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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for a variation requiring assessment for Bravecto (EMEA/V/C/002526/VRA/0059)

INN: fluralaner

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

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 31 March 2023 an application for a variation requiring assessment for Bravecto.

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Scope of the variation

Bravecto (fluralaner) is already authorised for use in cats and dogs for the treatment of flea and tick infestations, as part of the treatment strategy for the control of flea allergy dermatitis (FAD), for the treatment of demodicosis and sarcoptic mange, for the reduction of risk of infection with *Babesia canis canis* and *Dipylidium caninum* via transmission by a vector, and for the treatment of infestations with *Otodectes cynotis* in cats only. Bravecto is currently authorised as chewable tablets and spot-on solutions of different strengths and is presented in packs containing 1 tablet, 2 tablets, 4 tablets, 1 pipette and 2 pipettes. Bravecto powder and solvent for suspension for injection for dogs contains 150 mg/ml fluralaner and is presented in packs containing 1 vial of powder + 1 vial of solvent and 1 vent needle, 2 vials of powder + 2 vials of solvent and 2 vent needles, 5 vials of powder + 5 vials of solvent and 5 vent needles, and 10 vials of powder + 10 vials of solvent and 10 vent needles.

Variation(s) requested	
I.II.1.d	Changes to strength, pharmaceutical form and route of administration - Change or addition of a new pharmaceutical form

The scope of this variation is to add a new pharmaceutical form, 150 mg/ml powder and solvent for suspension for injection, for dogs, to the already existing marketing authorisation. This new pharmaceutical form also introduces a new route of administration.

At the time of submission, the applicant applied for the following indications for the proposed new pharmaceutical form:

This veterinary medicinal product is a systemic insecticide and acaricide that provides:

- immediate and persistent flea (Ctenocephalides felis and Ctenocephalides canis) killing activity for 12 months

- persistent tick (Ixodes ricinus, Ixodes hexagonus, and Dermacentor reticulatus) killing activity from day 3 after treatment for 12 months

- persistent tick (Rhipicephalus sanguineus, Hyalomma marginatum) killing activity from day 4 after treatment for 12 months.

The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

For the treatment of demodicosis caused by Demodex canis.

For the treatment of sarcoptic mange (Sarcoptes scabiei var. canis) infestation.

For reduction of the risk of infection with Babesia canis canis via transmission by Dermacentor

reticulatus from day 3 after treatment for up to 12 months. The effect is indirect due to the veterinary medicinal product's activity against the vector.

For reduction of the risk of infection with Dipylidium caninum via transmission by Ctenocephalides felis for up to 12 months. The effect is indirect due to the veterinary medicinal product's activity against the vector.

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 2, Part 3 and Part 4

Scientific advice

The applicant received scientific advice from the CVMP for the development of a new antiparasitic veterinary medicinal product for dogs. The scientific advice pertained to the safety and clinical development of the dossier. Though these refer to a different product formulation, the outcome of some of the questions are considered relevant for the current procedure, and these will be addressed below.

The applicant generally adhered to the advice received.

Applicability of Article 40(5)

This application involves a change to the pharmaceutical form as the primary change and, consequentially, a change to the route of administration, both of which are eligible product developments within Article 40(5). The applicant has demonstrated an improvement of the benefit-risk balance of the veterinary medicinal product in accordance with criterion (b) of Art. 40(5) of Reg (EU) 2019/6 through this product development. This claim is assessed in a dedicated section within Part 5 of this report.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided an updated summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) , has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

The manufacture of the active substance fluralaner takes place outside the EEA.

A declaration confirming GMP compliance for the active substance manufacturing sites was provided from the Qualified Person (QP) at Vet Pharma Friesoythe GmbH..

GMP certification, which confirms the date of the last inspection and shows that the sites are authorised has been provided.

Drug product

Batch release takes place at vet Pharma Friesoythe GmbH, Germany for which GMP certification has been received. The drug product manufacture, packaging, and labelling operations, batch control and batch release of the commercial drug product are performed in the EEA and GMP certification have been provided for all sites.

Quick Response (QR) code

With this variation procedure the applicant has submitted request for the provision of information via Quick Response (QR) codes in the labelling and package leaflet. The applicant has provided a completed request form accompanied by an appropriate description and visual representation of the information available to users through the QR code. The request is in line with the general principles of acceptability and procedure document (EMA/364980/2017_rev.2).

The platform hosting the QR code is a website with the following web address (URL): mix.bravecto.com hosted by the MAH. The URL resolves to a country selector where users are redirected to the instructional video captioned. The applicant indicates these web pages will be accessible to the public via the URL but will be implemented in such a way as to prevent indexing by search engines, as opposed to a promotional product information site.

The information provided to users is statutory (i.e., the mixing instructions of the suspension from the summary of product characteristics) and additional information (relating to visualization of the mixing instructions of the suspension) by means of a video clip.

The script and draft content of the information provided through the QR code are included in Part 1 of the dossier.

The location of the QR code in the PI is acceptable.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements. The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

The submitted QR code is acceptable and in line with the approved product information. Translations of the approved video and script were done in conjunction with the existing linguistic review procedure for the product information.

Part 2 - Quality

Composition

The finished product is presented as a powder and solvent for suspension for injection, containing 150 mg/mL fluralaner as active substance. For this pharmaceutical form (powder and solvent for suspension for injection) the particle size of the active substance is critical and different to other pharmaceutical forms of Bravecto authorised. Therefore, the active substance used in this product and obtained after recrystallisation is referred to in this report as LPS (large particle size) fluralaner.

The powder is composed of the aforementioned substance only, whereas the solvent is composed of carmellose sodium, poloxamer 124, disodium phosphate dihydrate, benzyl alcohol (preservative), hydrochloric acid, concentrated, sodium hydroxide and water for injections.

For the preparation of the reconstituted suspension, 15.0 ml of the solvent are withdrawn with a suitable syringe from the solvent vial and transferred into the LPS fluralaner vial.

Containers and closure system

LPS fluralaner and the solvent are filled into 20 ml, clear, colourless Type I glass vials, closed with bromobutyl rubber stoppers, and sealed with aluminium seals. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The pack size is consistent with the dosage regimen. The immediate packaging complies with the relevant Ph. Eur. monographs. Certificates of analysis have been provided for the rubber stoppers, the aluminium seals and the Type I glass vials.

The sterilized LPS fluralaner vial and solvent vial are packaged into a carton box. A sterile 25G venting needle is included in the carton box.

Product development

Information on relevant physico-chemical properties of the drug substance has been provided as per the Guideline on development pharmaceutics for veterinary medicinal products (EMA/CVMP/QWP/684556/2022). Polymorphism and particle size distribution (PSD) are relevant physico-chemical properties for the proposed pharmaceutical form

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. and USP standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC. The concentration of the benzyl alcohol preservative has been adequately justified in view of the results of the preservative efficacy test.

The formulation development studies have been described in detail.

The proposed filling volume of 16 mL for the solvent vial has been adequately justified. The maximum number of times that the stopper can be pierced has been adequately justified in view of the data presented. The results of the fragmentation test, self-sealing test and extractable/leachable studies have been provided for the container closure system and are acceptable.

The applicant has justified the selection of process parameters in the final manufacturing process and has identified the different critical process parameters (CPPs) with an impact on the manufacturing development of the proposed drug product. The selected process parameters and CPPs are aligned with the information presented in sections P.3.3 and P.3.4. Sufficient information

has been provided to justify that the scalability of the manufacturing process does not impact the quality of the drug product.

The proposed sterilization methods for the powder have been adequately selected and justified.

Description of the manufacturing method

Powder:

The manufacturing of the powder consists of mixing the pre-sieved LPS fluralaner, filling in the glass vials and performing terminal sterilisation in the final container. The manufacturing is considered standard as per Annex II to the Guideline on Process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012). In general, the manufacturing process of the powder has been adequately described and with sufficient level of detail. A narrative description, list of equipment, flow diagram of the manufacturing process and in-process controls are included. IPCs performed during manufacture of the powder consist of fill weight of each vial during filling, appearance during filling (presence of stopper and cap), and bioburden after filling and before sterilisation. The bioburden before sterilisation is acceptable, and the description and validation of the analytical method for its control have been provided.

The description and validation of the analytical method for the IPC for bioburden of the LPS fluralaner vial has been provided.

The applicant has not provided validation data on the manufacturing of the powder. Instead, the applicant has included the process validation protocol with a commitment to validate the manufacturing process on at least three batches within the proposed size range. This is acceptable as the manufacturing process is considered standard. The updated validation protocol submitted is in line with the requirements of the Annex I to the Guideline on Process validation for finished products and is acceptable. The proposed holding time of 90 days before sterilisation has been adequately validated on two batches of the powder.

Validation of the sterilisation cycle of the fluralaner vials has been presented and is acceptable.

Solvent:

The manufacturing of the solvent consists of mixing the carboxymethylcellulose sodium, disodium phosphate dihydrate, poloxamer 124, and benzyl alcohol in water for injections, followed by pH adjustment, filling in the glass vials and terminal sterilisation. The manufacturing process is considered standard as per Annex II to the Guideline on Process validation for finished products.

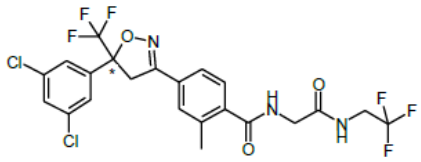
In general, the manufacturing process of the solvent has been adequately described. The information on mixing times, mixing speeds, and temperature during manufacturing has been provided. The bioburden before sterilisation has been adequately selected. The proposed holding time before terminal sterilisation has been adequately validated and is acceptable.

The applicant has not provided validation data on the manufacturing of the solvent. Instead, the applicant has included the process validation protocol with a commitment to validate the manufacturing process on at least three batches within the proposed size range. This is acceptable as the manufacturing is considered standard. The updated validation protocol submitted is in line with the requirements of the Annex I to the Guideline on Process validation for finished products and, therefore, is acceptable.

Control of starting materials

Active substance

The drug substance included in Bravecto powder and solvent for suspension for injection is fluralaner:(±)-4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydroisoxazol-3-yl]-2-methyl-N-[2-oxo-2-(2,2,2-trifluoroethylamino)ethyl]benzamide (racemic mixture of R and S enantiomer). Fluralaner's structure is as follows:



$C_{22}H_{17}Cl_2F_6N_3O_3$ 556.29 g/mol (racemic mixture)

The LPS fluralaner is a white to pale yellow crystalline solid, it is poorly soluble in water, hexane and toluene, and soluble in acetone, ethyl acetate, methanol, acetonitrile and N,N-dimethylacetamide. LPS Fluralaner is a racemate with an onset melting temperature of 174–175°C.

LPS fluralaner exhibits polymorphism. The polymorphic form used for Bravecto does not change during the manufacturing process of the active or during the manufacturing of the finished product (powder).

Crystalline form I is controlled in the specification of the drug substance and the drug product (powder). The proposed IR method for the identification of the crystalline form I has been validated for that purpose.

For the drug substance, the ASMF Procedure is used. In the dossier, only the information from the recrystallisation of fluralaner to obtain certain PSD is added. The rest of the information of the drug substance is covered by the aforementioned ASMF. The applicant has adequately performed validation of the recrystallisation process of fluralaner

It has been demonstrated that the recrystallisation does not impact the impurity profile of the drug substance. The specification of the drug substance LPS fluralaner includes tests for appearance, colour of solution, water content, residue of ignition, assay, related substances, residual solvents, PSD and microbial test. The description of the analytical methods has been adequately provided. In general, analytical methods have been adequately validated.

Batch analysis data on batches of the active substance after recrystallisation have been provided. The results are within the specification limits and are consistent from batch to batch.

The drug substance is packed in transparent polyethylene (PE) bags. A list of specification tests has been provided for the PE bags and is acceptable. A certificate of analysis has been provided for the PE bags. Stability data has been provided of the drug substance after recrystallisation for 6 months under accelerated condition (40°C/75% RH) and for 36 months under long-term condition (25°C/60% RH). In view of these results, the proposed retest period proposed for LPS fluralaner can be accepted.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. and USP standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The product does not contain any materials derived from human or animal origin. In any case, BSE/TSE-free certificates are provided for all excipients.

Control tests on the finished product

Powder:

The specification of the powder includes relevant tests such as appearance, colour, identification, of the active substance, assay, water content, PSD, bacterial endotoxins, dissolution, sterility, extraneous matter package observation fill weight and syringeability.

Solvent:

The specification of the solvent includes relevant tests such as description, colour, identification, assay of benzyl alcohol, density, particulate matter, bacterial endotoxins, sterility, and fill volume and package observation The specification is acceptable.

Suspension:

The specification of the reconstituted suspension includes relevant tests such as appearance, identification and assay of the drug substance, identification and assay of benzyl alcohol, degradation products redispersibility, particle size distribution, pH, density and bacterial endotoxins.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines. Satisfactory information regarding the reference standards used for assay of drug substance and assay of benzyl alcohol has been presented.

Batch analysis results are provided for the powder and solvent confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

A risk assessment on elemental impurities in powder and solvent has been provided as per Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products EMA/CVMP/QWP/153641/2018. Compliance with Ph. Eur. general monograph 2619 has been demonstrated.

Stability

Relevant stability data are provided for pilot-scale batches of the powder and the solvent stored under long term conditions for 36 months at 30 ºC/65% RH, and for up to 12 months under accelerated conditions at 40 ºC/75% RH. The proposed stability conditions are acceptable according to the VICH GL3. The batches of powder and solvent are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing. The reconstituted suspension were tested under long-term and accelerated stability conditions.

All stability results with the powder, the solvent and the suspension met the shelf-life specification limits. Based on the stability results provided, a shelf-life of 36 months in the proposed packaging without any special storage condition can be accepted for the powder and the solvent.

In addition, the applicant has conducted freeze-thaw studies for the solvent, the powder and the reconstituted suspension. All samples have been found to be stable after 3 freeze-thaw cycles.

The storage claim "This veterinary medicinal product does not require any special temperature

storage conditions" is in line with the Guideline on Declaration of storage conditions (EMA/CVMP/QWP/857608/2022) and is acceptable in view of the data presented.

The applicant has presented the results of a photostability study on the solvent, the powder and the suspension exposed to light in the glass container and compared to a dark control as per VICH GL51. The results show that the solvent, powder and suspension are not sensitive to light. Therefore, no storage precaution regarding protection from light is required.

In-use stability studies have been performed on aged batches and batches at the beginning of the proposed shelf life of the reconstituted suspension. The suspension was found to be stable after 13 weeks. The preservative efficacy has been demonstrated for up to 13 weeks and compliance with the criteria A of the Ph. Eur. 5.1.3 has been demonstrated. An in-use shelf-life of 3 months can be accepted.

Overall conclusions on quality

The variation submitted is to add a new pharmaceutical form, Bravecto 150 mg/ml powder and solvent for suspension for injection for dogs.

The information on quality of the drug substance is accepted. The active substance is the same and from the same supplier as that already authorised in other pharmaceutical forms of Bravecto. However, different particle size is needed for the suspension and the active substance therefore undergoes a recrystallisation process in order to obtain the adequate PSD. The recrystallisation process of the active substance is described in detail and validated. In addition, the information on starting materials, intermediates, characterisation and stability is adequately provided.

