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Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Fluralaner Intervet (EMEA/V/C/006356/0000)

INN: Fluralaner

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

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Introduction

The applicant Intervet International B.V. submitted on 29 September 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Fluralaner Intervet, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 16 May 2023 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

At the time of submission, the applicant applied for the following indications:

This veterinary medicinal product is a systemic insecticide and acaricide that provides:
- immediate and persistent flea (Ctenocephalides canis and C. felis) killing activity for 1 month,
- immediate and persistent tick (Dermacentor reticulatus, Ixodes hexagonus, I. ricinus and Rhipicephalus sanguineus) killing activity for 1 month.

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 D. reticulatus for 1 month. The effect is indirect due to the product's activity against the vector.*

For reduction of the risk of infection *with Dipylidium caninum via transmission by C. felis for 1 month. The effect is indirect due to the product's* activity *against the vector.*

The active substance of Fluralaner Intervet is fluralaner, an ectoparasiticide belonging to the isoxazoline group, with inhibitory activity on GABA- and glutamate-gated chloride channel located in nervous system of invertebrates, preventing the postsynaptic uptake of chloride ions by GABA- and glutamate-gated ion channels and thus resulting in depolarization, paralysis and death of the target parasite. The target species is dogs.

Fluralaner Intervet chewable tablets is presented in 5 different strengths containing 45 mg, 100 mg, 200 mg, 400 mg and 560 mg of fluralaner. Each strength will be available in packs containing 1, 2, 3 or 6 chewable tablets.

The rapporteur appointed is Ricardo Carapeto García and the co-rapporteur is Marcin Glanda.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 15 May 2025, the CVMP adopted an opinion and CVMP assessment report.

On 27 June 2025, the European Commission adopted a Commission Decision granting the marketing authorisation for Fluralaner Intervet.

Scientific advice

The applicant received scientific advice from the CVMP. The scientific advice pertained to the efficacy (clinical development) of the dossier, and will be addressed below.

The applicant generally adhered to the scientific advice received.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a 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) with reference number PSMF5527014338, 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

Fluralaner

Manufacture and quality control testing of the active substance fluralaner and its intermediate take place outside the EEA. A GMP declaration for the active substance manufacturing sites involved was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an onsite audit by the MIAH or a corporate representative of the MIAH.

Finished product

Batch release of the finished product takes place at Intervet GesmbH, Vienna, AT. The site has a manufacturing authorisation issued on 3rd June 2022 by the competent authority of Austria. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for activity indicated above, has been provided.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file was 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.

Part 2 - Quality

Composition

The finished product is presented as a chewable tablet containing fluralaner as active substance (5.46%w/w) and pork liver flavour, sucrose, maize starch, sodium lauryl sulfate, disodium pamoate monohydrate, magnesium stearate, aspartam, glycerol, soya-bean oil and macrogol 3350 as excipients.

Five different strengths are proposed (45 mg, 100 mg, 200 mg, 400 mg and 560 mg) to cover a dog body weight range between 2 kg and 56 kg.

Containers and closure system

The tablets are packaged on a 5-ply aluminium blister sealed with PET aluminium foil lid stock.

The blisters are packed into a carton box with 1, 2, 3 or 6 tablets.

Adequate specifications have been proposed for packaging materials, and certificates of analysis demonstrating compliance with these specifications have been provided.

Product development

The pharmaceutical development report submitted is based on the authorised product Bravecto which contains 13.64% of fluralaner. The components of this product and its manufacturing process are essentially the same. Additionally, the Marketing Authorisation holder and the manufacturer responsible for the batch release of Bravecto are the same as the ones proposed in this application.

Therefore, the development strategy for Fluralaner Intervet was to leverage Bravecto formulation and manufacturing experience. This section includes appropriate information about its composition, which is the same as in Bravecto, except for minor differences in the ratios of some excipients and in the active substance concentration.

Appropriate criteria to avoid potential dosing mistakes among different strengths have been established and the description of the pharmaceutical form appropriately justified.

All the studies conducted during the formulation and the manufacturing process development are appropriately described, as well as the proposed container closure system and stability preliminary studies.

This section also includes a dissolution development report for smaller and for the larger tablets.

Description of the manufacturing method

The manufacturing process is the same as for Bravecto and consists of the preparation of a mass which enables the manufacture of chewable tablets. All the tablet sizes are formed from identical bulk mass.

The description of the manufacturing process and the IPCs established are considered adequate. Appropriate information regarding equipment working capacity and process parameters has also been provided.

The manufacturing process is considered a standard process and its validation has been performed satisfactorily.

Control of starting materials

Active substance

Information on the control of starting materials has been provided. Fluralaner is a non-compendial active substance. The supporting data for the active substance is provided in the form of an ASMF. The version of the ASMF supplied with this application has already been approved in relation to Bravecto.

Excipients

The excipients included in Fluralaner Intervet are the same as in Bravecto.

The excipients sucrose, maize starch, sodium lauryl sulfate, magnesium stearate, aspartame, soya-bean oil and macrogol 3350 are well known excipients controlled in accordance with their respective Ph. Eur. monographs.

Regarding non-pharmacopoeial excipients (pork liver flavour and disodium pamoate monohydrate), appropriate information has been provided.

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

A valid TSE declaration from the manufacturer of the finished product confirming compliance with the Ph. Eur. monograph and the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev. 3) has been provided.

An adequate viral safety evaluation in accordance with Ph. Eur. has been submitted for the excipient pork liver flavour.

Control tests on the finished product

Finished product specifications for release and shelf life include the following tests: appearance, identification, assay of fluralaner, degradation products, uniformity of dosage units, water content, texture analysis, dissolution assay and microbial quality.

The finished product specifications control those parameters appropriately for the dosage form and are in accordance with the Ph. Eur. monograph "Tablets" and with the Guideline VICH Topic GL39 Guideline on test procedures and acceptance criteria for new veterinary drug substances and new medicinal products. All of them are adequate for this pharmaceutical form.

The analytical methods have been appropriately described and validated in line with VICH GL1 and VICH GL2.

Batch data for the validation batches has been provided. All results are within the specifications as proposed for release and are comparable between batches.

An adequate characterization of the potential impurities that may be present has been provided, as well as a detailed Elemental Impurities Risk Assessment.

Stability

Compliance with the Note for Guidance on Start of Shelf-life of the Finished Dosage Form (EMEA/CVMP/453/01) has been confirmed by the finished product manufacturer.

Two stability studies according to VICH conditions applying a bracketing design have been provided:

- Pivotal study: it covers a 36 month period (at 30ºC/65% RH) and 12 month period (at 40ºC/75% RH).
- Stability study performed on validation batches. This study covers 24 months at 30ºC/65% and 12 months at 40ºC/75% RH.

Shelf-life specifications have been tested in these studies and no significant changes have been observed in any of them.

No changes have been observed in the photostability study and temperature cycling and temperature excursion studies have been also included with satisfactory results.

Overall conclusions on quality

The finished product is presented as a chewable tablet containing fluralaner as active substance (5.46%w/w) and pork liver flavour, sucrose, maize starch, sodium lauryl sulfate, disodium pamoate monohydrate, magnesium stearate, aspartam, glycerol, soya-bean oil and macrogol 3350 as excipients. Five different strengths are proposed (45 mg, 100 mg, 200 mg, 400 mg and 560 mg).

The tablets are packaged on a 5-ply aluminium blister which are sealed with an aluminium lidding foil. Its composition has been well described. The blisters are packed into a carton box with 1, 2, 3 or 6 tablets.

Information on the development, manufacture and control of the active substance and the 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.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way.

Part 3 – Safety documentation (Safety and residues tests)

Fluralaner is an ectoparasiticide of the isoxazoline class which acts as an antagonist on ligand-gated chloride channels (gamma-aminobutyric acid [GABA]-receptor and glutamate-receptor). Fluralaner is currently used in veterinary medicinal products as an insecticidal and acaricidal treatment in both companion and food-producing animals.

