaner/kg bodyweight.

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

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

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

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

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

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

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

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

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

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

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

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

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

The recommended dose rate for Frontpro, which was authorised as an informed consent of NexGard, will remain unchanged as a result of this variation.

It is noted that the CVMP Guideline on data requirements for veterinary medicinal products intended to reduce the risk of transmission of vector-borne pathogens in dogs and cats (EMA/CVMP/EWP/278031/2015) stipulates that at least one laboratory study and one clinical trial is

needed for each claimed vector-borne pathogen, unless otherwise justified. However, it is accepted that a high level of efficacy against *C. felis* (and consequently transmission of the VBP *D. caninum*) was demonstrated in the presented laboratory dose confirmation studies.

The VBP infection rate in the vectors used in the dose confirmation study (Lab 3) was also much higher than that reported in the field according to published literature. In this study, the *D. caninum* infection rate of the batch of fleas used each week to infest the dogs ranged from 13% to 37%, compared to a reported 2.23% prevalence in *C. felis* in Europe (Beugnet, 2014b). All animals were also repeatedly infested, which served to mimic a high and prolonged infection pressure.

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

Overall conclusion:

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

2.4. Evaluation of criteria for prescription status in line with Article 34 of Regulation (EU) 2019/6

The applicant suitably justified the appropriateness of the newly proposed therapeutic indications for a veterinary medicinal product not subject to prescription, in line with the provisions of Article 34 of Regulation (EU) 2019/6 and the relevant CVMP guidance (Guideline on the application of Article 34 of Regulation (EU) 2019/6; EMA/CVMP/273040/2022).

The applicant has presented an evaluation against Article 34(1) of Regulation (EU) 2019/6, wherein eight criteria are specified which necessitate that a veterinary medicinal product (VMP) be subject to veterinary prescription. In line with the dossier requirements of section I.2.1 of Annex II to Regulation (EU) 2019/6, the applicant has also presented an evaluation against Article 34(3), wherein seven conditions are specified which must be met in order for a non-prescription status to be considered justified for certain VMPs falling within the scope of paragraph 1. It must be noted that for VMPs not listed in Article 34(1), the classification of the VMP is ultimately based on the provisions of Article 34(2) taking into account the justification provided by the applicant according to section I.2.1 of Annex II. This situation applies to this variation application.

In relation to the proposed indication for the treatment of tick infestation with *Hyalomma marginatum*, while the applicant did not discuss it in line with the provisions of Article 34, it is noted that Frontpro is already authorised for the treatment of infestation with a number of tick species in dogs, i.e. *Dermacentor reticulatus*, *Ixodes ricinus*, *Ixodes hexagonus*, and *Rhipicephalus sanguineus*. As such, and also given that no new warnings specific to the new tick species are included in the product information, it is considered that the addition of *Hyalomma marginatum* to the list of target ticks will not have any impact on the current non-prescription status of the product, i.e. that this indication does not fall within the criteria of Article 34(1), and there are no special precautions within the meaning of Article 34(2) in the product information.

With regards to the claims for the reduction of the risk of infection with *Babesia canis canis* and *Dipylidium caninum* via transmission by *Dermacentor reticulatus* and *Ctenocephalides felis*, respectively, the applicant has provided argumentation to demonstrate that the proposed indications are not considered to impact the non-prescription status of the product and referred to each of the individual criteria set out by paragraphs 1 - 3 of Article 34 of Regulation (EU) 2019/6.

The applicant claimed that these additional indications would not fall under any of the eight categories of a veterinary medicinal product (or, in this case, an indication) for which classification as subject to prescription is mandatory, as described in paragraph 1 of Article 34. The CVMP agrees that these indications do not fall within the criteria of Article 34(1).

For veterinary medicinal products not listed in Article 34(1), the classification of the VMP is ultimately based on the provisions of Article 34(2). With regards to paragraph 2 of Article 34, the CVMP agrees that Frontpro is not a narcotic drug nor does it contain special precautions within the meaning of Article 34(2), i.e. being of such a nature that not complying with them could lead to serious negative consequences for the treated animal, the user, or to the environment. This conclusion is reached taking into account the justification provided by the applicant according to section I.2.1 of Annex II to Regulation (EU) 2019/6. From the justification provided it is clear that the newly proposed indications do not require a modification in the use of the product and that the proposed indications rely on the existing product's mode of action, nor are additional warnings required that would qualify as a special precaution within the meaning of Article 34(2). Introduction of these additional indications therefore would not result in a change with regards to current safety profile of the VMP or the (development of) resistance to the active substances.