The information on quality of the drug product is sufficiently provided. The compositions of the powder and solvent are sufficiently laid down and their developments have been adequately explained. The manufacturing processes of the powder and the solvent are standard and have been adequately described and validated. The information on excipients is acceptable. The specification of solvent, powder and reconstituted suspension are acceptable and in line with the relevant guidelines. Acceptable batch and stability data have been provided. Based on the stability results provided, a shelf-life of 36 months in the proposed packaging without any special storage condition can be accepted for the powder and the solvent. An in-use shelf-life of 3 months when stored below 30°C for the suspension is accepted.

Overall, the proposed variation is acceptable from quality perspective.

Part 3 – Safety documentation (Safety and residues tests)

This application concerns a variation to add a new pharmaceutical form, 150 mg/ml powder and solvent for suspension for injection for dogs, to the already existing marketing authorisation. This new pharmaceutical form also introduces the subcutaneous route as a new route of administration.

The active substance fluralaner is a potent acaricide and insecticide. Fluralaner has been found, on the molecular level, to be a potent antagonist of the arthropod ligand-gated chloride channels (GABA-receptor and glutamate-receptor), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes resulting in uncontrolled activity of the central nervous system and death.

Most of the toxicity studies included in this application had already been submitted and assessed by the CVMP during the initial product application (EMEA/V/C/002526) or subsequent variations. When new data were provided, they have been discussed in detail in this report. For the other studies, only the conclusions were summarized, when relevant for this variation.

Safety tests

See also part 4.

Pharmacology

Pharmacodynamics

See also part 4.

The ectoparasitic properties of the active substance in Bravecto 150 mg/ml powder and solvent for suspension for injection for dogs, fluralaner, have already been assessed in the applications for Bravecto chewable tablets and spot-on. Briefly, fluralaner has been found to be a potent antagonist of the arthropod ligand-gated chloride channels (GABA-receptor and glutamate-receptor), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes resulting in uncontrolled activity of the central nervous system and death. Several pharmacological differences exist between GABA-gated chloride channels of insects and vertebrates. The binding affinity of fluralaner to receptors of ligand-gated chloride channels is significantly lower in mammals, and this could implicate that binding to other mammalian GABA receptors will be low as well. In addition, no evidence of neurotoxic potential below other effect levels has been observed in the repeated dose toxicity studies or target animal safety studies conducted in the dog and cat. The primary route of exposure of the ectoparasites is via feeding and less via contact activity.

The general pharmacodynamic information proposed for section 4.2 of the SPC is considered appropriate.

Pharmacokinetics

The pharmacokinetics of fluralaner were also assessed by CVMP in the applications for Bravecto chewable tablets and spot on. Only the conclusions are summarised below.

A new pharmacokinetic study following subcutaneous injection of the candidate product in dogs was provided; see also Part 4. In addition, a new pharmacokinetic study following subcutaneous injection of the candidate products in rabbits was provided to be used for the risk characterization. The latter

is summarized below in more detail.

Summary on pharmacokinetics (as previously concluded by CVMP)

Absorption:

After oral administration to dogs, fluralaner appears to be readily but incompletely absorbed: at doses of 12.5, 25, and 50 mg/kg bw, mean fluralaner C_{max} were reached within 1 day (T_{max}). Oral bioavailability of fluralaner was slightly decreasing with increasing oral dose in dogs: with mean values of 34%, 27% and 20% for 12.5, 25 and 50 mg/kg bw. After oral and intravenous administration, fluralaner demonstrated a long mean apparent half-life ($t_{½}$=12-15 days) and long mean residence time (MRT=15-20 days).

Distribution:

Once orally absorbed, fluralaner is well distributed to tissues. Highest concentrations were found in fat, followed by liver, kidney and muscle. Volume of distribution was found to be moderate (Vz=3 l/kg), and a very low clearance (Cl of approx. 0.1 l/kg/h).

Plasma protein binding:

An *in vitro* study of fluralaner plasma protein binding demonstrated that approximately 100% of fluralaner is bound to plasma proteins in cats and dogs.

Metabolism:

Unchanged parent fluralaner was found primarily in faeces of dogs (approx. 90% of the dose), suggesting that this is the main route of elimination. Renal excretion appears to be a minor route of excretion, with less than approximately 0.001% of the dose found in urine as unchanged fluralaner. Metabolites were not investigated in plasma or urine in the target animals. Therefore, this may suggest that a major part of fluralaner is not absorbed and excreted unchanged in the faeces. The absorbed part may then (after metabolism) be excreted via bile or via urine. Fluralaner undergoes enterohepatic circulation, resulting in continuous reuptake of fluralaner.

Pharmacokinetic study in dogs:

See also part 4, where the pharmacokinetic properties following subcutaneous injection of the candidate product to dogs at a dose of 15 mg/kg bw are described in detail. Briefly, prolonged persistence and slow elimination from plasma was observed. Mean C_{max} was 775 ng/ml, achieved between 30 and 72 days (with median T_{max} of 37 days); mean $AUC_{0\text{-}inf}$ was 158.000 days*ng/ml. After reaching C_{max}, fluralaner concentrations slowly declined, with a mean $t_{1/2}$ of 130 days (91.7 to 170 days). Mean plasma concentration values for fluralaner were measurable in all dogs through D450.

Pharmacokinetic study in rabbits:

A pharmacokinetic study in rabbits was provided, which was appropriately designed and GLP compliant. The objective of this study was to determine the plasma pharmacokinetic profile of Total-, R- and S-fluralaner and metabolite AH362502 (A0730364) following single subcutaneous administration of the candidate product. The animals, 10 female rabbits, were dosed with 10 mg fluralaner/kg bw.

For bioanalysis and pharmacokinetics, blood plasma samples were collected pre-dose and at predefined timepoints up to 141 post-dose, i.e. before and approx. at 8 and 24 hours after administration, and 2, 4, 6, 8, 11, 15, 22, 29, 36, 43, 50, 57, 71, 85, 99, 113, 127, 141 days after administration. Samples were assessed using a validated HPLC-MS/MS method and the following parameters were determined: C_{max}, T_{max}, AUC_{last}, using the software package SAS®. These

parameters are used to derive a VMP-equivalent TRV used in the risk characterization.

The total-fluralaner concentration profile indicated that systemic exposure occurred in all animals, characterized by a long absorption phase leading to a plateau and then followed by a slow decline. Mean C_{max} for Total-fluralaner was 104.7 ng/ml achieved at day 57; Mean AUC_{last} of 11025.1 days*ng/ml. The study was appropriately conducted, and the results can be accepted.

Toxicology

Most of the toxicity studies provided were submitted and assessed by CVMP in the applications for Bravecto chewable tablets and spot on, or in the MRL procedure (fluralaner for use in poultry). Only the conclusions are summarized below. In addition, a new skin irritation study, eye irritation study, skin sensitization study and acute subcutaneous dose toxicity study in rats were provided, using the candidate product. These studies are summarized in more detail below.

Single-dose toxicity

Summary on single-dose toxicity (as previously concluded by CVMP)

From the acute oral dose toxicity study in rats , the CVMP concluded that an LD50 of > 2000 mg/kg bw for fluralaner could be derived for this study. From the acute dermal dose toxicity study in rats , the CVMP concluded that an LD50 of > 2000 mg/kg bw for fluralaner could be derived for this study.

Acute subcutaneous dose toxicity study in rats

A GLP-compliant study to evaluate the safety of the 'Fluralaner 15% Injectable Suspension for Dogs' following a single subcutaneous injection to Sprague Dawley rats was provided. The test animals (5 female and 5 male Sprague Dawley rats, 8-9 weeks old, weight 219-280 grams at day of dosing), received a subcutaneous single injection into the dorso-scapular region; limit test: 2000 mg/kg bw. The test item was the candidate formulation and the observation period up to 16 days. Examinations included mortality, clinical observations, injection site assessments, body weights, food consumption and gross necropsy.

There were no unscheduled deaths, remarkable body weight changes (all animals gained weight during the course of the study), test article-related food consumption effects or clinical findings. Dark red foci on the lungs of 2 males and 1 female was observed, which was attributed to carbon dioxide inhalation at euthanasia. Injection site assessments revealed minor swelling for 5/5 males and 4/5 females at 30 minutes postdosing on Day 1 which was still observed for 1 male and 2 females at the end of the study (Day 16). At the scheduled necropsy, the injection site swelling for each animal was confirmed to be a firm white mass in the subcutaneous tissue in the dorso-scapular region. These injection site swellings and corresponding white masses were attributed to the subcutaneous presence of the test article.

An LD50 of > 2000 mg product/kg bw could be derived from this study, corresponding to 281 mg fluralaner/kg bw. Overall, it can be concluded that fluralaner and the candidate product have a low acute toxic potential.

Repeat-dose toxicity

Summary on repeat-dose toxicity (as previously concluded by CVMP)

Several repeated dose studies with fluralaner were performed in rats and dogs. The liver appears to be the most sensitive organ (changes noted include increased organ weight, hepatocellular fatty

change, and effects in related blood parameters). These effects were considered adverse by CVMP.

From the subacute oral dose toxicity studies in rats (14 days, 28 days), CVMP concluded that a NOAEL of 60 mg/kg bw/day could be derived. From the subacute oral dose toxicity studies in dogs (28 days), CVMP concluded that no NOAEL could be derived.

From the subacute dermal toxicity studies in rats (14 days, 28 days), CVMP concluded that a NOAEL of 50 mg/kg bw/day could be derived.

From the sub-chronic oral dose toxicity study in rats (90 days), CVMP concluded that a NOAEL of 40 mg/kg bw/day could be derived. From the sub-chronic oral dose toxicity study in dogs (90 days), CVMP concluded that a NOEL of 2 mg/kg bw/day could be derived.

From the sub-chronic repeated dermal dose toxicity study in rats (90 days), CVMP concluded that a NOAEL of 50 mg/kg bw/day could be derived.

From the chronic oral dose toxicity study in dogs (365 days), CVMP concluded that a NOEL of 1 mg/kg bw/day could be derived.

Tolerance in the target species

See also Part 4. Briefly, a tolerance study in the target species using the subcutaneous injection route and administering 1x, 3x, 5x the clinical dose of 15 mg/kg bw was provided. Effects at the injection site were observed that included swellings or nodules. Moreover, an association between product administration and neurological effects in the target animal cannot be excluded.

Reproductive toxicity, including developmental toxicity

Summary on reproductive toxicity, including developmental toxicity (as previously concluded by CVMP)

For the pivotal one-generation reproduction study in rats, CVMP concluded that adverse effects were observed at the lowest dose. The parental and foetal LOAEL was therefore 50 mg/kg bw/day. The reproduction NOEL was set at 100 mg/kg bw/day.

For the pivotal two-generation reproduction study in rats CVMP concluded that the parenteral LOAEL was 8 mg/kg bw/day, though effects were marginal. The reproduction NOEL was set at 50 mg/kg bw/day. The pup NOEL was 50 mg/kg bw/day.

For the pivotal developmental (oral) toxicity study in rat, CVMP concluded that the NOEL for maternal and foetal organisms was 100 mg/kg bw/day.

For the pivotal developmental (oral) toxicity study in rabbit, CVMP concluded that the NOEL for maternal and foetal organisms was 10 mg/kg bw/day.

For the pivotal developmental (dermal) toxicity study in rabbit with fluralaner suspended in 0.5% carboxymethylcellulose aqueous solution, CVMP concluded that for foetal toxicity the NOAEL can be set to 100 mg/kg bw/day.

Genotoxicity

Summary on genotoxicity (as previously concluded by CVMP)

The potential mutagenic effects of fluralaner were investigated in three *in vitro* tests (Ames test, mouse lymphoma thymidine kinase locus test, chromosomal aberration test in human lymphocytes)

and one *in vivo* test on genotoxicity (micronucleus test in bone marrow cells of the mouse).

The results of all four mutagenicity tests were negative. CVMP concluded that fluralaner does not have mutagenic potential.

Carcinogenicity

Studies on fluralaner for carcinogenic potential were not submitted. The absence of a carcinogenic study was justified by the negative results in all mutagenicity assays and the absence of pre-neoplastic lesions in repeated dose toxicity studies. CVMP concluded that fluralaner is unlikely to have carcinogenic potential.

Other requirements

Special studies

Studies on irritation (skin and eyes) and sensitisation with the active substance fluralaner were submitted and assessed by CVMP during the applications for Bravecto chewable tablets and spot on. In addition, three new studies were provided with the candidate product: a skin irritation study in rabbits, an eye irritation study in rabbits and a skin sensitization study in guinea pigs. To assess dermal exposure, *in vitro* skin penetration studies were also provided. These studies were submitted and assessed by CVMP in the applications for Bravecto chewable tablets and spot on.

Skin irritation:

A dermal irritation study using 'Fluralaner 15% injectable suspension for dogs' was performed in rabbits (3 males, 6 months age, 3.6-3.7 kg body weight at treatment) in accordance with OECD guideline 404. The product (0.5 ml) was applied to the skin and held in place with a gauze patch and bandage to ensure good skin contact. The patch was removed after 4 hours, the application site cleaned and then the skin was scored according to the method of Draize, direct, 1h, 24h, 48h and 72 hours after removal of the patch. The test item did not elicit skin reactions (score 0). It can therefore be concluded that 'Fluralaner 15% injectable suspension for dogs' is non-irritating to the skin.

The CVMP previously concluded, based on a skin irritation study in rabbits using fluralaner, that fluralaner is non-irritating to the skin.

Eye irritation:

An eye irritation study using 'Fluralaner 15% injectable suspension for dogs' was performed in rabbits (3 males, 7 months age, 3.6 – 3.8 kg body weight at treatment): in accordance with OECD guideline 405. The product (0.1 ml) was applied into the conjunctival sac of one eye. The other eye served as control. The treated eye was scored according to the method of Draize at 1h, 24h, 48h, 72h and 7 days after application. Sodium fluorescein was used to aid in revealing possible corneal damage at 24 hours and at all subsequent observations. Pain was minimized by following the procedures described in OECD 405 on the use of topical anaesthetics and systemic analgesics.

The test item only showed conjunctival redness (score 1) 1h after application, which disappeared at the next observation. It can therefore be concluded that 'Fluralaner 15% injectable suspension for dogs' is non-irritating to the eye.

The CVMP previously concluded, based on an eye irritation study in rabbits using fluralaner, that fluralaner is non-irritating to the eye.

Skin sensitisation:

A skin sensitisation test (Guinea pig maximisation test of Magnusson and Kligman) using the formulation was performed in guinea pigs. This study was performed in accordance with OECD guideline 406, although 1-chloro-2,4-dinitrobenzen (DNCB) was used as a positive control, which is not one of the substances preferred in the GL.

Twenty test animals (10 male, 10 female) and 10 control (5 male, 5 female) were tested. Males were of approximately 10 weeks of age on the day prior to intradermal induction dosing, with body weights ranging from 404 to 608 grams, while females were of approximately 11 weeks of age on the day prior to intradermal induction dosing and body weights ranged from 341 to 550 grams. During induction, animals were intradermally (0.1 ml/site) exposed to 'Fluralaner 15% injectable suspension for dogs', using FCA as an adjuvant, followed after 1 week by occlusive epidermal induction (0.8 ml/site) kept 48 hours under occlusive dressing. The concentrations of test item, 5% and 100% respectively, were based on results from intradermal and topical range finding tests. The product caused no irritation, and so on day 6, 10% w/w sodium lauryl sulfate was used to create local irritation just before the topical induction phase. However, it appeared that no visible skin reactions were observed during the induction phase in most of the animals. It is noted that during the topical induction buprenorphine (0.03 mg/kg, subcutaneous) was administered at the time of wrap removal and continued once every 24 hours for a total of 3 doses. While opioids may suppress the immune system, this is not demonstrated for buprenorphine based on the provided literature; in fact, it appears that buprenorphine is rather associated with a slight immune stimulating effect.