A full safety file in accordance with Article 8 of Regulation (EU) 2019/6 was provided.

Most of the toxicity studies included in this application had already been submitted and assessed by the CVMP either during the marketing authorization applications for the companion animal products 'Bravecto chewable tablets for dogs' and 'Bravecto spot-on solution for dogs/cats', or during the application for the establishment of Maximum Residue Limits (MRL) for fluralaner in chickens (i.e. EMEA/V/C/002526, EMEA/V/C/2526/X/0005 or EMEA/V/MRL/004380/FULL/0001).

Safety tests

Pharmacology

The pharmacological properties of the active substance fluralaner have already been assessed by the CVMP in applications for other fluralaner-containing products. The current evaluation supports the conclusions of the previous assessments. See also part 4.

The general pharmacodynamic and pharmacokinetic information proposed for sections 4.2 and 4.3 of the SPC is appropriate.

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 laying hens). The current evaluation supports the conclusions of the previous assessments. Only the conclusions are summarised below.

Single-dose toxicity

Summary on single-dose toxicity

From an acute oral dose toxicity study in rats, it was concluded that that an LD_{50} of > 2000 mg/kg bw for fluralaner can be derived for this study. From an acute dermal dose toxicity study in rats, an LD_{50} of > 2000 mg/kg bw for fluralaner can be derived. Based on these data, it is concluded that the substance has low acute toxic potential.

Repeat-dose toxicity

Summary on repeat-dose toxicity

Repeated dose toxicity was extensively studied in rats (including studies with durations of 14, 28 and 90 days; oral or dermal exposure) and dogs (28 and 90 days, and 52 weeks; oral exposure). 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 are considered adverse.

From the subacute oral dose toxicity studies in rats (14 days, 28 days), a NOAEL of 60 mg/kg bw/day can be derived . From the subacute oral dose toxicity studies in dogs (28 days), a LOAEL of 20 mg/kg bw/day is set as effects are observed at all dose levels.

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

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

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

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

Tolerance in the target species

Target animal tolerance is based on a pivotal target animal safety (TAS) study, supported by other pre-clinical studies and pharmacovigilance data from countries in which Fluralaner Intervet is already authorized, along with relevant information from published literature. It is considered that the scope of the data provided is appropriate and the fundamental safety study in the target species shows adequate tolerance to Fluralaner Intervet in the most sensitive category (puppies). There are no concerns regarding animal safety tolerance. See also part 4.

Reproductive toxicity, including developmental toxicity

Summary on study of the effect on reproduction

The potential systemic effects of fluralaner in reproduction were investigated in two pivotal one- and two-generation studies in rats.

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

For the pivotal two-generation reproduction study in rats, a LOAEL of 8 mg/kg bw/day is set for parental toxicity. The reproduction NOEL is set at 50 mg/kg bw/day based on post-implantation, post-natal and breeding loss at the higher dose. The pup NOEL is 50 mg/kg bw/day based on reduced body weight, clinical signs, pathological findings, and delayed physical and sexual development.

Study of developmental toxicity

The potential toxicological effects of fluralaner on pregnant females and embryo-foetal development were investigated via oral exposure in one pivotal study in rats, and two pivotal studies in rabbits as well as in one pivotal prenatal development dermal study in rabbits.

For the pivotal developmental (oral) toxicity study in rat, the NOEL for maternal and foetal toxicity is set at 100 mg/kg bw/day.

For the pivotal developmental (oral) toxicity study in rabbit, the NOAEL for maternal toxicity is set at 50 mg/kg bw/day based on reduction on food consumption and increased post-implantation loss. For the 2nd developmental (oral) toxicity study in rabbit the developmental toxicity NOAEL is set at 10 mg/kg bw/day based on the increase in fusions in cervical vertebra 2 at 25 mg/kg bw/day.

Additionally, a dermal development study was performed in rabbit. The NOAEL is set at 100 mg/kg bw/day based on foetal malformations at the higher dose.

Genotoxicity

The potential mutagenic effects of fluralaner was 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. It is 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. It is 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´.

Skin irritation

A dermal irritation study using the active substance was performed in rabbits. The test item did not elicit any skin reactions at the application site of any animal at any of the observation time points (all scores 0). Based upon this study, fluralaner is considered to be non-irritating to the skin.

Eye Irritation

An eye irritation study using the active substance was performed in rabbits. Slight reddening of both the conjunctiva and the sclera and slight ocular discharge were observed in all three animals at the 1-hour observation. These effects were reversible and were no longer evident 24 hours after treatment and may be due to the mechanical effect when administering a fine dust. No other effects were observed. Based upon this study, fluralaner is considered to be non-irritating to the eye.

Skin Sensitisation

A skin sensitisation test using the active substance was performed in guinea pigs.

During challenge, the skin on the flank of test animals was exposed to 25% fluralaner (highest non-irritant concentration) in aqueous polysorbate 80 (0.1% (v/v)) or vehicle alone during 24 hours under an occlusive dressing. After challenge, no effects were noted in all control animals. Slight erythema (score 1) was observed in 4 out of 10 fluralaner-exposed test animals at 24 hours after removal of the dressing (i.e., 48 hours after start of challenge), however these effects were no longer evident at 48 hours after removal of dressing (i.e., 72 hours after start of challenge). Moreover, the effects were not observed at 24 or 48 hours after re-challenge (25% fluralaner, same test group, opposite flank), which would have been expected if the effects observed at 24 hours had been the result of sensitising properties of fluralaner. Therefore, the effects observed after the first challenge at 24 hours are considered to be non-specific.

Based upon this study, it can be concluded that fluralaner is non-sensitising.

In vitro skin penetration studies

Two in vitro skin penetration studies were provided. It can be concluded 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%).

Observations in humans

Fluralaner has been developed exclusively for veterinary use. No study data are available on health effects of fluralaner in humans. Isoxazoline antiparasitics 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 for these veterinary medicinal products has therefore been updated with the user safety

warning 'Hypersensitivity reactions in humans have been reported'. This hazard has been included in the product information of Fluralaner Intervet.

Development of resistance and related risk in humans

Not applicable.

Excipients

The applicant has provided information on the common use and safety profile of the individual excipients in the final formulation of Fluralaner Intervet. Most of the excipients of Fluralaner Intervet are not expected to cause any systemic effects and are not of toxicological concern. However, macrogol 3350, soya bean oil, aspartame, sodium lauryl sulfate, and disodium pamoate, may produce hypersensitivity reactions, as well as adverse local effects including local irritation and skin reactions. However, since dust generation (potentially resulting in eye irritation) and prolonged user contact (potentially resulting in skin irritation and sensitization) with components of Fluralaner Intervet are not expected at application based on the product properties (i.e., tablets which are not subdivided), local adverse effects for users by contact with this solid product are deemed unlikely. Therefore, it can be concluded that the toxicity of Fluralaner Intervet will be determined by its active substance.

User safety

The applicant presented a user safety risk assessment which was conducted in accordance with CVMP guideline (EMEA/CVMP/543/03-Rev.1).

Fluralaner Intervet chewable tablets for dogs will be supplied in an aluminium foil blister(s) sealed with PET aluminium foil lid stock; pack sizes will contain 1, 2, 3 or 6 tablets per blister card. The maximum strength tablet contains 560 mg fluralaner. The product is to be administered up to once monthly. The main potential routes of exposure are considered to be dermal contact by adult users (owners/professionals) during administration of Fluralaner Intervet to dogs and accidental oral ingestion by children.

