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Veterinary Medicines Division

## Committee for Veterinary Medicinal Products (CVMP)

# CVMP assessment report for a variation requiring assessment for Bravecto TriUNO (EMA/V/C/006311, EMA/VRA/0000263135)

INN: Fluralaner / Moxidectin / Pyrantel

**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, Intervet International B.V. (the applicant), submitted to the European Medicines Agency (the Agency) on 3 March 2025 an application for a variation requiring assessment for Bravecto TriUNO.

## *1.2. Scope of the variation*

| **Variations requested** | |
|---|---|
| G.I.7.a | Addition of a new therapeutic indication or modification of an approved one |

The variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: 'treatment of infections with *Angiostrongylus vasorum'*. Additionally, the product information has been 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

Bravecto TriUNO is currently authorised for use in dogs with, or at risk from, mixed parasitic infestations by ticks or fleas, gastrointestinal nematodes, lungworm and/or heartworm. The veterinary medicinal product is exclusively indicated when use against ticks or fleas and gastrointestinal nematodes is indicated at the same time. The veterinary medicinal product also provides concurrent efficacy for the prevention of heartworm disease and prevention of angiostrongylosis.

The proposed variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: for the treatment of infections with *Angiostronglyus vasorum* (the causative agent of angiostrongylosis). Additionally, the applicant has proposed to align the product information with version 9.1 of the QRD template.

Bravecto TriUNO is a fixed-combination product containing the active substances fluralaner, moxidectin and pyrantel (as pyrantel embonate) and is presented as a chewable tablet with six different strengths available. The recommended minimum treatment dose is 10 mg fluralaner/kg, 0.025 mg moxidectin/kg and 5 mg pyrantel/kg bodyweight (bw), to be administered orally. The currently authorised dose rate is also proposed for the additional indication.

With the introduction of the proposed indication, Bravecto TriUNO 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 indication will not present an unacceptable risk for the user or the environment. Target animal tolerance is discussed below.

To support the proposed additional treatment claim, two laboratory dose confirmation studies were conducted. Both studies were conducted within the European Union using the commercial formulation of Bravecto TriUNO, and in accordance with VICH GCP standards.

The two laboratory dose confirmation studies involved dogs with induced infections of *A. vasorum*. The studies were performed in accordance with the requirements provided in the VICH GL19 Efficacy of anthelmintics: Specific recommendations for canines (EMA/CVMP/VICH/835/1999), although it is noted that EMA and VICH guidance do not provide recommendations specific for *A. vasorum*. However, it is stated that efficacy of such veterinary medicinal products should be at least 90% when calculated and interpreted using the procedure described in Section 4.2 of VICH GL7 Efficacy of anthelmintics: general requirements (EMA/CVMP/VICH/832/1999).

The first study was a GCP-compliant, randomised, blinded, single-site, negatively controlled, non-terminal efficacy study, conducted in the EU. Twenty laboratory Beagle dogs were included in this study, with a range of ages and bodyweights included in the population. The dogs were randomly allocated to two groups, the IVP treatment group (n=10) and the control group (n=10). The sample size was in line with the recommendations of VICH GL19 and GL7 (i.e. the inclusion of at least 6 animals in each experimental group). Aside from on select procedure days, animals were pair-housed for the study duration, which is considered to comply with VICH GL19 specification that housing should follow strict requirements of welfare.

According to VICH GL19 Efficacy of anthelmintics: Specific recommendations for canines, dose confirmation studies should be conducted using naturally or artificially infected animals. Dogs were inoculated with approximately 250 infective L3 larvae on Day -56, in line with the prepatent period of *A. vasorum*. For the *A. vasorum* strain used in this laboratory study infective L3 larvae were harvested from experimentally infected *Achatina fulica* and *Helix aspersa* snails. The applicant states that, before treatment, all dogs were adequately infected, with the maximum number of L1 larvae recovered ranging between 3 and 1,319 in the IVP group and between 18 and 1,805 in the control group. After treatment, all 10 dogs in the control (CP) group were adequately infected at each post-treatment sampling time point, with numbers of L1 larvae recovered ranging between 70 and 55,030. Therefore, the artificial infection was considered valid as per the pre-defined criteria in the study protocol. Whilst the relevant guidelines do not specify a number of infective forms required to produce an adequate infection with *A. vasorum*, given that all of the control animals were considered to be adequately infected with the range of faecal larval counts exceeding the minimum of 5 nematodes specified in VICH GL19, it can be accepted that the inoculate volume was adequate. The origin and number of infective L3 larvae used for challenge are therefore considered to be acceptable, and in line with current guidance.