During the challenge, animals were dermally exposed to the undiluted product under a 25 mm Hill top chamber (non-irritant concentration; 0.3 ml) for 24 hours. Following that, there were no dermal observations noted in the test group. Dermal observations in the challenged control group were limited to discrete or patchy erythema lesions (Grade 1) in 3 animals. This would indicate that the test-item is non-sensitising.

With the positive control, DNCB (0.05% and 0.1%), which is not mentioned as a preferred substance in OECD guideline 406, no skin reactions were observed during the induction phase. During the challenge, skin reactions were observed with higher dermal scores being in the test group when compared to the control group.

The CVMP previously concluded, based on a skin sensitisation study in guinea pigs using fluralaner that fluralaner did not have sensitising properties.

It is however noted that although skin sensitisation tests appeared negative, sensitivity reactions have been observed in humans, as revealed during the periodic safety assessments of already authorised Bravecto products. The product information of these products has therefore been updated with the user safety warning '*Hypersensitivity reactions in humans have been reported*'. The CVMP therefore concludes that, despite the outcome of the provided skin sensitisation test, hypersensitivity reactions also cannot be excluded for the candidate product.

***In vitro* skin penetration studies:**

Two *in vitro* skin penetration studies were provided. The CVMP previously concluded that the dermal delivered doses of fluralaner in human skin studies were 6.2-fold lower than in rabbits (4.01% versus 25.02%) and 3.7-fold lower than in rats (4.75 % versus 17.7%). The CVMP assessment included fluralaner recovered in the receptor fluid and exposed skin as dermal delivered doses, as well as fluralaner measured in the stratum corneum as absorbable dose.

Observations in humans

Fluralaner has been developed exclusively for veterinary use. No study data are available on health effects of fluralaner in humans. Isoxazoline anti-parasitics in general are currently not used in human medicine; therefore, it is also not possible to extrapolate observations from other isoxazolines to fluralaner.

However, it is noted that sensitivity reactions have been observed in humans, as revealed during the periodic safety assessments of already authorised Bravecto products, even though skin sensitisation tests provided for fluralaner, Bravecto chewable tablets or spot on, appeared negative. The product information of these products has therefore been updated with the user safety warning '*Hypersensitivity reactions in humans have been reported*'.

Development of resistance and related risk in humans

Not applicable.

Excipients

The toxicity of this product will be determined by its active substance. The excipients of the candidate product, i.e., carboxymethylcellulose sodium, poloxamer 124, disodium phosphate dihydrate, benzyl alcohol, hydrochloric acid and sodium hydroxide (as needed), and water, are not expected to cause any systemic effects and are not of toxicological concern. However, benzyl alcohol, being present in the candidate product at a concentration of 2%, may produce hypersensitivity reactions, including local irritation and skin reactions (ref. Martindale the complete drug reference; accessed online). Therefore, hypersensitivity reactions due to the presence of benzyl alcohol cannot be fully excluded and a warning is in place.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-rev.1). In addition, it is noted that the applicant has followed the conclusions of the scientific advice provided by the CVMP (EMA/CVMP/SAWP/108794/2021).

Hazard characterization:

Subacute oral dose toxicity studies in rats (14 days, 28 days):	NOAEL of 60 mg/kg bw/day.
Subacute dermal toxicity studies in rats (14 days, 28 days):	NOAEL of 50 mg/kg bw/day.
Subchronic oral dose toxicity study in rats (90 days):	NOAEL of 40 mg/kg bw/day.
Subchronic oral dose toxicity study in dogs (90 days):	NOEL of 2 mg/kg bw/day.
Subchronic repeated dermal dose toxicity study in rats (90 days):	NOAEL of 50 mg/kg bw/day.
Chronic oral dose toxicity study in dogs (365 days):	NOEL of 1 mg/kg bw/day.
One-generation reproduction study in rats:	Parental and foetal LOAEL of 50 mg/kg bw/day. Reproduction NOEL of 100 mg/kg bw/day.
Two-generation reproduction study in rats:	Parenteral LOAEL of 8 mg/kg bw/day Reproduction NOEL of 50 mg/kg bw/day. Pup NOEL of 50 mg/kg bw/day.
Developmental (oral) toxicity study in rat:	Maternal and foetal NOEL of 100 mg/kg bw/day.

Developmental (oral) toxicity study in rabbit:	Maternal and foetal NOEL of 10 mg/kg bw/day.
Developmental (dermal) toxicity study in rabbit:	NOAEL of 100 mg/kg bw/day.

Fluralaner does not have mutagenic potential and is unlikely to have carcinogenic potential. Fluralaner or the candidate product is non-irritating to the skin or eye.

Skin sensitisation test results were negative. However, although skin sensitisation tests previously assessed for fluralaner or Bravecto chewable tablets and spot on were also negative, sensitivity reactions have been observed in humans, as revealed during the periodic safety assessments for these products. Thus, hypersensitivity reactions cannot be excluded for the candidate product.

In vitro skin penetration studies revealed that the dermal delivered doses of fluralaner in humans are 6.2-fold lower than in rabbits (4.01% versus 25.02%) and 3.7-fold lower than in rats (4.75 % versus 17.7%).

Exposure:

The user, which is a professional user (e.g., veterinarian or veterinary assistant), may get exposed to the product when preparing the suspension, when administering the suspension to the animal or when disposing the syringe plus needles.

The relevant exposure scenarios are accidentally spilling the product or accidental self-injection. Also, splashing into the eyes may accidentally occur. Hand-to-mouth or hand-to-eye contact are negligible when personal hygiene measures are maintained, which is a reasonable assumption for a professional user.

The product consists of 2 vials, one containing the active substance as a powder and one containing the solvent. When preparing the product (reconstituted suspension), the user could be exposed to the solvent when injecting it into the vial with the powder or by spilling a drop. When administering the product or disposing the injection equipment, the user could be exposed to the whole product. Exposure to the product can be considered incidental since the users are professionals, which are well trained and know how to maintain personal hygiene measures.

After self-injection the product may be released from the injection site during a prolonged period and therefore lead to both short-term and long-term effects. For accidental self-injection the exposure estimated is 10% of the volume injected to a 40 kg dog, i.e., 600 mg fluralaner, corresponding to 4 ml of the product. The user will be exposed to 400 µl of the product, equivalent to 60 mg fluralaner, which is considered reasonable worst case. This exposure corresponds to 1 mg/kg bw for a 60 kg adult user, and it was considered acceptable by CVMP in a scientific advice. For dermal exposure the CVMP considers exposure to one drop, i.e. 50 µl, a reasonable worst case. This exposure corresponds to 0.125 mg/kg bw for a 60 kg adult user.

Risk characterization:

Qualitative

Based on the hazard characterization, irritating effects are not expected for this product. However, as stated previously, although skin sensitisation test results were negative, hypersensitivity reactions cannot be excluded for the candidate product since sensitivity reactions in humans have been observed. Moreover, hypersensitivity reactions due to the presence of the excipient benzyl alcohol cannot be fully excluded. Note that when accidentally injected with the product, the product remains in the body for a long period.

Quantitative

Parenteral exposure to the VMP

Differentiation between long- and short-term effects of exposure seems appropriate, since fluralaner is expected to remain in the human body for a prolonged period after accidental self-injection. It is assumed that the user may self-inject 400 µl of the product, equivalent to 60 mg of fluralaner. For a 60 kg adult this corresponds to 1 mg/kg bw.

No relevant NOAELs derived from subcutaneous toxicity studies are available, only NO(A)ELs from oral toxicity studies, and VMP-equivalent toxicology reference values (TRV) for the single subcutaneous exposure to the VMP are thus generated. Route-to-route extrapolation is therefore performed by comparison of the systemic exposure after oral and subcutaneous administration, i.e., the subcutaneous (external) dose that corresponds to the same systemic exposure related to the NO(A)EL from the oral toxicity studies is calculated. This approach and the procedures for calculating the margins of exposure (MOEs) were considered acceptable when dose linearity over the relevant dose range can be assumed. The following equation is used:

$$\text{TRV X } \frac{\text{Toxicology Exposure (Cmax or AUC)}}{\text{VMP} - \text{PK Exposure (Cmax or AUC)}} = \text{VMP} - \text{equivalent TRV}$$

TRV:	NO(A)EL from a toxicity study (i.e., mg/kg bw/day)
Toxicology Exposure:	PK value from a toxicity study with fluralaner for the most relevant exposure endpoint (C_{max} or AUC) associated with the TRV
VMP – PK Exposure:	PK value from a single-dose PK study with the VMP (i.e., the same PK endpoint, the same laboratory or target animal species, and the same nominal fluralaner dose as the 'Toxicology Exposure' value above)
VMP-equivalent TRV:	TRV expressed in terms of VMP PK

Long term parenteral exposure to the VMP:

As a toxicological reference value, the oral NOEL of 1 mg/kg bw/day from the 52-week oral toxicity study in dogs is taken. This value is extrapolated to a subcutaneous NOEL by adjusting for subcutaneous versus oral bioavailability. The latter is done by comparing the AUC_{day365} derived from the oral toxicity study (when administering 1 mg/kg bw/day) to the AUC_{day450} derived from the subcutaneous (pharmacokinetic) study (administering 15 mg/kg bw) and dividing the calculated AUC_{day450} by 15, as dose proportionality is demonstrated and considered also applicable for the lower subcutaneous dose range of 1 to 15 mg/kg bw. A mean AUC_{day450} of 139,000 days*ng/ml was calculated for the pharmacokinetic study. The mean AUC_{day365} for the oral toxicity study was calculated to be 1,465,491.41 days*ng/ml, based on a linear trapezoidal method with linear interpolation. Plasma data for fluralaner were available for day 1, day 171 and day 358 (the latter assumed to be equal to day 365 concentrations); day 86 was assumed to have equal concentrations to day 171, as steady state is reached approximately at day 86, i.e., 5x half-life of 17 days retained by the applicant. This results in a subcutaneous NOEL of 158 mg/kg bw and a MOE of 158 (158/1), which is acceptable when considering systemic toxicity.

It is not clearly explained how the applicant concluded on a half-life of 17 days. One study describes a $t_{1/2}$ in the range of 13.26 to 16.89 days after intravenous administration and it is assumed that the highest value is taken as worst case. It is noted, however, that a $t_{1/2}$ after oral administration would be more appropriate since the AUC_{day365} is determined in an oral study. In a second study, a $t_{1/2}$ for fluralaner in the range of 9.27 to 16.24 days was retained. Therefore, based on all kinetic data, the

assumption of a $t_{1/2}$ of 17 days can be accepted, since a longer $t_{1/2}$ results in a later estimated onset of steady state and a subsequent lower estimate of the AUC_{day365}, all resulting in a lower VMP-equivalent TRV and a subsequent more protective user risk characterization.

Short term parenteral exposure to the VMP:

As a toxicological reference value, the oral NO(A)EL of 10 mg/kg bw/day from the oral developmental toxicity study in rabbits is taken. It is noted that the most sensitive endpoint for maternal toxicity in this study are the adverse effects noted in liver and related blood chemistry, which are not considered acute effects. However, this TRV is considered the most relevant as it is the lowest maternal/foetal NOAEL for the short-term studies and includes exposure of pregnant rabbits and foetuses.

The oral NOAEL is extrapolated to a subcutaneous NOEL by adjusting for subcutaneous versus oral bioavailability. The latter is done by comparing the AUC_{day22} and C_{max} derived from the 22-day oral developmental toxicity study to, respectively, the AUC_{day141} extrapolated to a study period of 22 days and the C_{max} from the single subcutaneous (pharmacokinetic) dose study. In both studies the administered dose was 10 mg/kg bw/day. The comparison of the AUC as well as the C_{max} The approach and the procedures for calculating short-term parenteral exposure to the VMP were accepted.

From the pharmacokinetic study, a mean AUC_{day141} of 11,025.1 days*ng/ml was calculated, extrapolated to a mean AUC_{day22} of 1,720.23 day*ng/ml (which can be considered a worst case since plasma concentrations are still increasing during the 22-day period), and the mean C_{max} for total fluralaner was 104.7 ng/ml. Based on a linear trapezoidal method with linear interpolation with plasma data available for day 6/7 post coitum (single dose) and day 27/28 post coitum (repeated dose), the mean AUC_{day22} for the oral developmental toxicity study was 19,207.11 days*ng/ml, and the mean C_{max} 1,421.27 ng/ml.

This results in a subcutaneous NOEL of 112 and 136 mg/kg bw, when adjusting using the AUC and C_{max} approach, respectively. This results in a MOE of 112 and 136, which is acceptable when considering systemic toxicity, including the risk for pregnant women.

While the equivalent subcutaneous TRV for long-term toxicity is 158 mg/kg bw and 112-136 mg/kg bw for short-term toxicity and, in general, it would be expected that the TRV is higher for short-term toxicity (i.e., acute effects), it should be noted that the most sensitive endpoint for short-term toxicity is not an acute effect. It is also noted that in the single subcutaneous dose toxicity study in rats no adverse effects were observed, although this study was limited in parameters.

Dermal exposure to the VMP

The CVMP considered dermal exposure to one drop, i.e., 50 µl, reasonable worst case. This exposure corresponds to 0.125 mg/kg bw for a 60 kg adult.

As a toxicological reference value, the dermal NOEL of 50 mg/kg bw/day derived from the 28-day repeated dose toxicity study in rat is considered the most relevant. The dermal toxicity studies were performed with fluralaner in an aqueous solution; this is considered acceptable, as effects of penetration enhancers do not have to be taken into account for the candidate product.

It was also acknowledged by CVMP that penetration of the human skin is lower than the rat skin. For the in vitro skin penetration studies (human versus rat skin) CVMP concluded that the dermal delivered doses of fluralaner in humans are 3.7-fold lower than in rats (4.75 % versus 17.7%). The equivalent human dermal NOEL would therefore be 185 mg/kg bw/day.

This would result in a MOE of 185/0.125 = 1480, which is well above the default factor of 10 when assuming intraspecies variation. No systemic effects are therefore anticipated after dermal exposure to the veterinary medicinal product. Note that the dermal NOAEL based on the 90-day dermal toxicity study was also set to 50 mg/kg bw/day, therefore even when fluralaner, which has a long half-life, remains somewhat longer in the body or when spillage occurs somewhat more frequent as a veterinarian may treat several animals in time, no risks are anticipated.

Genotoxic impurities

Evaluation and control of potential mutagenic impurities are discussed in the quality part of the dossier. The applicant identifies CATFA (ChloroAcetyl-*N*-(2,2,2-TriFluoroethyl)Amide), a class 2 mutagen (i.e., "control at or below acceptable limits [Threshold of Toxicological Concern(TTC)-based acceptable intake]") and hydroxylamine hydrochloride, a non-mutagenic carcinogen (i.e., "a permitted daily exposure value [PDE] was derived from literature in accordance with guideline ICH M7") as the potential mutagenic impurities that are likely to arise during the synthesis and storage of the veterinary drug substance fluralaner. The rest of the structures are classified as class 5 (i.e., "Treat as non-mutagenic impurity").