Adults can become dermally exposed every time they administer the tablets, moreover dog owners and veterinarians may treat more than one dog per day, resulting in additional dermal exposure. The user would be exposed to 0.1% w/w of fluralaner content during administration. Considering the worst case where the higher strength of Fluralaner Intervet is used to treat two animals, the user would be exposed to 0.56 x 2 mg active substance via dermal contact (0.01867 mg/kg bw/day) assuming and adult body weight of 60 kg. The estimated MOE, taking into account the dermal NOAEL of 50 mg/kg bw/day, is higher than 100.

It is considered that the greatest risk would be accidental ingestion of the largest tablet by a child (560 mg fluralaner). The calculated exposure caused by accidental intake of a large size tablet by a 12.5 kg child is 44.8 mg/kg bw/day. Considering the oral NOAEL of 10 mg/kg bw/day, the estimated MOE for oral exposure in child is less than 100 (0.22) and appropriate risk control options are required. The risk will be mitigated, in part, by the primary packaging which, as demonstrated by the applicant, is child resistant in accordance with ISO 14375:2018, as well as by the inclusion of appropriate warnings and safety measures on the product information.

Section 3.5 of the SPC has been updated to reflect on the risk of hypersensitivity as well as to follow ABCD format.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005 -Rev.1- Corr.1). The environmental risk assessment can stop in Phase I and no Phase II assessment is required because Fluralaner Intervet will only be used in non-food producing species.

Overall conclusions on the safety documentation: safety tests

Fluralaner Intervet chewable tables for dogs contains fluralaner as active substance, an ectoparasiticide of the isoxazoline class which acts as an antagonist on ligand-gated chloride channels (gamma-aminobutyric acid [GABA]-receptor and glutamate-receptor). Fluralaner is currently used in veterinary medicine as an insecticidal and acaricidal treatment in companion and food-producing animals.

A full safety file in accordance with Article 8 of Regulation (EU) 2019/6 has been provided.

Pharmacology:

The CVMP had previously assessed and concluded on the pharmacological particulars of fluralaner; the same conclusions are retained for this application. Pharmacodynamics and pharmacokinetics are addressed in Part 4. The general pharmacological information proposed for section 4 of the SPC is considered appropriate.

Toxicology:

The main toxicological findings can be summarised as follows:

- The acute oral and dermal LD_{50} for fluralaner in rats was estimated to be >2000 mg/kg in rats.
- The potential systemic effects following sub-chronic and chronic exposure (oral and dermal) have been comprehensively investigated in the rat. The studies conducted meet with requirements (GLP and relevant OECD guidelines). The liver appears to be the most sensitive organ for effects (increased organ weight, hepato-cellular fatty change, effects in related blood parameters). These effects were observed at dose levels above 20 mg/kg in the oral studies and above 100 mg/kg in the dermal studies. Sub-chronic and chronic (up to 52 weeks) effects following oral exposure in dogs were also comprehensively investigated. Reductions in cholesterol, phospholipids and triglycerides were consistently observed, although no histopathological changes of the liver were reported. It can be concluded that the dog is more sensitive to the effects of fluralaner than the rat and that systemic exposure of fluralaner is greater in dogs than in rats.
- The oral NOAEL for maternal toxicity and NOEL for embryo/foetal development are determined to be 10 mg/kg bw/day, as derived from the rabbit developmental toxicity study. In the developmental toxicity study the oral NOEL for maternal and foetal organisms in rats is set at 100 mg/kg bw/day.
- Studies on carcinogenicity were not conducted for fluralaner. This is justified by the negative results in all genotoxicity tests and the absence of any pre-neoplastic lesions in the multiple repeat-dose studies, conducted up to chronic duration and at a wide range of dose levels.
- Fluralaner was non-irritating in an ocular irritation study and non-irritating in a dermal irritation study. It is not considered a sensitiser based on results of a maximization test conducted in albino guinea pigs. However, hypersensitivity reactions to fluralaner have been reported in periodic safety

assessments for a similar product (i.e., 'Bravecto chewable tablets') and this is adequately captured in the product information. No effects on the nervous system have been reported for fluralaner in the toxicity tests provided.

The data presented are considered adequate to characterise the toxicity profile of the active substance.

User safety:

A user safety assessment in line with the relevant guidance document was presented. The potential health risk of the product to adult users is considered low and acceptable when used in accordance with the SPC. The worst-case scenario for user safety is the ingestion of a tablet by a child, with an estimated margin of exposure (MOE) of 0.22. The risk identified will, in part, be mitigated by the inclusion of appropriate safety advice/warning statements in the SPC and package leaflet, as well as by the child resistant packaging. The SPC has been updated to adapt the risk management measures to the ABCD format and reflect on the risk of hypersensitivity reactions.

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

Fluralaner Intervet is a chewable tablet containing fluralaner as active substance. Fluralaner is an acaricide and insecticide belonging to the isoxazoline group. It is efficacious against ticks (*Dermacentor reticulatus*, *Ixodes hexagonus, I. ricinus* and *Rhipicephalus sanguineus*) and fleas (*Ctenocephalides canis* and *C. felis*) on the dog.

The proposed dose is 10 – 22.5 mg/kg of fluralaner, and the product may be administered as frequently as one treatment per month, year-round.

The dossier submitted in support of efficacy contains both proprietary studies and references to published literature. Many of the studies provided were previously assessed by the CVMP in the context of the marketing authorisation application for 'Bravecto chewable tablets for dogs'.

Pharmacology

Pharmacodynamics

Fluralaner is a well-known isoxazoline ectoparasiticide for systemic use. It acts as a potent inhibitor of parts of the arthropod nervous system, by antagonistically acting on its ligand-gated chloride channels (GABA-receptor and glutamate-receptor).

Several studies were provided investigating the mode of action of fluralaner. One study investigated if the activity on ticks and fleas is exerted by contact or via feeding, two studies investigated its action on immature stages of ticks and fleas and another one compared its action on *C. felis* versus *C. canis*. Two additional studies and one publication focused on its activity on the relevant receptors (Ozoe et al., 2010).

Additionally, susceptibility to fluralaner of tick isolates from different geographic regions were compared: Two studies compared *R. sanguineus* isolates from the EU and the United States (US) on a molecular and functional level. One study compared the GABA-receptor binding sites of *H. longicornis* isolates from the US and Australia (AU). Further studies compared fluralaner's activity on *C. felis* isolates from the US, AU and EU.

Furthermore, an in vitro study compared the acaricidal activity of fluralaner against three tick species (*A. americanum*, *R. sanguineus* and *H. marginatum*).

Based on the data provided, the CVMP can conclude that:

- Fluralaner has a high potency against ticks and fleas by exposure via immersion (although this is not the predominant in vivo route of exposure).
- Adult ticks were identified to be the least susceptible tick stage.
- Fluralaner had an impact on the inhibition of reproduction calculated from flea mortality and control of oviposition, pupae and flea emergence.
- Fluralaner demonstrated very similar potency in unfed adult fleas of *C. felis* and *C. canis*.
- Laboratory clinical data using strains of United States (US) and Australian (AU) origin are considered representative of the EU.
- Clinical laboratory data collected for *R. sanguineus* in the US is considered as representative for the EU.

Generally, pharmacodynamics is adequately described in section 4.2 of the SPC.

Pharmacokinetics

The applicant provided information on the pharmacokinetic properties of Fluralaner Intervet to describe the absorption, distribution, metabolism and elimination of the active substance fluralaner by summarising and comparing the most relevant pharmacokinetic data generated in the studies submitted.

The applicant conducted three pharmacokinetic pilot studies (non-GLP) to determine the blood plasma profile after single oral (PO) administration: PK study 1, PK study 2 and PK study 3. While the study phase of these studies was not conducted in accordance with Good Laboratory Practice (GLP) regulations, it was conducted according to local regulations and Test Site standard operating procedures (SOPs), which is acceptable. Fluralaner treated groups were administered with the final formulation (manufactured under GMP in the studies 2 and 3) at a target dose of 10 mg/kg bw. Certificates of analysis for the active substance, the study protocols and statistical analysis were provided.