Dogs in the treatment group were treated orally on Day 0. The applicant states that the IVP was administered as proposed in the SPC, at the recommended therapeutic dose (RTD) corresponding to a minimum of 10 mg fluralaner + 0.025 mg moxidectin + 5 mg pyrantel/kg bodyweight. The bodyweight recorded on Study Day (SD) -1 was used to determine the dose administered on SD 0. After

administration, one animal in the IVP group vomited during the post-treatment observation time (one hour). The tablet was successfully re-administered.

The primary efficacy variable was assessed as the reduction of faecal larval counts in the IVP group in comparison to the CP group. The reduction of faecal larvae count based on geometric means increased from approximately 44% and 58% in weeks 1 and 2, respectively, to above 99.9% and 100% in weeks 3 and 4, respectively. The mean maximum faecal larval count (based on geometric means) in the IVP group was significantly different from the mean maximum faecal larval count in the control group in weeks 3 and 4 ($p<0.0001$). Efficacy calculations were conducted using Abbott's formula based on geometric means data, in accordance with VICH GL7. In line with the revised VICH GL7, where >90% efficacy is observed based on geometric means data, % efficacy based on arithmetic means should also be calculated and in this case 100% efficacy was demonstrated at week 4.

With regard to the secondary efficacy parameters, antibody titres increased after inoculation on SD -56 in both study groups and remained on a similar level after treatment. Towards the end of the study, a slight decrease in antibody titre was observed in both groups, however, the titre was lower in the IVP group. Antigen titres increased after inoculation on SD -56 in both study groups. They decreased markedly and returned almost to baseline after treatment in the IVP group but continued to increase in the CP group (with a slight decrease at SD 28). This would reflect product efficacy for the prevention of larvae development into adult worms. Respiratory frequency increased in both groups post-inoculation, as would be expected with angiostrongylosis. Two observations of a deepened normal quality of respiratory sound and one of a deepened normal respiratory quality with wheeze (SD 7) were observed in the IVP group. Overall, no clinically relevant differences were seen between the treatment and control groups with regard to respiratory parameters.

With regard to safety, the IVP appears generally to have been well-tolerated. No serious adverse events were observed and all adverse events were resolved prior to the end of the study. One animal administered the IVP vomited shortly after dosing and consequently close temporal association made product association possible. However, it is noted that the product information includes emesis as a common adverse event for the product, which would appear appropriate. Overall, the adverse events seen in the IVP group are consistent with those already described in the product literature (digestive tract disorders e.g. diarrhoea, emesis).

The second study was conducted largely in line with the relevant guidelines: VICH GL9 Good clinical practices (CVMP/VICH/595/98), VICH GL7 Efficacy of anthelmintics: general requirements (EMA/CVMP/VICH/832/1999), and VICH GL19 Efficacy of anthelmintics: specific recommendations for canines (EMA/CVMP/VICH/835/1999). The study objective was to evaluate the efficacy of 12.5% (w/w) fluralaner + 0.03% (w/w) moxidectin + 6.25% (w/w) pyrantel chewable tablets for the treatment of angiostrongylosis in dogs experimentally inoculated with infective (L3) stages of lungworms *(Angiostrongylus (A.) vasorum*). The study was both randomised and blinded, with study personnel responsible for safety and efficacy evaluation unaware of treatment allocation. Certificates of analysis were presented for the IVP, which was confirmed as the final formulation.