CATFA:

The TTC-based acceptable intake of 0.0025 µg/kg bw/day is considered to be protective for a lifetime of daily exposure. To address less-than-lifetime (LTL) exposures to mutagenic impurities, an approach is applied in which the acceptable cumulative lifetime dose is uniformly distributed over the total number of exposure days during LTL exposure. This allows higher daily intake of mutagenic impurities than would be the case for lifetime exposure and still maintains comparable risk levels. The following equation is used: *0.0025 µg/kg bw/day * (365 days * 70 years)/total number of treatment (user exposure) days.*

For the candidate product the applicant assumes an exposure day once a year. Assuming a dog lifetime of 15 years, results in 15 exposure days. This exposure assumption is not acceptable; the veterinarian might treat several dogs and the number of exposure days will depend on the frequency of accidental injection and the working time of the veterinarian. The CVMP considers a more reasonable worst-case scenario an accidental injection incident once a year for a working time of 40 years, resulting in 40 exposure days. The acceptable intake (AI) would then 0.0025 µg/kg bw/day * (365 days * 70 years human lifetime) / 40 exposure days = 1.6 µg/kg bw.

According to ICH M7 Note 5, monofunctional alkyl chlorides are much less potent carcinogens when compared to multifunctional alkyl chlorides, which justifies a ten-fold higher intake and leads to an AI of 16 µg/kg bw. Based on the estimated injected dose of 1 mg/kg bw (or 0.001 g/kg bw), the acceptable limit of CATFA in fluralaner is (16 µg/kg bw)/(0.001 g/kg bw) = 16,000 µg/g (or ppm). The analytical method to detect CATFA, with an LOD of 100 ppm, detected no CATFA in fluralaner. Therefore, the impurity CATFA might be present in fluralaner in a quantity far below the limit of 16,000 ppm.

Hydroxylamine

For hydroxylamine, which is stated to be non-mutagenic in an AMES-test, a PDE of 23 µg/day was derived. The applicant divided it by a bodyweight of 50 kg. However, 60 kg is the default value for an adult bodyweight, and this would result in a PDE of 0.38 µg/kg bw/day.

The LTL exposure AI is then: 0.38 µg/kg bw/day * (365*70) / 40 = 243 µg/kg bw.

Based on the estimated injected dose of 1 mg/kg bw (or 0.001 g/kg bw), the acceptable limit of hydroxylamine in fluralaner is (243 µg/kg bw)/(0.001 g/kg bw) = 243,000 µg/g (or ppm). The analytical method to detect hydroxylamine (derivatised to acetoxim) with an equivalent LOQ of

0.24 ppm for hydroxylamine, detected no hydroxylamine (as acetoxim) in a 10,000 times diluted fluralaner-sample. Therefore, the impurity hydroxylamine might be present in fluralaner in a quantity far below the limit of 243,000 ppm.

When considering the exposure of the user to potential mutagenic impurities, the Applicant has assumed that exposure will occur once a year at a maximum, based on the product being administered every 12 months. It is also assumed that based on an expected dog lifetime of 15 years, this could result in 15 exposure days over the user's lifetime (70 years). However, considering that this veterinary medicinal product will be administered by a veterinarian, it is inevitable that more than one animal will be treated per year and for longer than a single animal's expected lifetime. However, it is also acknowledged that the frequency of accidental exposure to the product is difficult to estimate. Based on the reported concentrations of the impurities being below the LOD of the analytical methods, an increase in predicted exposure will still result in calculated acceptable limits far above the concentrations detected.

Risk management and communication:

Based on the risk characterization it is concluded that there is no risk for systemic toxicity after dermal exposure to this product or when the product is accidentally injected. In particular when personal hygiene measures are maintained, which is expected for a professional user.

However, hypersensitivity reactions cannot be excluded for this product. Sensitivity reactions have been observed in humans in contact with other Bravecto products, as revealed during the periodic safety assessments, even though skin sensitisation tests provided were negative. The product information of these products has been updated with the user safety warning '*Hypersensitivity reactions in humans have been reported*'. Also, the excipient benzyl alcohol has been associated with hypersensitivity reactions. A warning for hypersensitivity reactions for this product is therefore also added to the user safety warnings of this product.

It is noted that target animal studies were provided in which dogs were treated with the veterinary medicinal product at a dose of 15 mg/kg bw, which appeared to result in effects such as injection site reactions, neurological symptoms and gastrointestinal effects. The gastrointestinal effects observed in the clinical studies in target animal are unlikely to be treatment-related and therefore not considered relevant for user safety. The possibility of injection site reactions is added to the user safety warnings of this product.

The applicant proposed the following user safety warnings:

Hypersensitivity reactions to fluralaner or benzyl alcohol in humans have been reported, which can potentially be serious. Also, injection site reactions may occur. Care should be taken to avoid accidental self-injection and dermal exposure when administering this veterinary medicinal product. In case of accidental self-injection with adverse effects, hypersensitivity reactions or injection site reactions, contact a physician and show the label or package leaflet. Wash hands after use.

It is recommended that this veterinary product is administered only by veterinarians or under their close supervision.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food producing species.

Overall conclusions on the safety documentation: safety tests

This application concerns a variation to add a new pharmaceutical form, 150 mg/ml powder and solvent for suspension for injection for dogs, to the already existing marketing authorisation. This new pharmaceutical form also introduces the subcutaneous route as a new route of administration. Most of the toxicity studies provided had already been submitted and assessed by the CVMP, in the applications for Bravecto chewable tablets and spot on products.

Pharmacology:

The CVMP had previously concluded on the pharmacological particulars of fluralaner. The general pharmacological information proposed for section 4 of the SPC is appropriate. See also Part 4.

Toxicology:

Several studies with the active substance fluralaner or with the final product were performed in rats, rabbits and dogs. The liver appears to be the most sensitive organ (changes noted include increased organ weight, hepatocellular fatty change, and effects in related blood parameters).

An overview of toxicity studies is presented below (new studies are in bold):

Acute single dose toxicity studies in rats (oral, dermal) **Acute subcutaneous study in rats using the candidate product**	LD50> 2000 mg/kg bw
Subacute oral dose toxicity studies in rats (14 days, 28 days)	NOAEL of 60 mg/kg bw/day
Subacute dermal toxicity studies in rats (14 days, 28 days)	NOAEL of 50 mg/kg bw/day
Subchronic oral dose toxicity study in rats (90 days)	NOAEL of 40 mg/kg bw/day
Subchronic oral dose toxicity study in dogs (90 days)	NOEL of 2 mg/kg bw/day
Subchronic repeated dermal dose toxicity study in rats (90 days)	NOAEL of 50 mg/kg bw/day
Chronic oral dose toxicity study in dogs (365 days):	NOEL of 1 mg/kg bw/day
One-generation reproduction study in rats:	Parental and foetal LOAEL of 50 mg/kg bw/day Reproduction NOEL of 100 mg/kg bw/day
Two-generation reproduction study in rats:	Parenteral LOAEL of 8 mg/kg bw/day Reproduction NOEL of 50 mg/kg bw/day Pup NOEL of 50 mg/kg bw/day
Developmental (oral) toxicity study in rat	Maternal and foetal NOEL of 100 mg/kg bw/day
Developmental (oral) toxicity study in rabbit	Maternal and foetal NOEL of 10 mg/kg bw/day
Developmental (dermal) toxicity study in rabbit	NOAEL of 100 mg/kg bw/day
Mutagenicity and carcinogenicity studies	Fluralaner does not have mutagenic potential and is unlikely to have carcinogenic potential
Skin and/or eye irritation studies using fluralaner **Skin and/or eye irritation studies using the candidate product**	Fluralaner or the candidate product is non-irritating to the skin or eye.
Skin sensitisation study using fluralaner **Skin sensitisation study using the candidate product**	Skin sensitisation test with fluralaner or products appear negative.

The acute subcutaneous study in rats using the candidate product revealed that injection site swellings may occur.

The skin sensitisation test provided using the final formulation was negative. In this study it appeared that no skin reactions were observed in most of the animals during the induction phase, even when sodium lauryl sulfate was used to create local irritation, since the test formulation is non-irritating. It is noted that during the topical induction buprenorphine (0.03 mg/kg, subcutaneous), an opioid, was administered at the time of wrap removal and continued once every 24 hours for a total of 3 doses. While opioids may suppress the immune system, this is not demonstrated for buprenorphine based on the provided literature; in fact, it appears that buprenorphine is rather associated with a slight immune stimulating effect.

Skin sensitisation tests provided were negative, as in other applications for fluralaner or Bravecto chewable tablets and spot on. However, it appears that sensitivity reactions have been observed in humans exposed to other Bravecto products, as revealed during the periodic safety assessments. The product information of these products has been updated with the user safety warning '*Hypersensitivity reactions in humans have been reported*'. The CVMP therefore concludes that hypersensitivity reactions cannot be excluded for the candidate product. In addition, the product contains excipient benzyl alcohol (2% v/v) which has been associated with hypersensitivity reactions. Adequate warnings are therefore in place in the product information.

User safety:

A user safety assessment in line with the relevant guidance document has been presented. Based on the assessment, the product does not pose an unacceptable risk to the user, a professional, when used in accordance with the SPC, when adequate user warnings are in place. The sentences in the product information are considered adequate.

Environmental risk assessment:

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pre-clinical studies

Bravecto150 mg/mL powder and solvent for suspension for injection for dogs is an aqueous suspension for parenteral administration (subcutaneous injection) containing the drug substance fluralaner in a defined particle size distribution (large particle size, "LPS", fluralaner). The product consists of 2.51 mg fluralaner powder, which is constituted before use with 15 ml of solvent, providing for a 150 mg/ml suspension for injection. The dose of the final product formulation administered subcutaneously to dogs is 15 mg fluralaner per kg bw (equivalent to 0.1 ml of constituted suspension for injection per kg bw).

The active substance fluralaner, is a member of the antiparasitic compound class of isoxazoline-substituted derivatives. Fluralaner is a potent inhibitor of parts of the arthropod nervous system by acting antagonistically on ligand-gated chloride channels (GABA-receptor and glutamate-receptor), and an established active substance.

Fluralaner is a systemic insecticide and acaricide, that is intended for the treatment of tick and flea infestations in dogs, providing immediate and persistent killing activity against the claimed tick and flea species for 12 months after a single injection.

Products including the same active substance have previously been authorized in the European Union (Bravecto chewable tablets for dogs, Bravecto spot-on solution for dogs/cats, Bravecto Plus spot-on solution for cats, Exzolt solution for use in drinking water for chickens).

This variation application is to add a new pharmaceutical form, 150 mg/ml powder and solvent for suspension for injection for dogs, to the already existing marketing authorisation. This new pharmaceutical form also introduces the subcutaneous route as a new route of administration. For this active substance and pharmaceutical form no marketing authorization exists within the Union.

Pharmacology

Pharmacodynamics

The applicant makes reference to the CVMP assessment of the dossier for the initial product application of Bravecto (EMEA/V/C/002526) and the conclusions that were drawn regarding the pharmacodynamics of fluralaner.

It was concluded that fluralaner is a potent acaricide and insecticide, that has a prominent feeding activity against ticks and fleas compared to a less potent contact activity (that is, the primary route of exposure is via feeding). Juvenile tick stages (larvae, nymphs) are more sensitive to the effect of fluralaner compared to adult ticks (adults are considered the least sensitive tick stage in comparison to juvenile ticks). No conventional ovicidal effect (inhibition of larval hatch) was observed for fluralaner. Fluralaner demonstrated similar potency for both flea species tested, *C. felis* and *C. canis*.

The change in pharmaceutical form is not expected to influence the pharmacodynamic particulars of the active substance fluralaner.

Pharmacokinetics

The new pharmaceutical form has a different pharmacokinetic profile than the already authorised oral and topical fluralaner formulations for dogs.

Though no specific ADME study was done with the injectable formulation, from which the exact distribution to individual tissues could be derived, the applicant did conduct one new pivotal pharmacokinetic study in dogs using the intended commercial formulation, a suspension for subcutaneous injection. Further pharmacokinetic data in dogs after repeated administration were generated in the pivotal margin of safety study.

There were no relevant gender related differences in bioavailability, distribution or excretion.

Absorption: The product is systemically absorbed from the injection site. Median T_{max} of 37 days (T_{max} ranked from 30 to 72 days). Mean C_{max}: 775 ng/ml (±179 ng/ml).

Distribution: Plasma concentrations were quantifiable in all animals, and exposure was generally similar between males and females. Exposure generally increased in an approximately dose proportional manner.

Excretion: After reaching C_{max}, fluralaner plasma concentrations slowly declined, with a mean fluralaner half-life of 130 days (range 92 to 170 days). At the end of 12-months, plasma levels were still in the range of the therapeutic concentration. Mean $AUC_{0\text{-}inf}$ of 158,000 days*ng/ml (±31,400 days*ng/ml). Mean concentration values for fluralaner were still measurable in all animals 450 days after treatment ($AUC_{t\text{-}last}$ was 139,000 ±28,600 (days*ng/mL). For the Bravecto chewable tablet, during the initial product application (EMEA/V/C/002526), it was demonstrated that

unchanged parent fluralaner was found primarily in faeces (approx. 90% of the dose). This therefore appears to be the main route of elimination. Renal excretion appears to be a minor route of excretion.

Steady State/ Accumulation: The pivotal margin of safety study demonstrated a variable individual fluralaner plasma concentration as indicated by a high Coefficient of Variation (CV ≥ 30%). CV was therefore higher as observed in the pivotal pharmacokinetic study (CV for $AUC_{0\text{-}inf}$ was 19.9% for males and females combined). Slight accumulation was observed between the first and the second dose. Maximum fluralaner concentrations were observed over a range from 29 to 85 days following the first and second doses. Steady-state fluralaner exposure was reached after five completed 4-month dosing intervals.

As both the terminal half-life and the dosing interval determine the magnitude of drug exposure reached after multiple treatments, this resulted in a relatively high extent of accumulation in the pivotal target animal safety study, in which a shortened 4-month dosing interval was chosen. This 4-month interval is however considered to cover a 'worst-case' scenario, as the long half-life and the shorter dosing interval resulted in a much higher exposure at steady state.

Based on the equation by Toutain and Bousquet-Mélou (2004), for a 12-month dosing interval the anticipated time to steady state would be approximately 520 days and the expected accumulation ratio ranged from 1.1 to 1.3.

Product-specific pharmacokinetics are adequately described in section 4.3 of the SPC, including the product-specific fact that prolonged persistence and slow elimination from plasma and the lack of extensive metabolism provide effective concentrations of fluralaner for the duration of the inter-dosing interval.

As the SPC adequately reflects that the duration of efficacy for all indications is 12 months, and it is recommended that this veterinary product is administered only by veterinarians or under their close supervision (hence, it will be administered by professionals), the risk that an animal will be re-treated applying a shorter treatment interval is considered negligible.

Development of resistance and related risks in animals

During the assessment of the initial product application, numerous *in vitro* study data on resistance had been evaluated by the CVMP.

The applicant claims that currently no resistance, *in vitro* or *in vivo*, has been reported against fluralaner. The outcome of the recent laboratory studies (using representative parasite isolates) as well as recent field trials done with the proposed new injectable formulation, support this statement. Also, an evaluation of pharmacovigilance reporting of Suspected Lack of Expected Efficacy (SLEE) events for 'Bravecto chewable tablets for dogs' and 'Bravecto spot-on solution for dogs' over a period of 3 years demonstrated no country-specific increase in incidence of SLEE.