In addition, a pivotal margin-of-safety study and a pivotal repeat-dose pharmacokinetic study were conducted with Fluralaner Intervet to demonstrate the safety of monthly administrations during the entire year, i.e., to investigate accumulation and achievement of steady state.

In the pivotal repeat-dose pharmacokinetic study, dogs were dosed at 3-times the maximum recommended clinical dose of 67.5 mg fluralaner/kg bw on 4 occasions thirty days apart, and in the pivotal target animal safety study, Fluralaner Intervet was administered orally at 22.5, 67.5 and 112.5 mg fluralaner/kg bw, corresponding to 1X, 3X, and 5X the maximum recommended clinical dose.

The mean accumulation ratios indicated that steady state upon monthly consecutive administrations of Fluralaner Intervet is achieved by the 2nd treatment interval (puppies) or between the 2nd and 3rd

treatment interval (adults), following administration of multipes of the maximum recommended clinical dose (up to 5X for puppies and 3X for adults).

The CVMP agrees that inclusion criteria, randomisation and methodology is adequate to the studies objectives. Blood sampling points were frequent enough to characterise the PK profile until day 30 (720 hrs). Quantitative determination of fluralaner was performed by HPLC-MS/MS in canine plasma and pharmacokinetic (PK) parameters calculated by Non-Compartmental Analysis (NCA) using Phoenix WinNonlin.

The bioanalytical methods used were either adequately validated according to current guidelines (pivotal and efficacy studies) or sufficiently qualified (pilot studies). According to the results, the following conclusions about the pharmacokinetic profile of fluralaner in the veterinary product are retained:

- Absorption: Following oral administration, fluralaner was readily and rapidly systemically absorbed, reaching individual maximum concentrations in plasma between a few hours and 3 days after administration.
- Distribution: Noting that non-interaction of fluralaner and another active substance was demonstrated (see below) and that the same minimum recommended fluralaner dose was used, data generated for a new fixed combination (IVMP1) was utilized for determination of fluralaner distribution. Considering the total body water (approximately 0.6 L/kg) of a dog, fluralaner distributed well into tissues. This is not unexpected based on the physicochemical properties of fluralaner with a molecular weight of 556.29 g/mol, a unionized state, and a high logPow value of 5.35. The mean apparent volume of distribution (Vz) was 2040 and 1400 mL/kg in males and females, respectively. These data are largely consistent with published data on fluralaner.
- Metabolism: No quantifiable phase I or II metabolite concentrations were analysed in faeces of dogs. In vitro, fluralaner was metabolically stable in all species tested (mouse, rat, dog, and cat).
- Elimination: Fluralaner concentrations declined slowly in plasma, with quantifiable concentrations until the last sampling time points in each study (30 – 52 days after treatment). Fluralaner had a long mean elimination half-life, being indicative of a low systemic clearance. The major route of excretion of fluralaner is via faeces (~90%) and, to a lesser extent, via the renal route.

Some of the studies mentioned above were not conducted with Fluralaner Intervet but with a new fixed combination (IVMP1) that is a combination of fluralaner and another active substance. To support bridging of efficacy information between IVMP1 and Fluralaner Intervet, non-interaction on pharmacokinetics between the active substances fluralaner and the additional active substance contained in IVMP1 was demonstrated. To justify this lack of interaction, the applicant provided a pivotal PK study. A lack of interaction between both active substances was concluded. The CVMP agrees that bearing in mind the mode of action of both active substances, along with the results of the main PK parameters when fluralaner is administered solely or in combination do not provide evidence for the presence of interaction. The justification for the observed discrepancies, an overall high inter-individual variability, is indeed considered the most likely cause for discrepancies observed.

Generally, pharmacokinetics are adequately described in section 4.3 of the SPC.

Development of resistance and related risks in animals

The applicant is not aware of any resistance reports, and states that no information about any resistance mechanism is currently known. A bibliographical review has been provided in order to support this conclusion.

The applicant included some references (French-Constant et al., 1993; Bass et al., 2004) to show the resistance mechanism to dieldrin, its relevance and the frequency of this mutation in fleas. The efficacy of fluralaner is not affected by this resistance mechanism. The review also included bibliographical references about the in vitro efficacy of fluralaner against some tick isolates resistant to common antiparasitic substances. Efficacy was demonstrated and fluralaner was not affected by the resistance to phenyl pyrazole (PPY), fipronil (Miller et al., 2012), dieldrin (CD), chlorpyrophos (OP), flumethrin (PY) and cypermethrin (AD), fluazuron (BZU), propoxur (CM), phoxim (OP) and deltamethrin (PY), and emamectin benzoate (EB). In addition, the applicant carried out a further search on peer-reviewed literature related to the possible emergenge of resistance to fluralaner, and no resistance emergence was found.

A list of the studies in which the efficacy of fluralaner was tested against known arthropod resistances to one or more chemical classes of ectoparasiticides applied in the field has been provided. Fluralaner showed efficacy against these isolates. Finally, the applicant has summarised the laboratory studies conducted in different countries. All parasite isolates used in laboratory studies originated from the field and multiplied in vivo in the laboratory, as recommended 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 (EMEA/CVMP/EWP/005/2000-Rev.4). Fluralaner demonstrated efficacy for the tick and flea isolates in all these studies. It is noted that only one study was conducted in Europe which makes the comparability among studies difficult with regards sensitivity of the different isolates.

In conclusion, the information included in section 4.2 of SPC regarding the mechanism of action of the active substance is consistent to that submitted with the references.

Dose determination and confirmation

Dose justification

In order to determine the oral fluralaner dose required for an intended one-month treatment interval for fleas and ticks, three studies were conducted with fluralaner doses ranging from 2.5 to 10.0 mg fluralaner/kg bw against adult stages of *A. americanum*.

The EU prevalent tick species *D. reticulatus* was chosen for the EU-specific dose determination study.

Dose determination studies

The proposed dose of 10 mg/kg once a month for Fluralaner Intervet was established based on the findings of three dose determination studies. These studies were conducted using the same methodology. The objective of these studies was to determine the effectiveness and pharmacokinetics of three different oral doses of fluralaner administered to dogs infested weekly with *Amblyomma americanum* ticks and evaluated over a 37/38 days study period following a single treatment.

It is noteworthy that these studies were conducted with the tick species *A. americanum* using isolates from the US. However, the applicant has adequately justified the use of this tick species. The studies were conducted in accordance with the VICH GL9 Good Clinical Practice (GCP).

The study design regarding sample size, masking, frequency of infestations, inclusion criteria, methodology and frequency of counting and the calculation methods is appropriate and in line with the relevant CVMP guideline (EMEA/CVMP/EWP/5/2000-Rev.4). The endpoint for the 'control claim' was

live tick counts whereas the endpoint for the 'treatment claim' was dead tick counts. Differences in counts between control and treated dogs were analysed using Abbot´s formula.

Study 1: Three different doses (2.5, 5.0 and 7.5 mg fluralaner/kg bw) were assessed. There were no abnormal health observations after treatment administration. Treatment generally resulted in a ≥ 90% reduction in live tick counts using arithmetic means as compared to the control group. Nevertheless, at the lower dose groups (2.5 and 5 mg/kg bw), efficacy rates lower than 90% were observed from day 23 onwards. At the 7.5 mg/kg bw dose, efficacy over 90% was observed on day 30 and 37, although on day 23, 89.3% efficacy was measured. The live and dead tick counts for all three treated groups were significantly different from the control group (P values ≤0.001) on all count days (2, 9, 16, 23, 30, and 37).