With regard to study animals, 16 clinically healthy Beagle dogs (8 male, 8 female) were included, ranging from 8.19 to 13.73 kg bodyweight and from 9.4 to 29.8 months of age. The sample size of 8 animals per group can be considered acceptable given that VICH GL7 and GL19 both recommend the inclusion of at least 6 animals per group. With regards to age and weight range, both can be accepted given that they are representative of the target population. With the exception of selected procedure days, animals were pair housed for the duration of the study, which is considered to comply with VICH GL19 specification that housing should follow strict requirements of welfare.

In accordance with the requirements for dose confirmation studies set out in VICH GL19, the infection was induced with an European isolate. Infective L3 larvae were harvested from experimentally infected

*Helix aspersa* / *Achatina fulica* snails. The inoculate volume was 200 (±10) infective *A. vasorum* larvae and whilst the relevant guidelines do not specify a number of infective forms required to product an adequate infection with *A. vasorum*, given that at least 6 of the control animals were considered to be adequately infected at the end of the study within a range of 185-2,225 larvae among 7 animals, and VICH GL19 specifies that a minimum of 5 nematodes in individual control animals is an adequate infection, it can be accepted that the inoculate volume was adequate. Inoculation was carried out 60 days before treatment on Day 0, in line with the prepatent period of *A. vasorum*.

Dogs in the treatment group were treated orally on Day 0. The IVP was administered as proposed in the SPC, at the recommended therapeutic dose (RTD) corresponding to a minimum of 10 mg fluralaner + 0.025 mg moxidectin + 5 mg pyrantel/kg bodyweight. The bodyweight recorded on SD -3 was used to determine the dose administered on SD 0.

The primary efficacy variable was assessed as the reduction of faecal larval counts in the IVP group in comparison to the CP group. The reduction of faecal larvae count based on geometric means increased from <0% and 38.1% in weeks 1 and 2, respectively, to 100.0% in weeks 3 and 4. The mean maximum faecal larval count (based on geometric means) in the IVP group was significantly different from the mean maximum faecal larval count in the control group in weeks 3 and 4 ($p<0.0001$). The percentage efficacy observed met the guideline requirements of >90%.

With regards to the secondary efficacy variables, changes in *A. vasorum* antibody and antigen levels across the groups over the course of the study were indicative of an adequate infection rate, but also of product efficacy with antigen levels reduced in the treated group compared to the control, reflective of product efficacy for the prevention of larvae development into adult worms. Mean respiratory frequencies increased in both groups post inoculation but were lower in the IVP group compared to the control group from SD 1-28, ranging from 48.5-66 in the control group and 36-48 in the IVP group. One animal in the IVP group on SD 1 was observed to have intensity of respiratory sound (slight) and quality of respiratory sound (deepened normal). All other respiratory abnormalities occurred in the untreated control group, which are expected for this study design.

The mean (arithmetic) bodyweight ranged from 11.69 – 12.60 kg for the untreated control group while it ranged from 11.15 – 11.65 kg for the IVP group from SD -68 to SD -3. On SD 28, the mean bodyweight was 12.71 kg for the untreated control group and was 12.15 kg for the IVP group. Three dogs in the IVP group and one dog in the control group were observed to have lost weight at SD -22. For one dog in the IVP group, this constituted a weight loss of over 10 percent of bodyweight, which would be considered significant. Veterinary examination found the animal to be healthy but thin, with a recommendation given to feed extra diet and reassess. The animal was reassessed at a later timepoint and had gained weight. Bodyweight increased again to 11.34 kg at SD -3 and 11.85 kg at SD 28. Given that weight loss is a known clinical symptom of angiostrongylosis, it is plausible that it could be explained by the clinical progression of the infection. Considering that the weight loss occurred pre-treatment, that the applicant has provided information on further action taken, and all animals concerned regained weight, no question is raised.