The risk of resistance development seems low. Also, the frequency of application is low (annually), and the efficacy of fluralaner against the claimed ectoparasites in the dog is high. To date, no ectoparasitic resistance against fluralaner has been reported among the target tick and flea species listed.

Prudent use advice as recommended in the Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products (EMA/CVMP/EWP/170208/2005-Rev.1) is included in the SPC (Section 3.4), as appropriate.

Dose determination and confirmation

Study design

The proposed dose was justified based on a dose determination study, and effectiveness was then confirmed in eight dose confirmation studies performed under experimental conditions.

All studies were performed in the target animal and were conducted in accordance with the general principles of 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.3) (hereinafter referred to as: "Guideline"). These clinical studies were also performed according to VICH GL 9 on Good Clinical Practice (GCP), which is in line with the CVMP Guideline.

Study Animals

Eight to ten dogs per group were included in the pivotal efficacy studies. The number of dogs used was therefore appropriate, as this was in line with Guideline recommendations (i.e., at least 6 animals per group).

The studies were predominantly conducted in Beagles and mixed breeds, including both male and female animals. The ability of the animals to retain parasites was demonstrated by a pre-infestation with ticks/fleas, and defined in accordance with the Guideline by an attachment rate of ≥ 25% for ticks and ≥ 50% for fleas. Animals were ranked by descending tick or flea infestation rates within each sex and randomly allocated to the study groups, except for studies conducted in the USA where a completely randomized design was used as required by the Center for Veterinary Medicine (CVM-FDA). The same procedure applied when co-infestations with ticks/fleas and efficacy assessments for ticks and fleas were performed in the same study. The study design used is sufficiently in line with the current Guideline.

It is noted that in most pre-clinical studies, conducted outside Europe, dogs were housed individually during the entire study, i.e. for more than one year. According to Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes, with the exception of naturally solitary animals, animals shall be housed in stable groups of compatible animals. In cases where individual housing is justified in accordance with Article 33(3), the duration of housing shall be limited to the minimum necessary and visual, auditory, olfactory and/or tactile contact shall be maintained. The CVMP considers that the minimum necessary duration of individual housing would have been between tick and flea infestation and collection (as detailed in 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). Between tick and flea collection and a new infestation, group housing would potentially have been possible. However, the applicant adhered to the conditions required by non-EU authorities for studies conducted outside the EU for this product. 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.

Infestation and counting procedure

All parasite isolates used in laboratory studies originated from the field and were multiplied *in vivo* (i.e., on host animals) in the laboratory. Infestations were conducted on dogs (that were sedated if necessary) using 50 unfed adult ticks (which is appropriate, as this was the least sensitive tick stage,

as concluded in the CVMP assessment report for Bravecto; EMEA/V/C/002526) and/or 100 unfed adult fleas of *C. felis*. The ticks' sex ratio was approximately 1 : 1 (female : male), with the exception of *I. ricinus*, for which 45 unfed females plus 5 males were used, as is considered appropriate for this tick species. Sex ratio used is considered sufficiently in line with the Guideline, that describes an approximate 10% males : 90% females ratio for *I. ricinus*.

The animals in all groups were infested with parasites, i.e., ticks and/or fleas, 2 days (SD-2) before treatment was administered (SD0). One group remained untreated to serve as a negative control. For the assessment of immediate (therapeutic) efficacy, the parasite burden of each animal was assessed in most studies on SD2, i.e., approximately 48 hours after treatment. For one dose confirmation study, the first timepoint for flea removal was however on SD1, and for another study (*D. reticulatus*), the first timepoint of tick removal/count was on SD3, i.e., approximately 72 hours after treatment.

For the assessment of persistent efficacy, the animals were frequently re-infested at predefined intervals.

Assessment of efficacy against ticks and fleas

The parasite burden of each animal was assessed by removal and count of all ticks and/or live fleas followed by a four-category assessment for ticks according to the Guideline. The calculation of efficacy was performed in general compliance with the Guideline, using arithmetic means (AM) (but also geometric means (GM)) of parasite numbers per group according to Abbott's formula.

For ticks, treatment at a certain time point was considered effective at an efficacy rate of > 90%. For fleas, treatment at a certain time point was considered effective at an efficacy rate of > 95%. This level of effectiveness is in line with the Guideline.

Studies done in different geographic regions

Laboratory studies and field trials were presented that were conducted in different geographic regions to allow the use of data for a global product development. From a 3R-perspective, this is considered appropriate.

Ultimately, for *R. sanguineus* and *C. felis*, dose confirmation studies included parasites that originated from the EU as well as from the US.

To assess the acaricidal contact activity of fluralaner for USA and EU isolates of *R. sanguineus,* initially, an *in-vitro* immersion study was performed. Results of this study indicated that the US isolates used were more susceptible to fluralaner than EU isolates. However, based on the intraclass correlation, both for dead and damaged tick counts a very high similarity was confirmed between these strains. Also, the GABA receptor fluralaner interaction site of USA and EU strains have been shown to be genetically similar.

Overall, based on the high degree of similarity between the different ***R. sanguineus*** isolates (USA strains versus EU strains), a genetically similar GABA receptor fluralaner interaction site, as well as highly comparable efficacy as demonstrated in the presented dose confirmation studies (and clinical field trials) that were performed using isolates of *R. sanguineus* both from the USA as well as from Europe, it can be accepted that the results from the US laboratory efficacy studies performed with fluralaner in *R. sanguineus* isolates are also of relevance to EU isolates.

The degree of similarity between the different ***C. felis*** isolates (USA and AUS strains versus EU strains) is also considered high enough to apply findings regarding the susceptibility to fluralaner of US and AUS strains to the EU strain. Reasons for this, is the genetic similarity of the GABA receptor fluralaner interaction site of the US, AUS and the EU *C. felis* strains; the equally susceptibility to

fluralaner of against *C. felis* isolates from the USA, EU and AUS strains (measured by means of an *in vitro* susceptibility test), and the fact that *in vivo* laboratory efficacy studies (and clinical field trials) indicate similar efficacy results for *C. felis* strains obtained from different geographical locations.

Overall, the results support that fluralaner's insecticidal potency against fleas from different geographic origins (EU, USA and AUS) was similar, and that fleas originating from EU, USA and AUS were equally susceptible to fluralaner. As a consequence, dose confirmation laboratory data collected in the USA and AUS are also considered representative for the EU.

Dose-limiting tick species

As fleas are known to be the most sensitive small animal ectoparasite to fluralaner, and *R. sanguineus* was identified as the dose-limiting tick species during the development and registration of 'Bravecto chewable tablet for dogs' (EMEA/V/C/002526), the applicant conducted the pivotal Dose Determination Study with *R. sanguineus* (though it is noted that this study also included an infestation with *C. felis* fleas on Day 186). The decision to use *R. sanguineus* for the pivotal dose determination study can be accepted, as effectiveness of the selected dose was subsequently confirmed in two laboratory dose-confirmation studies for the tick species *R. sanguineus, D. reticulatus, I. hexagonus* and *I. ricinus*, as well as in a pivotal clinical trial.

Dose determination study

The pivotal dose determination study was an appropriately designed, GCP (non-GLP) compliant study, that aimed to examine the efficacy of the IVP of a single dose, at three different dose levels (10, 15 or 20 mg fluralaner/kg bw) in dogs infested with *A. americanum* and *R. sanguineus* ticks, and *C. felis* fleas. Though all parasite strains were of USA origin, findings regarding the susceptibility to fluralaner of USA strains are also applicable to European strains.

Forty Beagle dogs were randomized into five groups of eight animals each. The ability of the animals to retain parasites was demonstrated by a pre-infestation with *A. americanum* ticks. Though this species is not considered for the efficacy assessments, outcome of this pre-infestation is considered to support the animals' general ability to retain parasites.

Dogs were studied for a minimum period of six-months following a single subcutaneous administration of the IVP. In addition, up until SD390, frequent blood samples were collected at predefined time points.

At D0, three groups were dosed with an aqueous suspension of fluralaner at a dose range of 10 mg/kg bw (applying a fluralaner 100 mg/ml injectable suspension), 15 mg/kg bw, or 20 mg/kg bw (applying a fluralaner 150 mg/ml injectable suspension). A fourth group was treated with another formulation type. A fifth group was left untreated.

The fluralaner 150 mg/ml injectable suspension was considered sufficiently representative of the final formulation.

An efficacy threshold of ≥ 90% based on arithmetic mean was determined. Up to SD390, each animal was repeatedly (15x) infested with *R. sanguineus* ticks. Counts were performed 48 hours post infestation. Additionally, on SD186, dogs were infested with *C. felis* fleas. Animals were also frequently (n=10) infested for *A. americanum* ticks up until SD209. As effectiveness against this species is however not claimed, this is not further assessed.

For both the *R. sanguineus* ticks as well as for the *C. felis* fleas, adequate infestation in the control group was achieved.

Results indicated that the other tested product formulation did not release effective amounts of fluralaner for effective flea and tick control.

For *C. felis* fleas, adequate infestation in the control group was achieved on SD187, and efficacy was 100% for treatment groups 2, 3, and 4 with calculations based on both arithmetic and geometric mean.

For the *R. sanguineus* ticks, adequate infestation in the control group was achieved on all count days. In all groups, effectiveness on Day 2 did not exceed 62.02% (arithmetic mean).

The 10 mg/kg bw dose was effective from SD14 up until SD 302 days (arithmetic mean: 91.63% on Day 302). The 15 mg/kg bw and 20 mg/kg doses were effective for 333 days (arithmetic mean: > 97%) and 363 days (arithmetic mean: 96.29%) respectively.

Efficacy on SD 363 was slightly below the efficacy threshold of 90% for the 15 mg/kg bw dose (arithmetic mean: 83.69%; geometric mean: 93.51%). However, 15 mg/kg bw was selected as the clinical dose to be used in future confirmation studies. This was considered appropriate both from a target animal safety- as well as from an environmental safety point of view. Also, at SD 363, tick count on 1 animal was considered disproportionately high (skewed) compared to the other dogs of this group. Finally, as the dose-limiting tick species *R. sanguineus* was used for determining the dose, it was expected that efficacy would be well above 90% for the other European tick species.

Overall, selection of the final clinical dose of 15 mg fluralaner/kg bw is considered adequately justified. It is therefore considered appropriate that effectiveness of this dose was carried forward in dose confirmation studies for tick and flea species.

Dose confirmation studies

With regards to effectiveness against ticks and fleas, to confirm the dose of 15 mg fluralaner per kg bw, two confirmatory studies (DC studies) were presented for all tick species considered relevant in dogs in Europe (*Dermacentor reticulatus*; *Ixodes hexagonus*; *Ixodes ricinus*; *Rhipicephalus sanguineus*).

Regarding flea species, only confirmatory studies regarding *C. felis* were presented. However, as was concluded in the pharmacodynamical section of the CVMP assessment report for Bravecto (EMEA/V/C/002526/0000), fluralaner demonstrates similar potency for both flea species tested, *C. felis* and *C. canis*. As such, the findings of the *in vivo C. felis* studies can be extrapolated to *C. canis*.

In total, eight DC studies were conducted, both in the USA as well as in the EU, all using the final formulation. In addition, one supportive study was conducted in Australia using Australian tick and flea strains. These studies confirmed that 15 mg fluralaner per kg bw administered once subcutaneously provided persistent killing activity on ticks (*I. ricinus*, *I. hexagonus*, *D. reticulatus* and *R. sanguineus*) and fleas (*C. felis*) for 12 months.

Dose Confirmation Studies for *R. sanguineus*

The objective of three studies (parasite origin: USA and EU) was to determine the duration of effectiveness of the IVP against infestations *R. sanguineus* ticks, the tick that is considered dose-limiting for fluralaner, for up to 52 weeks.

In all three studies, an adequate and sufficient tick challenge could be confirmed. In all three studies, treatment resulted in a ≥ 90% reduction in live *R. sanguineus* tick counts as compared to the control group from Day 7 to 365.

An additional supportive dose confirmation study (parasite origin: AUS) confirmed persistent efficacy (for up to one year) against infestations of *R. sanguineus* ticks. In this study, the IVP was 100% effective against existing tick infestations 7 days after IVP administration (tick counts on Day 9; first

day of assessment). Efficacy against new tick infestations was maintained for 12 months (efficacy (arithmetic means): 92.6% on Day 365).

Dose Confirmation Studies for *I. ricinus*

The objective of two studies (parasite origin: EU) was to confirm the efficacy of the IVP against *Ixodes ricinus* for up to 52 weeks. On all but 1 occasion, both studies achieved adequate and vigorous tick infestation.

One study demonstrated that the IVP was 83.8% effective at 48 hours after treatment, and efficacy exceeded 98.9% up to 11 months (338 days). Efficacy was 89.1% on SD 366. Efficacy was therefore slightly below the required threshold of 90% at the end of the claimed period of efficacy. As however efficacy of the second study did support efficacy above the required threshold (in fact, in that study efficacy was 96.2% on SD 394) and duration of efficacy could also be confirmed in the presented clinical trials, it can be accepted that also for *I. ricinus*, effectiveness of the selected dose is considered appropriately demonstrated.

The second study demonstrated that the IVP was 94.97% effective against existing tick infestations 7 days after IVP administration (when persistent efficacy was first assessed). Efficacy against new tick infestations was maintained for 12 months (SD 366: efficacy was 99.16%).

Dose Confirmation Studies for *D. reticulatus* and *I. hexagonus*

The objective of two studies (parasite origin: EU) was to confirm the efficacy of the IVP against *D. reticulatus* and *I. hexagonus* for up to 12 months following treatment.

An adequate and vigorous tick challenge could be confirmed in both studies.

The first study demonstrated that for *D. reticulatus*, treatment was 78.5% effective against existing tick infestations after 48 hrs (100% effective after 7 days). Based on the arithmetic means of live tick counts, the IVP was ≥ 96.7% effective up to one year. For *I. hexagonus*, treatment was 81.3% effective against existing tick infestations after 48 hrs (100% effective after 7 days). Based on the arithmetic means of live tick counts, the IVP was 92.9% effective up to one year (SD 393)

The second study demonstrated that for *D. reticulatus*, treatment was 93.1% effective against existing tick infestations after 72 hrs (100% effective after 7 days). Based on the arithmetic means of live tick counts, the IVP was >/=99.3% effective up to one year. For *I. hexagonus*, the IVP was ≥ 99.5% effective up to one year (arithmetic means of live tick counts).

Hyalomma marginatum

With regards to the (minor) tick species *Hyalomma marginatum*, the applicant only presented a GLP-compliant *in-vitro* study that evaluated the acaricidal activity of fluralaner against the tick species *Amblyomma americanum*, *R. sanguineus* and *Hyalomma marginatum*, after contact exposure of adult ticks by immersion in declining fluralaner test concentrations.

Results of this *in-vitro* study do suggest that *H. marginatum* is more sensitive towards fluralaner than *R. sanguineus*. However, according to the Guideline, reference to non-autochthonous species (such as *H. marginatum*) may only be made in the SPC and package leaflet if the efficacy has been reliably shown. As a single in-vitro study is not considered adequately reliable, it was not considered appropriate to include effectiveness against this non-autochthonous tick species.

The applicant therefore ultimately decided to withdraw this indication.

Dose Confirmation Studies for *C. felis*

The objective of two studies (parasite origin: US and EU) was to assess persistent efficacy against *C. felis* for up to 12 months. An adequate flea infestation and a sufficient flea challenge were confirmed for both studies.