In conclusion, in line with the provisions of Article 34 of Regulation (EU) 2019/6, the CVMP agrees that the three newly proposed indications are compatible with the current not-subject-to-prescription status of Frontpro.

In order to ensure safe and effective use of the product, including when the product is to be used for the additionally proposed indications, the applicant was requested to consider whether any additional guidance is needed on e.g. timing of treatment administration, and ensure that all information included in the product information in relation to the additional indications is sufficiently clear and readily understandable for the end-user and compatible with the classification of the veterinary medicinal product as not subject to prescription. The applicant's position was that additional guidance regarding the timing of treatment administration is unnecessary, as appropriate guidance regarding the treatment schedule is already included in the product information.

The applicant considers that although risk-based use of a veterinary medicinal product generally requires consideration of epidemiological factors, this requirement is not considered critical for the proposed indications, as the distribution of the vectors and the associated vector-borne pathogens largely coincide. The CVMP can accept the argumentation provided by the applicant, given that the effect of the veterinary medicinal product against *B. canis canis* and *D. caninum* is mediated through activity on the vectors, and that adequate information regarding this mode of action, as well as the treatment schedule against the vectors, are included in the relevant sections of the product information.

However, some textual amendments were included by the applicant in the package leaflet section "4. Indication for use", to ensure that the product information is readily understandable for the non-professional user. The proposed changes are considered acceptable as these are considered to facilitate readability for the non-professional user. No further changes to the product information were deemed necessary and this is considered acceptable.

In conclusion, given that the data package provided by the applicant is considered appropriate to support the additional indications and the fact that the proposed indications are considered compatible with the not-subject-to-prescription status of Frontpro, the CVMP considers that the proposed therapeutic indications are acceptable and therefore the current grouped variation can be approved.

2.5. Alignment of the product information with version 9.1 of the QRD template

In order to align the product information of Frontpro with version 9.1 of the QRD template, a number of minor editorial amendments have been made in the SPC and package leaflet and can be accepted.

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, Ixodes hexagonus, Rhipicephalus sanguineus*) infestations in dogs. The active substance is afoxolaner, an insecticide and acaricide belonging to the isoxazoline family, which is to be administered at a dose of 2.7–7 mg/kg body weight. The product is presented as chewable tablets of 4 different strengths.

The proposed grouped variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of tick infestation with *Hyalomma marginatum*, reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days, and reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days. Additionally, the product information is being aligned with version 9.1 of the QRD template.

3.1. Benefit assessment

Direct therapeutic benefit

Frontpro was authorised as an 'informed consent' of NexGard.

As this is a variation to introduce three additional indications to existing presentations of the product Frontpro chewable tablets for dogs, the direct benefits would arise from the inclusion of these indications.

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

In addition, Frontpro was claimed to provide immediate and persistent tick killing activity for an additional tick species, *Hyalomma marginatum*, for one month. Efficacy against this non-autochthonous tick was assessed in a laboratory study using the product NexGard.

Additional benefits

Hyalomma marginatum ticks are known vectors for Crimean-Congo haemorrhagic fever virus, a virus that may infect the target species, dogs, without causing overt signs, but has been described to cause haemorrhagic fever in humans.

No further additional benefits are foreseen.

3.2. Risk assessment

Quality:

Quality remains unaffected by this variation.

Safety:

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

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 additional indications.

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 this veterinary medicinal product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment:

Frontpro is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

3.3. Risk management or mitigation measures

Risk management or mitigation measures remain unaffected by this variation.

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

3.4. Evaluation of the benefit-risk balance

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

The product has been shown to be efficacious for the reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days and for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days. In addition, Frontpro can be accepted as providing immediate and persistent tick killing activity for an additional tick species, *Hyalomma marginatum*, for one month.

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

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

The benefit-risk balance (also with regards to the legal status being non-prescription) remains unchanged.

4. Conclusion

Based on the original and complementary data presented, 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: change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of tick infestation with *Hyalomma marginatum*, reduction of the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* for 30 days, and reduction of the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* for 28 days. Additionally, the product information has been aligned with version 9.1 of the QRD template.

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 and IIIB.

As a consequence of this variation, sections 3.2 and 4.2 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.