Study 2: Three different doses (2.5, 5.0 and 7.5 mg fluralaner/kg bw) were assessed. There were no abnormal health observations after treatment administration. Treatment generally resulted in a ≥ 90% reduction in live tick counts using arithmetic means as compared to the control group. Nevertheless, at 2.5 mg/kg, efficacy higher than 90% was only achieved on day 2. At 5 mg/kg bw, the threshold of efficacy of 90% was achieved at all days except the last one (day 38). At 7.5 mg/kg bw, the threshold efficacy of 90% was achieved at all days except the last two (days 30 and 38). The dead tick counts for all three treated groups were significantly different from the control group (P values<0.001) on all count days (2, 9, 16, 23, 30 and 38).

Study 3: Three different doses (5.0, 7.5 and 10 mg fluralaner/kg bw) were assessed. There were no abnormal health observations after treatment administration. At 5 mg/kg bw, efficacy rates above 90% were achieved on days 3, 10, 17 and 24. At 10 mg/kg bw, efficacy rates over 90% were observed on all study dates. At 7.5 mg/kg bw, efficacy rates over 90% were observed for the 3, 10, 17, 24 and 38 count dates but not on day 31. The live tick counts for the three treated groups were significantly different from the control group (P values <0.0001) on all count days. The dead tick counts for the IVP treated groups were significantly different from the control groups (P values ≤0.0003) on all tick collection days. It is noted that in this study, tick counts were carried out 72 hours after infestations.

Out of these three dose determination studies, only one was conducted with the proposed 10 mg/kg bw dose. However, bearing in mind the results of these studies, and considering those reported for the dose confirmation (see below), the CVMP agrees that the selection of the dose is acceptable.

Dose confirmation (DC) studies

Dose confirmation studies in ticks

It is noted that studies conducted for 'Bravecto chewable tablets' for the target canine tick species in the EU, *R. sanguineus, D. reticulatus, I. ricinus* and *I. hexagonus*, had already shown that *R. sanguineus* is the dose limiting tick species. These studies were evaluated by CVMP during the registration and subsequent variation procedures for 'Bravecto chewable tablets for dogs' and/or 'Bravecto spot-on solution for dogs/cats'.

The applicant provided dose confirmation studies against ticks conducted with Fluralaner Intervet and with a new fixed combination (IVMP1) . Data of adequate quality and comparability has been presented to support that there is no interaction between fluralaner the additional active substance in the IVMP1 with respect to pharmacokinetics or efficacy. Efficacy data obtained for IVMP1 is considered representative and supportive for Fluralaner Intervet; the pharmacokinetic profile of fluralaner in the new fixed combination IVMP1 was shown to be comparable that of fluralaner administered alone or in combination with the additional active substance in the new fixed combination IVMP1. Part of these

data was discussed in a scientific advice procedure and has been supplemented with other available data, as requested in the scientific advice report.

All the DC studies submitted that used the final formulation of Fluralaner Intervet were conducted in accordance to GCP requirements. The conduct and evaluation of the studies complied with current quality standards: A minimum of two DC studies for the dose-limiting tick species *R. sanguineus* (as well as for *C. felis* fleas, see below under DC studies for fleas) were provided. Additionally, one speed-of-kill study with *D. reticulatus* was provided.

Dose confirmation laboratory data have been obtained against *R. sanguineus* in two studies. The objective of these studies was to demonstrate that Fluralaner Intervet is effective in dogs against infestations of *R. sanguineus* for at least one month following treatment. Both studies shared the same design which is in accordance with the requirements stated in the CVMP guideline (EMEA/CVMP/EWP/005/2000-Rev.4). In one study, the administration of Fluralaner Intervet to dogs resulted in a >98% reduction ($P < 0.0001$) in live *R. sanguineus* counts and an increase in dead tick counts ($P \leq 0.0013$) compared to the control group on Days 2 through 51. In the second study administration of Fluralaner Intervet resulted in a >99% reduction ($P < 0.0001$) in live *R. sanguineus* counts and an increase in dead tick counts ($P \leq 0.0002$) compared to the control group on Days 2 through 51. Treatment with Fluralaner Intervet resulted in an increase ($P \leq 0.0002$) in dead tick counts as compared to the control group on all count days.

The applicant provided four dose confirmation studies conducted for Fluralaner Intervet against ticks. These studies were generally well designed and conducted. The results of these studies support the efficacy of Fluralaner Intervet against the tick species *R. sanguineus*. The CVMP already concluded that *R. sanguineus* is the dose limiting tick species, therefore these conclusions can be extrapolated to the following tick species relevant for the EU: *Dermacentor reticulatus*, *Ixodes hexagonus* and *Ixodes ricinus*.

In addition to these studies, the applicant has provided six studies conducted with the new fixed combination product IVMP1. Despite the differences of every study, the overall results support the immediate and persistent efficacy of Fluralaner Intervet, in accordance with the requirements set in the relevant CVMP guideline (EMEA/CVMP/EWP/005/2000-Rev.4).

In those instances which involved studies performed in the USA, the study protocols in question were provided to, and approved by the CVM-FDA and IACUC of the relevant study facility. While this is accepted, for future applications, the 'General principles and requirements' for studies presented in support of applications for marketing authorisation should be applied as detailed in the Annex II to Regulation (EU) 2016/6, Section I.1.7: "All experiments in animals shall be conducted taking into account the principles laid down in Directive 2010/63/EU, notwithstanding the place of conduct of the experiments".

In addition, supportive dose confirmation laboratory data against *A. americanum*, *H. longicornis* and *I. holocyclus* have been provided that further prove the safe and efficacious use of Fluralaner Intervet in other tick species currently not prevalent in the EU. Since these tick species are not part of the proposed indications, these studies were not considered further.

Dose confirmation studies in fleas

The applicant conducted two studies to determine the onset of activity of Fluralaner Intervet against fleas (*Ctenocephalides felis*).

In the first study live flea counts for the treated groups were significantly different from their respective control groups, reaching 88.7% efficacy at 6 h ± 15 min ($p \leq 0.0003$) post-treatment. In contrast, 9.1%, 0.0% and 58.4% efficacy was observed at time points 1, 2 hours and 4 hours. The

result at 4 hours after treatment was invalidated and a new study was carried out. In this new study, 82.9% efficacy was observed at 4 hours after treatment.

In addition, a third study was conducted to determinate the speed to kill of Fluralaner Intervet. This is in line with the Guideline EMEA/CVMP/EWP/005/2000-Rev.4. The results from this study supports the intended indication of immediate killing activity for fleas for Fluralaner Intervet. According to Abbott's formula, percentages close to 100% were observed at both the 12 and 24 hour timepoints on all study days (i.e., 7, 14, 21, 28, 35, 42 and 49 days after of treatment), with P values <0.0001. These results demonstrate the speed of action and the duration of effect, and confirm the effectiveness of the dose of Fluralaner Intervet for the intended indication. In addition, the number of flea eggs collected from treated dogs was significantly reduced (P <0.0001). These data are consistent with the 100% reduction in live counts observed for this treatment group.

Furthermore, three studies that were conducted investigating both *C. felis* and *R. sanguineus*, also support the efficacy of the proposed dose of Fluralaner Intervet for the intended indication.

The applicant also indicated that the efficacy data obtained with the new fixed combination IVMP1 can be considered representative for Fluralaner Intervet. This approach has been previously confirmed by the CVMP. The dose confirmation studies conducted with the new fixed combination IVMP1 , and the results from studies carried out in the US, Brasil and AU can be considered to support the efficacy of Fluralaner Intervet against *C. felis*, with close to 100% efficacy observed at 12 hours post-infestation. All of these studies were conducted in line with the requirements set in the relevant CVMP guideline (EMEA/CVMP/EWP/005/ 2000-Rev.4).

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

Reduction of the risk of infection with *Dipylidium caninum* via transmission by *C. felis* for 1 month

The applicant submitted three laboratory studies for this intended indication. In addition, laboratory and field data obtained for the registered product 'Bravecto chewable tablets for dogs' were also provided.