In the first study , treatment was effective (both therapeutic and persistent) against *C. felis* fleas. Based on arithmetic means, treatment resulted in ≥ 99% reduction in live flea counts on all count days (except Day 1) and was also effective for the prevention of *C. felis* infestations (no more than 1 egg total for all dogs in the IVP treated group for all egg collection days except on Day 1).

In the second study, the IVP was 92.2% effective against existing flea infestations 7 days (first day of evaluation) after IVP administration. Efficacy against new flea infestations was maintained (100%) for 12 months.

It is noted that at SD7, efficacy was below the threshold of 95%, whilst effectiveness is claimed at that point. As however efficacy in all remaining assessment points and all remaining studies clearly exceeded the efficacy threshold of 95%, this single measurement was considered an incidental finding.

A supportive study (parasite origin: AUS) also assessed persistent efficacy against infestations of *Ctenocephalides felis* fleas up to one year. Arithmetic means of flea control against existing flea infestations demonstrated a 99.7% efficacy on day 2 (99.8% based on geometric means), and 100.0% efficacy for all remaining post-treatment counts.

Onset of efficacy and speed of kill

Separate studies assessed the *onset of efficacy*, defined as the initial time needed to achieve killing of at least 90% of ticks and 95% of fleas already present on the animal before treatment administration.

Two studies supported that D. reticulatus and I. ricinus ticks are killed within 72 hours (day 3 after treatment). A third study supported that R. sanguineus ticks are killed within 96 hours (day 4 after treatment). The fourth study supported that C. felis fleas that infested the animal prior to treatment administration were killed within 48 hours after treatment (i.e., immediate).

The *speed of kill* was defined as the time needed to achieve killing of at least 90% of ticks and 95% of fleas after the initial onset of efficacy and over the whole 12-month duration of efficacy. Time point of efficacy assessment was at 48 hours after each re-infestation in most studies but 24 hours for fleas in one study). Thus, for newly infesting ticks the speed of kill over the whole 12-month duration of efficacy is 48 hours. For newly infesting fleas, the speed of kill over the whole 12-month duration of efficacy is 24 hours.

In summary, the presented studies supported that *I. ricinus* and *D. reticulatus* ticks already present on the dog prior to treatment are killed within 72 hours after treatment. *R. sanguineus* ticks already present on the dog prior to treatment are killed within 96 hours after treatment. Newly infesting ticks are killed within 48 hours, from one week through 12 months after treatment.

Fleas already present on the dog prior to treatment are killed within 48 hours after treatment. Newly infesting fleas are killed within 24 hours, from one week through 12 months after treatment.

These results confirm the information about the speed of kill as indicated in the SPC.

Flea- and tick-borne disease transmission: Reduction of the risk of infection with Babesia canis and Dipylidium caninum

Babesia canis and *Dipylidium caninum* transmission prevention studies were conducted for two different pharmaceutical forms of fluralaner, Bravecto chewable tablets and Bravecto spot-on.

Regarding reduction of the risk of infection with *Babesia canis* and *Dipylidium caninum*, no separate (pre-) clinical data was submitted in current procedure. However:

- pharmacodynamics of all fluralaner-containing products (being tablets, spot-on or injectable) for all products are identical;
- reduction of the risk for infection with *Babesia canis canis* and *Dipylidium caninum* has already been demonstrated in several fluralaner-containing products;
- though pharmacokinetics differ, the SPC mitigates the risk of infection prior to day 3 after treatment ("*For reduction of the risk of infection with Babesia canis canis via transmission by Dermacentor reticulatus from day 3 after treatment for up to 12 months*');
- the effect of fluralaner on the vector borne diseases itself is nil, rather; the effect is indirect, and fully the result of the fast speed-of-kill against fleas and ticks;
- and finally, the speed of kill has been demonstrated to be similar for the injectable suspension as for the chewable tablets (within 24 hours for fleas and within 48 hours against ticks at all infestation time points). It is known that transmission time for both vector borne diseases normally occurs after this period.

From a scientific point of view, the proposed claim: *Reduction of the risk of transmission* of these vector borne diseases could therefore be granted.

Mange mites

With regards to mange mites (*Demodex (D.) canis* and *Sarcoptes (S.) scabiei* var. *canis*), the applicant referred to the efficacy already demonstrated against these species for 'Bravecto chewable tablets' and 'Bravecto spot-on solution'. Also, the applicant highlighted some pharmacokinetic characteristics of current fluralaner injectable (high volume of distribution, indicating a high tissue distribution, and long terminal half-life). However, considering that the new product application is an injectable with an entirely different posology, the CVMP considered that further justification for this approach was needed.

The applicant therefore ultimately decided to withdraw these indications.

Tolerance in the target animal species

The applicant presented a GCP-compliant pivotal target animal safety study. This study was designed according to VICH GL43 (Target Animal Safety Guideline).

A negative control (sodium chloride for injection) was included. As required by VICH GL43, animals received treatment at 0, 1x, 3x and 5x multiples of the recommended treatment dose (RTD) (i.e., 0, 15, 45, or 75 mg/kg bw) on 6 occasions, once every 4 months, reaching steady-state exposure. Necropsy was conducted 42 days after the sixth dose (SD638), corresponding with maximum mean plasma fluralaner concentration.

The study was performed in accordance with the requirements of VICH GL43 and included an appropriate number of 32 (8 animals per group, 4 groups) healthy, naive 6-month-old Beagle puppies. Minimum weight was 5.8 kg at SD -1. It is noted that as a special warning is proposed in Section 3.5, that states that "*In the absence of available data, the veterinary medicinal product*

should not be used on dogs less than 6 months old". As also (pre-) clinical studies implemented this minimum age, this warning is considered appropriate.

Throughout the study, animals were assessed for mortality, clinical observations (cage side observations and clinical assessments), and injection site assessments (swelling and erythema by visual inspection and palpation with caution for swelling, consistency (when applicable), pain, and increase in temperature), body weight (gain), and food consumption. Also, veterinary physical examinations, clinical pathology parameters (haematology, coagulation, clinical chemistry, C-reactive protein, phospholipids, and urinalysis), toxicokinetic parameters, organ weights, and macroscopic and microscopic examinations were evaluated.

Safety assessments in the pivotal TAS study:

Unscheduled deaths

There were 2 unscheduled deaths in this study; two 3xRTD males that were administered 45 mg/kg/bw dose were euthanized early, on SD8 and SD475, respectively.

At SD8, one animal was diagnosed with prolapse of the rectum, which was considered an incidental finding and not likely to be treatment related.

Another animal was euthanized on SD475 because of multiple recurring convulsions with bilateral forelimb stiffness and mild salivation. Clinical presentation (a markedly increased C-Reactive Protein (CRP) along with increased fibrinogen indicative of acute inflammation) and microscopic findings (that included mild mixed cell vascular/perivascular inflammation of the right extramural coronary artery of the heart, minimal to mild vascular and/or perivascular inflammation affecting arteries in the submucosa of the stomach) were considered consistent with polyarthritis ("steroid responsive meningitis-arteritis (SRMA)"). Death of this animal was therefore also not considered test article related.

There were no clinical signs that were attributable to test article administration. There were also no adverse test article-related effects on body weight, body weight gain, or food consumption, when considering pre-existing differences among the groups at study initiation.

Urinalysis, haematology, clinical chemistry and coagulation

There were no differences in parameters that were considered to be test article related. Occasional differences among groups, even those that achieved statistical significance, showed no dose response, and were considered incidental, consistent with biologic variation, and/or negligible in magnitude. Mild effects on plasma lipid parameters were observed after prolonged high plasma fluralaner concentrations, however, these effects were not considered test article related due to the lack of a discernible pattern, individual values being mostly within reference ranges. The change in plasma lipid parameters was not considered clinically relevant in all cases.

Injection Site Assessments

The injection site was clipped and/or shaved and marked for better visualization. Test article-related findings were (non-painful) swellings at the injection site, most often nodules. Swellings in the 1xRTD group typically were detected from approximately 2 weeks after the injection for a period of 1-2 weeks before they were undetectable.

When only the first dosing cycle of this study is taken into consideration, swellings were detectable for an average of 11-14 days. However, small nodules were occasionally noted prior to the next administration through deep subcutaneous palpation of the marked injection site. As in field-like conditions, dosing will not be repeated every 119 days into the same anatomical area, it was not considered appropriate to include prolonged swellings at the injection site as an adverse event.

Pathology

There were no test article-related organ weight changes. Animals with persistent swellings did have Test Article-related gross findings at the administration site: nodules and findings of material accumulation (minimal to moderate granulomatous inflammation, minimal histiocytic infiltration, and minimal to moderate fibrosis of the subcutaneous). Injection site findings were not associated with systemic adverse clinical signs.

Overall conclusion of the pivotal TAS study was that the product is safe when used as recommended. However, injection site abnormalities in terms of (non-painful) swellings at the injection site can be expected. The observations are adequately addressed in section 3.10 of the SPC.

Cross-study assessment of Adverse Events

In light of this submission, the applicant conducted 18 studies, in which a total of 1,049 dogs were treated subcutaneously with the IVP at a dose of 15 mg/kg bw. Three clinical trials (one pivotal, European clinical trial and two small, supportive clinical trials performed in Australia) were performed. In all of the presented studies, general health observations were performed regularly throughout the animal phase of each study to assess systemic tolerance as well as local tolerance.

The results from the pivotal target animal safety study were also reflected in the pre-clinical and clinical studies, where the main adverse reactions reported were (non-serious) injection site reactions.

In the total number of animals, 28 adverse events were considered 'relevant'. The largest number of adverse events were observed in the pharmacokinetic study and the margin of safety study.

No (treatment-related) adverse events were observed in the majority of dose determination/ confirmation studies.

In the margin of safety study, when only the first dosing cycle of this study is taken into consideration, swellings were detectable for an average of 11-14 days.

In the pivotal pharmacokinetics study, seven out of eight animals had small visual and/or palpable swellings at the injection site, starting one day post injection with a mean persistence of 73 days (range 37-100 days) in males and 83 days in females (range 48-100 days). Maximum swelling size was 4.08 x 4.55 cm. According to the study report, these "swellings" were attributable to the presence of test article subcutaneously and were not considered to be reactions to the test article. This conclusion is however not fully agreed, as in most animals, the swelling increased in the days following the injection (for example, Animal no. 1487M: Day 10: 0.72 cm x 0.57 cm x 0 cm; Day 11: 3.80 cm x 4.07 cm x 0 cm). An increase of the swelling would not be expected in case the swelling was only caused by presence of the test article. However, it has to be noted that unlike the situation in the field, in this study, the injection site was clipped and/or shaved and marked for better visualization of injection site reactions.

In the onset of efficacy study, small swellings were observed in two dogs on SD 0, which resolved within two and 24 hours, respectively. A fast resolution of the swelling is considered indicative for the presence of test article under the skin.

In incidental animals, erythema at the site of injection (spontaneously resolving, maximum duration several days) was observed in some of the dose determination/confirmation studies and in the TAS study.

Occurrence of erythema was however rare and in some studies erythema was also observed in animals of the control group. There was also no significant difference between the findings of erythema in treated and controlled animals.

In the pivotal clinical trial 'pain' due to the injection was noted on five occasions. However, pain was not considered the result of the product, as the test article is a non-irritant aqueous suspension. Pain was therefore considered the result of the subcutaneous injection with a large-diameter needle.

It is noteworthy that no injection site reactions were observed in any of the field studies.

Injection site swelling (Palpable and/or visual swellings, non-inflammatory, non-painful, self-resolving over time) was correctly included as a common adverse event.

Hyperaemic mucous membranes

In one study, (slight) hyperaemic mucous membranes were observed in two animals, in proximity to administration of the treatment. (Day 1, duration: 2 days). The applicant therefore included this observation as an uncommon adverse event.

(Sudden) deaths

In the pivotal clinical trial, three animals treated with the IVP, were unexpectedly 'found death' (E32-17-1; E24-02-3; E25-01-2). Of these cases, one animal was hit by a car. In the remaining two animals, relation to treatment cannot be fully excluded based on the fact that no formal diagnosis was available. However, considering the considerable interval between treatment and onset of clinical signs, being 116 days and 146 days, whilst the median T_{max} of the IVP is 37 days, noticing that these animals were older (11 and 12 years) and therefore the likelihood of a concurrent condition is considered to increase, and, finally, noticing the fast course of the disease, an obvious relation with treatment is not considered demonstrated.

Overall, a relation to treatment could not be confirmed and appears not very likely in case of these animals.

In a clinical trial, one animal (A28A) demonstrated inappetence and lethargy, which was considered a 'severe event'. The animal was ultimately euthanized. It was noted that this animal had accidentally received 125% of the intended dose. Ultimately, no definite diagnoses could be made in this dog (non-specific clinical signs, owners refused investigations). However, as this event occurred very late in time (SD306) and taking into account that for Bravecto injectable the median T_{max} is 37 days, an association with product administration is not expected; the death of this dog was therefore considered unlikely to be treatment related. In another clinical trial, an animal spontaneously died at SD80. This animal (a 12-year-old Chihuahua) was lethargic and known to suffer from a heart murmur. The animal arrived dead at the clinic, demonstrated an enlarged abdomen/thorax, and was suspected of having succumbed due to cardiac decompression. Though a relation with treatment can never be fully excluded based on the presented data, it is acknowledged that this death is more likely linked to the (pre-existing) heart failure.

No other sudden, or unexplained deaths occurred in the (remainder of) the studies.

Neurological symptoms

In three of the presented studies, in singular dogs, symptoms were incidentally observed that could be considered as neurological signs, seizures/convulsions and tremors.

Symptoms were generally heterogeneous. In most cases, a clear relation with treatment and the development of neurological symptoms could not be confirmed. However, in three cases that were included in the Pivotal Clinical Trial Study and in one case that was included in another study, product association was considered possible. In these cases, there was a temporal association with the T_{max} range, a spontaneous resolution of the clinical signs, and the signs were consistent with the neurological adverse events known for Bravecto tablets (and specified under SPC section 3.6 for that product).

Therefore, a possible association between administration of the product and the development of neurological signs, seizures/convulsions and tremors cannot be ruled out. Given that neurological signs, seizures/convulsions and tremors are known adverse effects for fluralaner, as reported in the SPC for Bravecto tablets, they were also included as adverse events for the injectable product.

As an exclusion criterion for the pivotal clinical trial, the applicant included: "At least one dog with known epilepsy" (two supportive clinical trials, however, did not exclude animals with a history of seizures).

These animals were excluded for the pivotal trial as, irrespective of any treatment, it was considered likely for animals with pre-existing epilepsy to develop seizures considering the long study period of the pivotal field study. In an attempt not to create a situation in which a pre-existing situation was considered correlated to treatment, it was decided to exclude these animals from the pivotal study. This decision is understandable, as the study period was indeed considerable and the development of seizures likely in this group of patients. However, as a result of this decision, treatment effect in dogs with pre-existing epilepsy could ultimately only be assessed in a single animal (that was included in a non-pivotal, supportive trial). It was therefore not considered appropriate to claim that treatment has been assessed as safe in animals that suffer from epilepsy. Also, treatment in these animals should be based on a benefit/risk assessment by the responsible veterinarian. This is adequately addressed in the SPC.

Whilst this warning is stronger than that accepted for Bravecto tablets, this strengthening is considered necessary given the prolonged period of effect of the formulation for Bravecto injectable compared to Bravecto tablets.