With regard to safety, the IVP appears generally to have been well-tolerated. No serious adverse events were observed. All animals recovered, with the exception of the animals in the untreated control group with respiratory abnormalities that were ongoing at the end of the study. Two adverse events were observed in the IVP group. One animal demonstrated hypersalivation on Day 0, at dosing and up to 40 mins post dosing. The applicant suggests that the hypersalivation was due to the animal being difficult to dose. However, it is noted that hypersalivation is listed as a potential adverse event in the product information, although uncommon. Given that the potential for the VMP to cause hypersalivation is already adequately represented in the product information, no question was raised.

Another animal was observed with abnormal skin/hair on SD 21 along with a cut on the right hind leg (pad was bleeding and painful). The animal was treated daily with an antibiotic and an NSAID for three days. At the re-assessment on SD 24, the cut had healed and no pain was observed. It is agreed that this adverse event is unlikely to be related to treatment administration.

In summary, based on the findings of these two dose confirmation studies, it can be accepted that Bravecto TriUNO, when administered on a single occasion at the recommended therapeutic dose, achieved an adequate level of efficacy to support an indication for the treatment of induced *Angiostrongylus vasorum (A. vasorum)* infections in dogs.

The data provided in support of this application demonstrate that, when used in accordance with the recommendations in SPC for the proposed indication, the veterinary medicinal product will not pose an unacceptable risk to the target animal.

It is noted that no new clinical trials have been submitted in support of the proposed indication. In a previous scientific advice given in the context of the 'prevention' indication, the CVMP advised that the omission of a clinical trial could be considered acceptable, given that the incidence of *A. vasorum* is very low and taking into account the aim to reduce the use of live animals for scientific purposes. This advice is also considered to be applicable for the current variation procedure. The results of the two dose confirmation studies provided appear to demonstrate an acceptable level of efficacy (>90%) in the treatment of *A. vasorum* infections. Furthermore, given that efficacy against both larval and adult stages of *A. vasorum* has already been accepted by CVMP in the context of the 'prevention' claim, the omission of clinical trial data is considered to be acceptable in this instance.

# 3. Benefit-risk assessment of the proposed change

Bravecto TriUNO is authorised in dogs with, or at risk from, mixed parasitic infestations by ticks or fleas, gastrointestinal nematodes, lungworm and/or heartworm. The product is exclusively indicated when use against ticks or fleas and gastrointestinal nematodes is indicated at the same time. The product also provides concurrent efficacy for the prevention of heartworm disease and angiostrongylosis. The active substances are fluralaner, moxidectin and pyrantel. Bravecto TriUNO is available as chewable tablets of six different strengths and is administered orally at a dose of 10-20 mg/kg body weight of fluralaner, 0.025-0.05 mg/kg body weight of moxidectin and 5-10 mg/kg body weight of pyrantel.

The proposed variation concerns change(s) to therapeutic indication(s) - addition of a new therapeutic indication or modification of an approved one: treatment of infections with *Angiostrongylus vasorum*. Additionally, the product information has been aligned with version 9.1 of the QRD template.

## *3.1. Benefit assessment*

The proposed benefit of Bravecto TriUNO is its efficacy in the treatment of angiostrongylosis (*Angiostrongylus vasorum*) in dogs, which was established in two laboratory dose confirmation studies.

## *3.2. Risk assessment*

### Quality:

Quality remains unaffected by this variation.

## Safety:

Safety for the user, environment and target animal remains unaffected by this variation.

Measures to manage the risks identified below are included in the risk management section.

*Risks for the target animal:*

Administration of Bravecto TriUNO in accordance with SPC recommendations is generally well tolerated.

*Risk for the user:*

The CVMP previously concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

*Risk for the environment:*

Bravecto TriUNO is not expected to pose a risk for the environment when used according to the SPC recommendations. The veterinary medicinal product should not enter water courses as this may be dangerous for fish and other aquatic organisms.

### *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 this product relevant to the target animal, the 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 product 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 treatment of angiostrongylosis in dogs.

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 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 Bravecto TriUNO 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 infections with *Angiostrongylus vasorum*. 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 3.9 of the SPC are updated. The corresponding sections of the package leaflet are updated accordingly.