These same studies have just been discussed in the dose confirmation section, supporting the indication of immediate flea killing activity. The CVMP agrees that the results from these studies also support the indication for the reduction of the risk of infection with *Dipylidium caninum* via transmission by *C. felis*.

Reduction of the risk of infection with *B. canis canis* via transmission by *D. reticulatus* for 1 month

The applicant provided a speed of kill dose determination study.

The study concluded that the optimal dose of fluralaner when combined with another active substance (new fixed combination IVMP1) was 10 mg fluralaner /kg bw, and its efficacy was confirmed for a thirty two-day period following treatment. The CVMP agrees with the study conclusions. The proposed approach to bridge efficacy data from studies conducted with the new fixed combination IVMP1 has been previously confirmed by the CVMP.

In summary, regarding the reduction of the risk of infection with *Babesia canis canis* and *Dipylidium caninum* the CVMP notes the following:

- pharmacodynamics of all fluralaner-containing products is identical;

- reduction of the risk for infection with *Babesia canis canis* and *Dipylidium caninum* has already been demonstrated by the applicant via proprietary study data for several fluralaner-containing veterinary medicinal products;
- the effect of fluralaner on these 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 adequate (within 12 hours for fleas and within 24 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 pathogens can therefore be accepted.

Tolerance in the target animal species

Tolerance in the target animal species is based on a pivotal target animal safety (TAS) study conducted with Fluralaner Intervet, supported by results from pre-clinical studies and pharmacovigilance data from countries in which Fluralaner Intervet is already authorised, along with relevant information from published scientific literature. These data are supported with the results from a pivotal target animal safety conducted with the new fixed combination IVMP1, together with results from three studies carried out in susceptible breeds with the MDR1-/- mutation, none of these three conducted with Fluralaner Intervet.

The pivotal target animal safety study fulfils the principles of the VICH GL 43. Thirty-two beagle puppies (16 males and 16 females), considered the most sensitive subpopulation, were allocated to four treatment dose groups, dosed at0, 22.5, 67.5, and 112.5 mg fluralaner/kg bw, corresponding to 0X, 1X, 3X and 5X the maximum recommended clinical dose (22.5 mg fluralaner/kg bw). Control animals received no fluralaner. The administration regimen (dose, frequency and duration) corresponded to the authorisation proposal. Dogs were administered monthly on three occasions. The study design is considered appropriate as this laboratory study was controlled, randomized and masked, and has been carried out according to GLP principles.

No local effects have been observed after oral administration. Neither were systemic adverse events observed (even in the 5X dose group), except for a generalised shivering of mild intensity in four dogs from different dose groups which was not related to Fluralaner Intervet. This information is correctly reflected in the SPC. There were no test item-related findings among the rest of the assessed parameters. In conclusion, the safety margin of Fluralaner Intervet in the target species is deemed acceptable.

In addition, the applicant provided the results of a target animal safety study conducted in Collie dogs sensitive to avermectin with the registered product `Bravecto chewable tablets´ which contains a fluralaner concentration of 13.64%. The design of this study is not in line with the recommendations of the aforementioned guideline, since only the 3X dose was used and administered once. The 3X dose of the registered veterinary medicine product used is equivalent to a 7.5X dose of Fluralaner Intervet, therefore, the results could be considered supportive of those for Fluralaner Intervet. No adverse reactions were observed in this study. It is concluded that the safety margin of Fluralaner Intervet in dogs sensitive to ivermectin is acceptable, since the active substance belongs to the isoxazoline family (also noting that Fluralaner Intervet does not contain macrocyclic lactones). However, repeated use was not tested and this is appropriately reflected in section 3.10 of the SPC.

A pivotal target animal safety study conducted with the new fixed combination IVMP1 was also submitted, which confirms the safety of the IVMP1 under repeated field use and further confirms the

results obtained with Fluralaner Intervet (fluralaner only). This was a controlled and masked laboratory study which enrolled thirty-two Beagle puppies and that followed the recommendations of the VICH GL 43 guideline. No treatment-related adverse effects were observed after oral IVMP1 administration of up to 100 mg fluralaner/kg bw and the additional active substance included. The steady state of fluralaner was reached after two or three treatments. These results are in line with the results obtained with Fluralaner Intervet in the pivotal target animal safety study. These data are considered supportive.

No safety studies were performed with Fluralaner Intervet in breeding, pregnant or lactating dogs. This is adequately reflected in the product information.

In conclusion, it is considered that the data provided is appropriate and that the pivotal safety study in the target species shows adequate tolerance to Fluralaner Intervet in the most sensitive subpopulation (puppies). There are no concerns regarding animal tolerance. The results of target animal safety studies have been adequately reflected in the product information.

Clinical trial(s)

Clinical trials with Fluralaner Intervet

The applicant provided a clinical trial conducted within the EU and several clinical trials conducted outside the EU, i.e., US, Brazil and Australia; however, their results are also considered representative for the EU.

A pivotal clinical trial studied the effectiveness of the final formulation of Fluralaner Intervet to treat and control natural infestations with cat fleas (*Ctenocephalides felis*) for at least 4 weeks (30 days) in client-owned dogs at multiple sites and under field conditions. The study design is multicentre, randomised and blinded and follows the VICH GL 9 of GCP and other applicable guidelines. A positive control product was used, which was an authorized veterinary medicinal product containing afoxolaner as the active substance (which belongs to the same isoxazoline family) and the same pharmaceutical form, chewable tablets, and route of administration, oral. A total of 112 households with 201 dogs were assigned to receive Fluralaner Intervet while 37 households with 70 dogs were assigned to receive the control product. The design and methodology of the study is considerate appropriate. An adequate infestation was noted according to the applicable guideline. Dosing tables were set up for 5 different weight bands, with possible doses ranging between 10 mg/kg bw and 22.5 mg/kg bw. A total of 3 doses were administered on Days 0, 30, and 60 at mealtimes, immediately before the dog was offered its food. Dosing was performed by the owner at home. The primary variable was the difference in live flea counts (collected from the primary dogs) on Days 30, 60, and 90 versus pre-treatment (visit 1). The household was the experimental unit with each household represented by one "primary dog".

A geometric mean live flea count was calculated for each timepoint across households using live flea counts from the primary dog. Furthermore, the % reduction at each timepoint was calculated, based on the comparison of the geometric mean live flea counts to baseline values. In the treatment group, flea count reductions in primary dogs based on geometric means at Days 30, 60, and 90 were 99.6%, 99.9%, and 99.9% respectively. These reductions were statistically significantly different from baseline values ($p<0.001$). Log transformed live flea counts {loge(x+1)} from each treatment group were analysed separately, at each post-treatment time point. A secondary efficacy evaluation to compare post-treatment results between study groups was carried out with a level of significance of $\alpha = 0.025$ and a non-inferiority margin of $\delta = 0.10$. The results showed that treatment with Fluralaner Intervet is

non-inferior to CP treatment at each post-treatment visit. Overall, demonstration of persistent killing activity is accepted. On the other hand, it is noted that immediate killing activity was not evaluated in this study but this indication was accepted based on the results of the dose confirmation studies (see above).

Secondary parameters assessed included evaluations of the species and number of ticks collected during the study, progression of signs of FAD, assessment of palatability, and assessment of safety. Regarding the evaluations of the species and number of ticks collected during the study, the data of this additional parameter were not sufficient to confirm the efficacy of Fluralaner Intervet in ticks. The indications against ticks were demonstrated based on the studies designed for this purpose (see below).

Regarding the progression of signs of FAD, the efficacy was measured by comparing the signs of FAD at day 90 post-treatment (visit 4) with those at baseline (visit 1), without comparison between the test group and the control group. In this period the animals had been treated 3 times (day 0, day 30 and day 60). Similar data were obtained with CP animals. The applicant provides the results of the comparison of the resolution of FAD signs in each animal. On day 90 (visit 4), resolution of the different clinical signs was reported in treated dogs. In addition, the summary of improvement was obtained by comparing the post-treatment V2, V3 and V4, FAD signs with that at the baseline (V1). The results demonstrated the non-inferiority of Fluralaner Intervet for visits 2 and 3, but not for visit 4. However, resolution of FAD signs was seen in most of the treated animals (91.5%). The indication that Fluralaner Intervet can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD) can thus be accepted.