Increased tiredness

Increased tiredness was observed in four animals in the pivotal clinical trial. Considering the proximity to IVP administration (SD0-2), this is considered possibly to be treatment related. In one dog, duration was 43 days, whilst in the other dogs, duration was 1-2 days. Increased tiredness was not noted in any of the other studies. It is correctly listed as an "uncommon adverse event".

In one clinical trial, on SD1, one dog was lethargic and demonstrated 'foaming from the mouth (potentially hypersalivation) on Study Day 1. These clinical signs were transient, resolving within the same day, and no other signs of neuropathy were observed in this animal. Also, none of the remainder of the animals were observed with 'foaming from the mouth'. Ultimately, this observation was considered less likely to be a neurological-related event. As it was only a single, very short-lasting observation, it was not considered appropriate to include as an adverse event.

Gastrointestinal symptoms

Unspecific gastro-intestinal adverse events (vomiting, diarrhoea) were frequently observed both in treated as well as in control animals. A clear relationship with treatment could not be established, as gastro-intestinal adverse events occurred throughout all timepoints, not only in the proximity of the time of IVP administration. As a clear relationship to the IVP is not considered demonstrated, the applicant did not include this as an adverse event.

Decreased appetite

In three studies, decreased appetite was observed in proximity to dosing: In the first study, inappetence was observed in two animals shortly after treatment (Day 1; duration: 2 days); in a clinical trial (n=1; decreased appetite for 2 days following injection) and in another study (n=2; one dog demonstrated decreased appetite between Day 3-9, and one dog demonstrated intermittent inappetence on SD0).

Considering that an association in time was present, the applicant assessed this event as potentially treatment-related and included it as an "uncommon adverse event", as is considered appropriate.

Weight gain/loss

Weight gain/loss was measured on several occasions throughout the studies. Overall, treatment did not result in a significant weight loss (or gain).

Pruritis

Pruritis was only observed in two of the field studies.

In the pivotal clinical trial, non-specific pruritis was observed in both treated (n=2)- as well as control (n=3)- animals. No relation with treatment could be confirmed, and this observation is considered most likely the result of another cause.

In a study, ten cases of unspecific pruritus were reported in nine dogs. The cases demonstrated a heterogeneous distribution pattern, but five cases occurred prior to SD67. It is noted that in this study, this was not a spontaneous observation: Owners were actively requested to inform on any increase in pruritis in the 'Owner observation of pruritis' (it is noted that results were indicative for an overall reduction of pruritis). Overall, a clear relationship to the IVP is therefore not considered apparent, and pruritis is correctly not included as an adverse event.

Target animal safety study in (MDR1 -/-) dogs: This study was assessed during the initial application procedure. In contrast to current product, where animals will be treated by subcutaneous injection, this study assessed safety in animals that were dosed orally at a dose of 168 mg/kg bw (3x the maximum oral RTD). As systemic exposure in case of subcutaneous use (15 mg/kg bw.) will not exceed that of oral administration, it is accepted that the conclusions of this study are also applicable to the new injectable formulation, and that therefore no additional safety concerns exist for MDR1(-/-) dogs when the product is used.

Reproduction

It is noted that during a study, one dog (a chihuahua) gave birth to three healthy puppies (at SD112).

Conclusions on tolerance

It is concluded that the product is in general well-tolerated at the recommended dose. Tolerance in dogs younger than 6 months has however not been demonstrated, and the SPC includes a warning that in the absence of available data, the veterinary medicinal product should not be used in dogs less than 6 months old.

The observations in the pivotal TAS study were mostly also noted in the pre-clinical and clinical studies, where the main adverse reactions reported were (non-painful) swellings at the injection site, most often nodules.

In addition, some animals in the clinical studies showed diarrhoea and weight loss. However, there was no evidence for a direct relation with treatment.

In three animals included in the clinical studies, a possible association between administration of the product and the neurological signs, seizures/convulsions and tremors was considered possible. Also given that neurological signs, seizures/convulsions and tremors are known adverse effects for fluralaner, as reported in the SPC for Bravecto tablets, these were included as adverse events for the injectable product.

The SPC and product information contain adequate warnings about the observed adverse effects and their frequency.

Clinical trials

Ticks and fleas

In support of this variation, the applicant presented three clinical trials (i.e., field studies) (one pivotal, two supportive (non-pivotal) trials). In all three trials, the final product formulation was used. As is considered appropriate, the suspension was administered as a subcutaneous injection, in accordance with the proposed dose of 15mg fluralaner per kilogram bw. For safety evaluation of the clinical trials, see section 'target animal tolerance'.

The pivotal clinical trial was a well-designed and well conducted, GCP compliant, multi-centre (Germany and Spain), randomized and examiner blinded study. Initially, dogs from France were also to be included. Ultimately, however, cases from France were excluded due to the impact of the COVID-19 pandemic, as proper remote monitoring was not feasible. As a result, only Germany and Spain remained as sites. Nonetheless, the study can be considered sufficiently representative of the European situation.

Relevant CVMP Guidelines (Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats" (EMEA/CVMP/ EWP/005/2000-Rev.3; 2016), and "Guideline on Statistical Principles for Veterinary Clinical Trials" (EMA/CVMP/EWP/81976/2010) were appropriately followed.

As is considered appropriate, the study was positive-controlled (afoxolaner containing chewable tablets). The comparative product has a similar indication as proposed for current IVP. Though dosing interval of the comparator is 4 weeks orally, as no product is currently authorized for dogs with an annual subcutaneous treatment regimen, use of the positive control product can be accepted.

The objective was to evaluate the efficacy and safety of the IVP administered once against natural infestations with fleas (*C. felis*) and/or ticks (*I. ricinus, D. reticulatus, R. sanguineus* complex and other) for 365 days.

To be included, at least one dog in the household had to be presented with a tick count of ≥ 4 and/or a flea count of ≥ 5 and the parasites had to be alive. In case there were several dogs in a household, all dogs in this household were enrolled into this study and assigned to the same treatment group. However, only one dog from the household meeting the inclusion criteria (the 'primary dog') was considered for efficacy evaluations. Dogs also had to be healthy, with an appropriate type of hair coat and temperament to allow count procedures, body weight of ≥ 2 kg, and be at least 6 months of age. As an exclusion criterion, the researchers included: "At least one dog with known epilepsy".

The study schedule involved 10 scheduled visits for tick and flea counts (Visit 1: SD0, Visit 2: SD 14, Visit 3: SD28; up until Visit 10: SD365) to veterinary clinics over a period of 365 days. Primary efficacy was based upon the percentage of primary dogs free of live ticks and free of live fleas (parasite free cases) at Visit 10. Additionally, percentage reduction of ticks in initially infested primary dogs (tick count ≥ 4 on SD 0) from the per protocol (PP) population and percentage reduction of fleas in initially infested primary dogs (flea count ≥ 5 on SD0) from the PP population was determined. Efficacy results based on arithmetic means were provided additionally.

Ultimately, excluding the cases from France, 666 privately owned dogs from 360 households

remained available for the statistical analysis. The study population was adequately balanced, and considered sufficiently representative for the target population, in terms of sex and breeds included. Included in the PP population were 330 dogs (n= 222 were treated with the IVP and n=108 with the positive control). Overall, the flea infested dogs had a flea burden ranging from 5 to 67 fleas at inclusion. The tick-infested dogs had a tick burden ranging from 4 to 36 ticks at inclusion. The infestation level for both ticks and fleas is considered adequate.

At Day 0, of the 330 dogs in the PP population, 198 were included with ticks only, 115 were included with fleas only, and 17 dogs were included with ticks and fleas. The co-infestation rate was approximately 5%, which was lower than expected. With regards to the tick species upon inclusion, *I. ricinus* was identified on 309 dogs, *R. sanguineus* on 87 dogs, *D. reticulatus* on 32 dogs and *I. hexagonus* on 15 dogs. All tick species are considered relevant European tick species. Though it is noted that fleas were not specifically identified, it can be assumed that the predominant species was *C. felis*, as this is considered the most relevant flea affecting dogs.

High levels of efficacy were observed throughout the study. At all visits throughout the study, the percentage of dogs free of ticks and/or fleas was above 95% after IVP treatment, and the percentage of tick-free cases in the IVP group was statistically significant non-inferior compared to the registered control product at all evaluation times throughout the study. It was noted that the targeted sample size number was not achieved for fleas in the PP population (85 dogs for fluralaner and 47 dogs for the positive control, instead of 140 vs 60 (as a result of the exclusion of cases from France)). Due to the insufficient number of cases for fleas, non-inferiority could not be calculated at Visit 10. The fluralaner group was however statistically significant non-inferior compared to the positive control at all other visits. Also, during all assessments, the percentage of dogs free of ticks and/or fleas was above 95% after IVP treatment.

In terms of efficacy, the overall conclusions of the study can therefore be accepted: The study supported that the IVP is efficacious against natural infestations with fleas (*C. felis*) and/or ticks (*I. ricinus, D. reticulatus, R. sanguineus complex* and *I. hexagonus*) for up to 12 months.

In addition to the pivotal clinical trial, the applicant presented two small, supportive, clinical trials that were both performed in Australia. Both studies were GCP compliant, non-blinded, and single armed (no untreated control group was included). Though no justification for the absence of a control were provided, these studies can be considered supportive for the claimed efficacy of the product, considering both studies demonstrated a very high levels of efficacy (99-100%) in treatment and control of flea infestations.

As the studies were performed in Australia, the situation is not considered fully representative for the field situation in Europe. However, considering the lack of protein sequence differences in fluralaner interactions sites between EU and AUS isolates of *C. felis*, as well as the demonstrated high similarity in fluralaner susceptibility of these two isolates in both *in vitro* and *in vivo*, it is acknowledged that the outcome supports efficacy of the product against fleas and FAD.

Both supportive trials had a similar objective: To confirm the clinical efficacy of the product against fleas (*Ctenocephalides* spp.) for up to 12 months under field conditions. Secondary objectives were safety assessment of the product. In addition, a pruritus visual analogue scale (PVAS) was used to record pruritus. Owners were asked to rate (number between 0 and 10) the primary dog's pruritus (itching) in the week prior to each visit indicating their evaluation of the dog's pruritus in the past week. Efficacy (recorded as the percentage reduction in arithmetic and geometric scores) was determined as a reduction in mean PVAS scores over the duration of the study.

To be included, at least one dog in the household had to be presented with a live flea count of ≥ 6, and be at least 6 months of age. All dogs within a household were assessed for flea infestation, and

the dog with the highest flea count was enrolled as the primary dog (whilst additional dogs within the household were enrolled as secondary dogs).

The study schedule involved 9 planned visits (Visit 1: SD0, Visit 2: SD30, Visit 3: SD60; up until Visit 10: SD365) to veterinary clinics over a period of 365 days. Also, each month the owners completed a monthly review form.

The IVP was considered effective if all post-treatment flea count assessments demonstrated mean live flea count reductions of 95% or greater as compared to pre-treatment SD0 count, and the mean counts at these timepoints were statistically significantly different and lower than SD0 count.

A second study ultimately included a total of 33 households. The final, per protocol data set consisted of the flea counts and pruritus scores from the 18 primary dogs. In addition, 6 secondary dogs were included. Male/female ratio was evenly distributed between these animals.

Efficacy based on arithmetic mean flea counts was 99.8% (SD30) and 100% (all other days). Also, the arithmetic means for all post-treatment flea counts were lower and significantly different to the arithmetic mean of the pre-treatment SD0 flea counts (p-values < 0.001). Noteworthy was that a significant deviation occurred which resulted in 14 primary dogs and 1 secondary dog receiving a fluralaner dose lower than the intended 15 mg/kg (due to dilution of the product). According to the full dataset, treatment in these animals also resulted in 100% effectiveness, further supporting a high level of efficacy.

A statistically significant reduction in pruritus score of at least 80% on SD30 and 87% on SD60 was demonstrated. The reductions reached at least 90% on SD120 and remained between 83% and 94% from SD120 to SD365. The reductions in pruritus scores were statistically significant and, based upon Owner comments during the study, also considered clinically significant.

In terms of efficacy, the study conclusion is therefore supported; a single subcutaneous administration of the IVP was effective to treat and control natural infestations of fleas (*Ctenocephalides* spp.) for 12 months with efficacy levels of 99.8 - 100%.

A third study ultimately included a total of 29 households. The final, per protocol data set consisted of the flea counts and pruritus scores from the 29 primary dogs. In addition, 22 secondary dogs were included. Male/female ratio was evenly distributed between these animals.

Efficacy based on arithmetic mean flea counts was 99.7% (SD30); and 99.4-100% (all other days). Also, the arithmetic means for all post-treatment flea counts were lower and significantly different to the arithmetic mean of the pre-treatment SD0 flea counts (p-values < 0.001).

A statistically significant reduction in pruritus score of at least 75% on SD30 and 80% on SD60 was demonstrated. The reductions in pruritis scores remained between 88% and 95% from SD120-365. The reductions in pruritus scores were statistically significant and, based upon owner comments during the study, also considered clinically significant.

In terms of efficacy, study conclusion is therefore supported; a single subcutaneous administration of the IVP was effective to treat and control natural infestations of fleas (*Ctenocephalides* spp.) for 12 months with efficacy levels of 99.4 - 100%.

Overall conclusion of the presented clinical trials is that Fluralaner 150 mg/ml powder and solvent for suspension for injection, when dosed at the proposed dose of 15mg fluralaner per kilogram bw. (administered as a subcutaneous injection), is efficacious against natural infestations with fleas (*C. felis*) and/or ticks (*I. ricinus, D. reticulatus, R. sanguineus complex* and *I. hexagonus*).

Flea Allergic Dermatitis (FAD)

The presence of Flea Allergic Dermatitis (FAD) at inclusion was assessed by the veterinarians at SD0. At inclusion, a total of 27 primary dogs presented skin lesions with a possible relation to FAD (IVP: 18 dogs, CP: 9 dogs). In the IVP treated primary dogs, FAD related skin lesions resolved to normal at Day 14 in 10 dogs (55.6%), Day 28 in 6 dogs (33.3%) and at Day 56 in 1 dog (5.6%). It can therefore be accepted that the product is also suitable to control FAD for up to 365 days.

Mange mites (Demodex canis; Sarcoptes scabiei var. canis)

No clinical data is submitted in support of the proposed indications for mites. The applicant therefore ultimately decided to withdraw this indication.

Overall conclusions on efficacy

Pharmacology

Pharmacodynamics

The active substance of Bravecto, fluralaner, is a member of the antiparasitic compound class of isoxazoline-substituted derivatives. Fluralaner is a potent inhibitor of parts of the arthropod nervous system by acting antagonistically on ligand-gated chloride channels (GABA-receptor and glutamate-receptor).

Fluralaner is an ectoparasitic substance with killing activity against fleas, mites and ticks. The applicant makes reference to the dossier / studies and previous assessment of the CVMP in the context of the initial product application (EMEA/V/C/002526) and the conclusions drawn regarding the pharmacodynamics of fluralaner. The change in pharmaceutical form is not expected to influence on the pharmacodynamic particulars of the active substance fluralaner.

The mode of action has been sufficiently described.

Pharmacokinetics

The pharmacodynamic and pharmacokinetic characteristics of fluralaner are generally well documented and have been satisfactorily evaluated in the dog.

The new formulation is systemically absorbed from the injection site. Median T_{max} of 37 days (T_{max} ranked from 30 and 72 days). Mean C_{max}: 775 ng/ml (±179 ng/ml). Fluralaner is highly bound to plasma proteins of the dog (approximately 100%). Plasma concentrations were quantifiable in all animals, and exposure was generally similar between males and females. Exposure generally increased in an approximately dose proportional manner.

After reaching C_{max}, fluralaner concentrations slowly declined, with a mean fluralaner half-life of 130 days (range 92 to 170 days). Mean $AUC_{0\text{-}inf}$ of 158.000 days*ng/ml (±31.400 days*ng/ml).

Mean concentration values for fluralaner were still measurable in all animals fluralaner 450 days after treatment. As was demonstrated during the initial product application of the chewable tablet (EMEA/V/C/002526), unchanged parent fluralaner was found primarily in faeces (approx. 90% of the dose), and this appears to be the main route of elimination. Renal excretion appeared to be a minor route of excretion.

Slight accumulation was observed between the first and the second dose. Maximum fluralaner concentrations were observed over a range from 29 to 85 days following the first and second doses. Five completed 4-month dosing intervals were sufficient to reach steady-state fluralaner exposure.

Development of resistance and related risks to animals

The risk of resistance development seems low. Also, the frequency of application is low (annually), and the efficacy of fluralaner against the claimed ectoparasites in the dog is high.

To date, no ectoparasitic resistance against fluralaner has been reported among the target tick and flea species listed.

Dose determination and confirmation

The proposed dose was justified based on a dose determination study and confirmed in eight dose confirmation studies performed under experimental conditions. In the dose determination study, efficacy of three different fluralaner doses (10-, 15- or 20 mg/kg bw.) against repetitive infestations with *R. sanguineus ticks* (and against a single infestation with *C. felis* fleas was assessed. Efficacy of the selected dose of 15 mg fluralaner per kg bw., the dose that was considered safe and effective, was confirmed in a minimum of two dose confirmation studies for each major ectoparasitic species.

Separate studies assessed the onset of efficacy, defined as the initial time needed to achieve killing of at least 90% of ticks and 95% of fleas already present on the animal before treatment administration, and the speed of kill, defined as the time needed to achieve killing of at least 90% of ticks and 95% of fleas after the initial onset of efficacy and over the whole 12-month duration of efficacy.

Efficacy was not adequately justified or demonstrated against mange mites, and only *in vitro* efficacy was demonstrated against the non-autochthonous tick species *H. marginatum*. These indications were therefore withdrawn by the applicant.

Tolerance in the target animal species

The applicant presented a GCP-compliant pivotal target animal safety study. The overall conclusion was that the product is safe when used as recommended. However, injection site abnormalities in terms of (non-painful) swellings at the injection site can be commonly expected.

The results from the pivotal TAS study were mostly reflected in the pre-clinical and clinical studies, where the main adverse reactions reported were (non-painful) swellings at the injection site, most often nodules. A possible association between administration of the product and neurological signs, seizures/convulsions and tremors could not be excluded. Given that neurological signs, seizures/convulsions and tremors are known adverse effects for fluralaner, these were included as adverse events for the current injectable product.

The SPC and product information contain adequate warnings about the observed adverse effects and their frequency.

Clinical trials

In support of this variation, the applicant presented three clinical trials (field studies) (one pivotal, two supportive (non-pivotal) trials) against ticks and fleas, as well as one study investigating flea allergy dermatitis. No clinical data were provided for other claims made (mites, vector-borne pathogens).

Overall conclusion of these clinical trials is that Fluralaner 150 mg/ml powder and solvent for suspension for injection, when administered subcutaneously at the proposed dose of 15 mg fluralaner/kg bw (administered as a subcutaneous injection), is efficacious against natural infestations with fleas (*C. felis*) and/or ticks (*I. ricinus, D. reticulatus*, *R. sanguineus* complex and *I. hexagonus*).

Part 5 – Benefit-risk assessment

Introduction

Bravecto (fluralaner) is already authorised for use in cat and dog for the treatment of flea and tick infestations, as part of the treatment strategy for the control of flea allergy dermatitis (FAD), for the treatment of demodicosis and sarcoptic mange, for the reduction of risk of infection with *Babesia canis canis* and *Dipylidium caninum* via transmission by a vector, and for the treatment of infestations with *Otodectes cynotis* in cats only. Bravecto is currently authorised as chewable tablets and spot-on solutions of different strengths and is presented in packs containing 1 tablet, 2 tablets, 4 tablets, 1 pipette and 2 pipettes.

This variation adds a new pharmaceutical form - a 150 mg/ml powder and solvent for suspension for injection for dogs. This new pharmaceutical form introduces a new route of administration - subcutaneous. The indications for the new pharmaceutical form are already approved for dogs in the chewable tablets and the spot-on solution. Bravecto powder and solvent for suspension for injection for dogs is presented in packs containing 1 vial of powder + 1 vial of solvent and 1 vent needle, 2 vials of powder + 2 vials of solvent and 2 vent needles, 5 vials of powder + 5 vials of solvent and 5 vent needles, and 10 vials of powder + 10 vials of solvent and 10 vent needles.

The application has been submitted in accordance with Article 62 of Regulation (EU) 2019/6.

Benefit assessment

Direct benefit

The benefit of Bravecto suspension for injection is its efficacy in immediate and persistent killing activity, as appropriate, for the treatment of tick and flea infestation in dogs for 12 months where an insecticide and/or acaricide activity is needed for a 12-months period. Efficacy was established in a large number of well-designed pre-clinical and clinical trials conducted to an acceptable standard and in accordance with GCP. It can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD). It also reduces the risk of infection with *Babesia canis canis* (via transmission by *D. reticulatus*) and infection with *Dipylidium caninum* (via transmission by *C. felis*) for up to 12 months.

The pre-clinical and clinical trials demonstrated that a dose of 0.1 ml of reconstituted suspension per kg body weight (equivalent to 15 mg fluralaner per kg body weight) is efficacious against *Ctenocephalides felis, Ctenocephalides canis*, *Ixodes ricinus, Ixodes hexagonus, Dermacentor reticulatus,* and *Rhipicephalus sanguineus* for 12 months.

Additional benefits

The new pharmaceutical form introduces a new route of administration - a subcutaneous injection. A new pharmaceutical form increases the range of available treatment possibilities against tick and flea infestations.

After one single administration, the product maintains persistent killing efficacy against ticks and fleas over a period of 12 months. Currently, there is no other veterinary medicinal product registered in the Union with single-dose year-round flea and tick-protection, and it is considered to reduce the risk to gaps in effectiveness due to a lack of treatment-interval compliance in situations

where an insecticide and/or acaricide activity is needed for a 12-month period.

The new pharmaceutical strength also facilitates a more accurate dosing compared to the already authorised presentations (tablet, spot-on). Dogs will be accurately dosed based on their actual body weight and not based on a weight band.

Furthermore, the total dose of fluralaner per kg bw per year for each dog is reduced. The fluralaner dose is 15 mg fluralaner per kg bw for a full 12 months of efficacy where an insecticide and/or acaricide activity is needed for a 12-months period. The dose of fluralaner per kg bw and the frequency of treatment is thereby lower than the dose for the existing Bravecto products (25 – 56 mg fluralaner/kg bodyweight within one weight band for 12-week efficacy), which is considered beneficial with a view on user safety, environmental safety and target animal safety.

Risk assessment

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety

Risks for the target animal

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

Risk for the user

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Based on the user safety assessment, the product does not pose an unacceptable risk to the user, a professional, when used in accordance with the SPC. The warning sentences proposed by the applicant are considered adequate.

It is noted that, due to its formulation, this product remains in the body for a prolonged period after accidental exposure. This may give concern when considering the risk, which is hypersensitivity reactions. However, the user is a professional, aware of the risks of certain veterinary medicinal products and expected to be aware of the user safety warnings of the candidate product. The injectable formulation is to be administered by a veterinarian (or under their close supervision).

Risk for the environment

Bravecto 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.

Resistance

The risk of resistance development seems low. Also, the frequency of application is low (annually), and the efficacy of fluralaner against the claimed ectoparasites in the dog is high.

To date, no ectoparasitic resistance against fluralaner has been reported among the target tick and flea species listed.

Risk management or mitigation measures

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

User safety

User safety risks have been identified, concerning risks associated with hypersensitivity reactions or injection site reactions. These risks are mitigated by warnings in the SPC.

Environmental safety

The product is not expected to pose a risk for the environment when used according to the SPC.

Resistance

Prudent use advice as recommended in the Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products (EMA/CVMP/EWP/170208/2005-Rev.1) was included in the SPC (Section 3.4), as appropriate.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product is subject to a veterinary prescription.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indications for the proposed new pharmaceutical form:

This veterinary medicinal product is a systemic insecticide and acaricide that provides:

- *immediate and persistent flea (Ctenocephalides felis and Ctenocephalides canis) killing activity for 12 months*
- *persistent tick (Ixodes ricinus, Ixodes hexagonus, and Dermacentor reticulatus) killing activity from day 3 after treatment for 12 months*
- *persistent tick (Rhipicephalus sanguineus, Hyalomma marginatum) killing activity from day 4 after treatment for 12 months.*

The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

For the treatment of demodicosis caused by Demodex canis.

For the treatment of sarcoptic mange (Sarcoptes scabiei var. canis) infestation.

For reduction of the risk of infection with Babesia canis canis via transmission by Dermacentor reticulatus from day 3 after treatment for up to 12 months. The effect is indirect due to the veterinary medicinal product's activity against the vector

For reduction of the risk of infection with Dipylidium caninum via transmission by Ctenocephalides felis for up to 12 months. The effect is indirect due to the veterinary medicinal product's activity against the vector.

The product has been shown to be efficacious for the treatment of flea and tick infestations in dogs (except for *H. marginatum*), as well as for reduction of the risk of infection with *Babesia canis canis* and *Dipylidium caninum*. The CVMP agreed to the following indications:

For the treatment of tick and flea infestations in dogs.

This veterinary medicinal product is a systemic insecticide and acaricide that provides:

- *immediate and persistent flea (Ctenocephalides felis and Ctenocephalides canis) killing activity for 12 months,*
- *persistent tick killing activity from day 3 to 12 months after treatment for Ixodes ricinus, Ixodes hexagonus, and Dermacentor reticulatus,*
- *persistent tick killing activity from day 4 to 12 months after treatment for Rhipicephalus sanguineus.*

Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance.

The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

For reduction of the risk of infection with Babesia canis canis via transmission by Dermacentor reticulatus from day 3 after treatment for up to 12 months. The effect is indirect due to the veterinary medicinal product's activity against the vector.

For reduction of the risk of infection with Dipylidium caninum via transmission by Ctenocephalides felis for up to 12 months. The effect is indirect due to the veterinary medicinal product's activity against the vector.

During the assessment, the applicant withdrew the indications for persistent tick killing activity for *Hyalomma marginatum*, for the treatment of demodicosis caused by *Demodex canis* and for the treatment of sarcoptic mange (*Sarcoptes scabiei* var. *canis*) infestations.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It 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.

Based on the data presented to date, the overall benefit-risk balance for the product is considered positive.

Evaluation of the scientific criteria of Article 40(5) of Regulation (EU) 2019/6

This application involves a change to the pharmaceutical form (i.e. it adds a new pharmaceutical form, 150 mg/ml powder and solvent for suspension for injection, for dogs, to the already existing marketing authorisation). The applicant has demonstrated an improvement of the benefit-risk balance of the veterinary medicinal product in accordance with Article 40(5)(b) of Regulation (EU) 2019/6.

The new pharmaceutical form will consequentially introduce a new route of administration - a subcutaneous injection.

After one single administration, the product maintains persistent killing efficacy against ticks and fleas over a period of 12 months, and this is considered to reduce the risk in gaps in effectiveness due to a potential lack of treatment-interval owner compliance in situations where an insecticide and/or acaricide activity is needed for a 12-months period.

The new pharmaceutical form also facilitates more accurate dosing. Dogs will be accurately dosed based on their actual body weight and not based on a weight band, as for the already authorised Bravecto tablets and spot-on.

When considering the user safety, the injectable formulation is to be administered by a veterinarian (or under their supervision) and therefore the risks of owner and child exposure, consequent to administration of the tablet or spot-on formulations in the home, is eliminated. Furthermore, in comparison to the spot-on formulation, for the injectable formulation, there will be no residues on the skin due to stroking of the animal. Overall, this new formulation is considered to be of benefit to user safety.

A reduction of the total dose of fluralaner per kg bw per year for each dog is noted: the fluralaner dose is 15 mg fluralaner per kg bw for a full 12 months of efficacy. As such, while the current Bravecto range doses are 25-56 mg/kg bw within one weight band for a 12-week efficacy, the new pharmaceutical form has demonstrated efficacy with 15 mg kg/bw for a full 12-month period. The dose of fluralaner per kg bw and the frequency of treatment is thereby markedly lower than the dose for the existing Bravecto products. Treatment with a lower dose is considered to reduce the risks as regards to environmental safety, as excretion to the environment is lowered, which is considered a benefit.

With regards to target animal safety, the adverse events for the Bravecto tablets include '*Mild and transient gastrointestinal effects such as diarrhoea, vomiting, inappetence, and drooling'*. These gastro-intestinal adverse events, that are known to occur commonly, are considered primarily the result of the oral formulation. These adverse events were not observed with this new injectable formulation (though a decreased appetite has been uncommonly observed in the dossier). As such, this is considered a benefit for target animal safety, in comparison to the oral formulation.

Considering the common local adverse events that are known to occur both for this injectable formulation as well as the spot-on formulation (i.e. '*injection site swelling*' after treatment with the injectable formulation, and '*mild and transient skin reactions such as erythema or alopecia at the application site'* after treatment with the spot-on product), it should be noted that the frequency of occurrence of these adverse events will be much less in case of the new formulation, as treatment is administered only once a year versus every three months for both the tablet, as well as the spot-on formulation, in case continuous treatment throughout the year is needed. This is also considered a benefit in terms of the new formulation, in comparison to the spot-on formulation.

Currently, no resistance against fluralaner has been reported. Therefore, the applicant's argumentation that the product will counteract the development of resistance cannot be assessed and is not accepted.

Conclusions

Based on the review of data on the safety and efficacy supporting the variation to the terms of the marketing authorisation of Bravecto to add a new pharmaceutical form, 150 mg/ml powder and solvent for suspension for injection, for dogs, and taking into account the justifications provided by the applicant, the CVMP considers that the addition of this pharmaceutical form, and its associated route of administration, to the product Bravecto has resulted in an improvement of the benefit-risk balance of the veterinary medicinal product due to reduction of risk in the areas of treatment compliance, user safety, environmental safety and target animal safety that is not counterbalanced by any increased risks posed by the new pharmaceutical form in situations where an insecticide and/or acaricide activity is needed for a 12-months period.

Appropriate wording is included in the Product Information.

Conclusion

Based on the original and complementary data presented the Committee for Veterinary Medicinal Products (CVMP) considers that the application for a variation to the terms of the marketing authorisation for Bravecto is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) No 2019/6), as follows: to add a new pharmaceutical form, 150 mg/ml powder and solvent for suspension for injection, for dogs.

The CVMP considers that the benefit-risk balance remains positive and, therefore, recommended the approval of the variation to the marketing authorisation for the above mentioned veterinary medicinal product.

With regard to Article 40(5), this variation meets the scientific criterion, because the applicant has demonstrated an improvement of the benefit-risk balance of the veterinary medicinal product (criterion (b) of Article 40(5)).