Regarding the evaluation of palatability, the results showed that more than 80% of the doses were freely taken, most within a minute of being offered. An additional 9.0% were freely consumed with food or other treatment, while 9.5% required force feeding. This evaluation was carried out by the owner. Dogs were dosed on three separate occasions at monthly intervals with Fluralaner Intervet (or CP) by the owner at home. Fluralaner Intervet was offered for free choice uptake. Owners documented if the tablet was accepted within 1 minute of offering or between 1 and 5 minutes of offering. If the dog did not take the IVP dose by itself within 5 minutes, the owner was permitted to use additional means to make the dose more appealing. This included hiding the tablet(s) in other food or treats. Percentage palatability was calculated as: No of animals with a palatability score of 1/Total no. of animals in the study group x 100. A palatability score of 1 was defined by the applicant as 'voluntary uptake within 5 minutes'. Palatability information was recorded for 579 doses of Fluralaner Intervet administered. 73.7% of doses were taken voluntarily within 1 minute, 81.5% within 5 minutes. Palatability at 2 minutes was not assessed.

These results cannot be considered fully supportive of a palatability claim given that the requirements established in the guideline on the demonstration of palatability of veterinary medicinal products (EMA/CVMP/EWP/206024/2011-Rev.1), acceptance is defined as '*voluntary full consumption within the maximum offering time (e.g., two minutes)*' and data provided is only demonstrative of a consumption time of less than 2 minutes for 80% of the study population.

Regarding the safety of Fluralaner Intervet, more adverse events were observed in animals treated (70%) compared to control animals, but this is consistent with the higher sample size (112 animals in the treated group versus 37 in the CP group). Overall, the most common AEs appeared in similar percentages in both groups (treatment and control), and none were associated with Fluralaner Intervet. It is possible to conclude that Fluralaner Intervet has an acceptable safety profile.

Therefore, the CVMP concludes that efficacy and safety of Fluralaner Intervet was demonstrated under actual field conditions and that the overall study data provided supports the indications against fleas and FAD as proposed in the SPC.

Brazilian field studies *C. felis*

Given their similarities, both studies are discussed together. These two studies have not a multicentric, randomized, blinded or controlled design. The final composition of the product used remains unknown. Both have been carried out in two regions of Brazil, with the objective to evaluate the efficacy against *Ctenocephalides felis* fleas in naturally infested domiciled dogs treated only once, by the oral route. The design does not follow the recommendations of the applicable guidelines and the sample size is limited and is not supported by any statistical study. The product was administered at a single dose ranging between 10 to 22.5 mg/kg body weight orally. Statistical analysis was based on pre- and post-treatment flea counting. A mixed variance analysis model was used to assess pre- and post-treatment flea counting, considering days D-3 (pretreatment) and D2, D5, D9, D16, D23, D30, and D37 (post-treatment) as fixed effect, and the household as factor. The product's efficacy evaluation of the first study was equivalent to 100%, from Day 2 of the study to Day 37, when the last flea count was performed. In the second study, 99% efficacy was observed for the product two days after treatment, and 100% efficacy between D5 and D30. On day 37, the observed efficacy was 99.7%.

Despite the high efficacy percentages obtained, given the weak design and without knowing the complete composition of the veterinary medicinal product used, these results are not considered further.

Australian flea field studies

Given their similarities, both studies are discussed together. These two are non-blinded and single-arm field efficacy studies conducted according to the GCP standards to confirm the efficacy and safety of three consecutive monthly treatments with Fluralaner Intervet to control natural infestations of field flea strains on dogs under domestic conditions, carried out in two regions of Australia. In the first study, all 102 treatments attempted were successful, while in the second study only 35 animals completed the study (24 primary dogs and 11 secondary dogs). The schedule was similar in both studies, establishing visits 2, 3 and 4 at approximately 30, 60 and 90 days after treatment. An adequate infestation was established, in accordance with the applicable guideline. Efficacy was defined and calculated as the percentage reduction of arithmetic means of the post-treatment flea counts compared to pre-treatment flea counts at each time point. Flea count results from both studies were greater than 95%.

Given the limitations of the design, the conclusions of both studies are only considered as supportive data.

Brazilian field studies *R. sanguineus*

Both studies share the same design and are thus discussed together. These clinical studies were conducted in Brazil to evaluate the efficacy of Fluralaner Intervet, administered once orally, for the treatment and control of *Rhipicephalus sanguineus* ticks in naturally infested domiciled dogs. It is not clear if the Fluralaner Intervet's final formulation is the same as that of the candidate product. The study was conducted according to the VICH GL9 and applicable guidelines. Thirty-three dogs from the northern region of Brazil, naturally infested by at least 5 *Rhipicephalus sanguineus* ticks in each study, were enrolled. There was no control group. Countings were 2 pre-treatment and up to 7 post-treatment (until day 37). Efficacy was calculated using the mean values of counting of live ticks. The mean was calculated as the antilog [1/n to log (x+1)]-1 but since the efficacy rates were 100% from D+5, no influence in the results is expected. In both studies, efficacy rates greater than 90% were

found throughout the experimental period and significant statistical differences were observed between D+2 and D-3 ($p \leq 0.001$).

The CVMP concludes that whilst the results were satisfactory, taking into account the limitations of the study design, limited conclusions can be retained and the results only can be considered as supportive.

Clinical trials conducted with a new fixed combination (IVMP1)

In their scientific advice, the CVMP agreed that the data generated on efficacy against fleas and ticks in the European field trial conducted using the new fixed combination IVMP1 can be used in support of field efficacy for Fluralaner Intervet), provided that data of adequate quality and comparability was presented to support that there is no interaction between fluralaner and the additional active substance contained in the new fixed combination IVMP1 with respect to pharmacokinetics or efficacy. No interaction has been demonstrated. As requested in the scientific advice report, the applicant has provided additional available data in support of this assessment (see also above).

The applicant conducted one multicenter field efficacy study in the EU according to current quality standards (i.e., GCP) and the relevant CVMP guidelines. This pivotal field study was conducted to evaluate the efficacy and safety of two new fixed combinations containing fluralaner, IVMP1 and a second new fixed combination, IVMP2 whose results are not relevant for this application and limited details are provided below. The products were administered once orally against natural infestations with fleas (*C. felis*) and/or ticks (*I. ricinus*, *I. hexagonus*, *D. reticulatus*, *R. sanguineus* complex) for 1 month in client-owned dogs at multiple sites and under field conditions; IVMP1 was administered once orally at doses of 10 mg fluralaner and together with another active substance /kg bw. The field study was multicentre (including 47 veterinary practices in Germany, France, Portugal and Spain), positive-controlled, randomized and partially-blinded. The positive control group was treated with an authorised veterinary medicinal control product (CP) formulated as a chewable tablet for dogs containing sarolaner, moxidectin and pyrantel embonate.

All dogs in a household (maximum of 4 dogs) were enrolled into this study and assigned to the same treatment group. Three treatment groups were established (IVMP1, IVMP2 or CP). However, only one dog from each household (primary dog) was considered for the efficacy evaluations. This is in agreement with the relevant CVMP guideline (EMEA/CVMP/EWP/005/2000- Rev.4).

On SD 0, each dog was thoroughly examined by the examiner to determine the health and suitability for inclusion in the study, and for any potential FAD (Flea Allergy Dermatitis)-related skin lesion. All findings were documented. A total of three scheduled tick and flea counts were performed for each primary dog: on SD 0 (prior to treatment administration), SD 7±1 and SD 31±2. Tick and flea counts for the other dogs in the household were only performed on SD 0. Counts were undertaken at weekly intervals and the tick species identified. For the immediate efficacy assessment, conclusions were retained based on the data from dose confirmation studies.

Approximately 120 primary dogs in each treatment (IVMP) group and 60 primary dogs in the CP group were sufficient to demonstrate non-inferiority of the IVMP groups in comparison to the CP group with estimated efficacy rates (parasite free animals) of 95% in both IVMP and CP groups and a tolerated non-inferiority of $\delta=0.10$, when the (one-sided) level of significance is set to $\alpha=0.025$, with a power of $1-\beta=0.8$.

Of the 343 dogs in the per protocol (PP) population, 130 were included with ticks only, 200 were included with fleas only, and 13 dogs were included with both ticks and fleas at visit 1. The co-infestation rate was approximately 4%, which is considerably lower than the expected co-infestation rate of 25%. Primary efficacy was based upon the percentage of primary dogs free of live ticks and

free of live fleas (parasite free cases) at Visit 3 (SD 31). Based on arithmetic means, percentage reduction of ticks and fleas was also above 99% in both IVP groups at all post-treatment time points. Non-inferiority comparison was not possible for IVMP1 and CP (ticks) since no dogs with ticks were found in these groups. The results, however, suggest non-inferiority of the IVMP1 group.

For fleas, the IVMP1 group was significantly non-inferior to the CP group ($p<0.0001$), the lower 97.5% one-sided confidence limit was well above -0.10 (-0.0225). Forty-four dogs presented skin lesions with a possible relation to FAD (FAS population). No dogs from the FAS population were withdrawn from the study before completion of the animal phase. In the PDP population (all primary dogs), a total of 38 primary dogs presented skin lesions with a possible relation to FAD. All skin lesions in primary dogs (PDP) resolved to normal at V2 or V3. In the IVMP1 group, FAD related skin lesions resolved to normal at V2 (Day 7) in 6 dogs (42.9%) and at V3 (Day 31) in 8 dogs (57.1%). In the CP group, FAD related skin lesions resolved to normal at V2 (Day 7) in 3 dogs (37.5%) and at V3 (Day 31) in 5 dogs (62.5%). No statistical comparison was carried out.

In addition, palatability was assessed. Since the formulation used in this study differs from the final Fluralaner Intervet formulation in the flavouring agent (in Fluralaner Intervet there is Pork liver flavor whereas in IVMP1 another flavor is used) the results were not taken into account for the evaluation of the palatability claim in Fluralaner Intervet. It is noted that these differences have no influence on bioavailability.

Regarding the safety, thirteen adverse events were reported during the study. The SPC adequately reflects these adverse events.

Therefore, the CVMP concludes that efficacy and safety of the IVMP1 was demonstrated under actual field conditions and the study supports the indications as proposed in the SPC of Fluralaner Intervet.

Based on the totality of data provided (efficacy studies and various pharmacokinetic studies for both Fluralaner Intervet and the IVMP1), and that non-interaction between the active substances in the new fixed combination IVMP1 was demonstrated, it can be concluded that efficacy against fleas and ticks under field conditions for Fluralaner Intervet is demonstrated by using the European field trial conducted for the new fixed combination IVMP1.

Brazilian field studies *R. sanguineus*

The aim of these studies was to evaluate the efficacy of the new fixed combination IVMP1 against *Rhipicephalus sanguineus* ticks in naturally infested dogs in two regions of Brazil. Dogs were treated once by oral route. Each study enrolled thirty-two healthy dogs naturally infested with at least 5 adult *R. sanguineus* ticks, confirmed by counts on Days -2 and 0 (before treatment). No control group was included. Both studies share the same design in accordance with the principles of VICH GL9-GCP and WAAVP 2013 guideline for evaluating the efficacy of parasiticides for the treatment, prevention and control of flea and tick infestation on dogs and cats (Marchiondo et al., 2013). The results showed significant statistical differences between the average count before treatment and the means from every count after treatment. The efficacy were also over 90% based on the geometric means.

Taking into account the study design, limited conclusions can be retained and the results can only be considered as supportive.

Brazilian field studies *C. felis*

The objective of these two studies was to evaluate the efficacy of the new fixed combination IVMP1 administered orally against *C. felis* fleas on naturally infested dogs. Both studies share the same design in compliance to the principles of VICH GL9-GCP and WAAVP 2013 guideline. After treatment, additional flea counts were performed on Days 7, 14, 21 and 30 to evaluate the IVMP1's efficacy. Each

study enrolled thirty-two healthy dogs naturally infested with at least 5 *Ctenocephalides felis* fleas. All dogs belonged to the same treated group, and no control group was added. The target dose of 10 mg fluralaner and the additional active substance /kg bw for the IVMP1 was used for treatment. Treatment resulted in a 100% reduction in flea counts compared to pre-treatment on all evaluation days (Days 7, 14, 21 and 30).

Despite the high efficacy results, the weaknesses noted in the study design precludes retaining final conclusions.

Australian flea field studies

The primary objective of these field studies was to confirm the clinical efficacy of new fixed combination IVMP1 to treat and control natural infestations of fleas (*Ctenocephalides* spp.) when administered orally once a month to privately owned dogs living under Australian field conditions. The design of these studies was a non-masked, single arm (no untreated control group), Good Clinical Practice (GCP), field efficacy study initiated during the active flea breeding season. All enrolled dogs (primary and secondary) were treated with the IVMP1 on Days 0, 30 ± 3 and 60 ±3. The IVMP1 was administered orally to all household dogs so that they received at least the minimum dose rates of 10 mg fluralaner and the additional active substance /kg bw. Both studies showed efficacy rates over 99%, being statistically significant based on arithmetic and geometric means. It is noted that the secondary parameter of pruritus reduction was assessed based on owner observations.

The CVMP agrees that the results of these two studies were satisfactory. However, taking into account the limitations of the study design, limited conclusions can be retained and the results can only be considered supportive.

Cross-study assessment of adverse events

In the 33 clinical and preclinical studies conducted by the applicant, a total of 743 dogs were treated with Fluralaner Intervet at the recommended dose of 10 mg fluralaner/kg bw. Reported adverse events (AEs) were examined by the responsible investigators for a causal relationship to the administration of Fluralaner Intervet. The reported adverse events were filtered by the applicant for further evaluation and limited to those assessed as 'related', 'possible', 'probable', and 'unknown/ not known'. Based on this analysis, the potentially treatment-related adverse events included gastrointestinal signs, general signs or symptoms, lethargy and neurological symptoms. The product information adequately reflects these findings.

The applicant has also included an additional precaution measure in the SPC section '3.5 Special precautions for use for animals' concerning the use of the product in dogs with pre-existing epilepsy: 'Use with caution in dogs with pre-existing epilepsy.'

Overall conclusions on efficacy

Pharmacodynamics

The applicant has provided a comprehensive summary of the pharmacodynamics of fluralaner, based on original data and published literature. The main pharmacodynamic characteristics have been suitably described in the SPC. Fluralaner is an ectoparasitic substance with killing activity against fleas and ticks.

The mode of action has been sufficiently described from proprietary studies.

Pharmacokinetics

The pharmacokinetic characteristics of fluralaner are generally well documented and have been satisfactorily assessed in dogs. The CVMP considers the information in section 4.3 of the SPC to have been adequately supported by the data provided.

Development of resistance and related risks to animals

The applicant has presented a summary of current knowledge concerning development of resistance to the active substance fluralaner. Limited information concerning mechanism of resistance is available. The information in the product information is acceptable.

Dose determination and confirmation

The dose of 10 mg/kg was established based on a number of dose finding studies (range: 2.5 mg/kg - 10 mg/kg), and supported by dose confirmation studies performed under experimental conditions.

The results from several laboratory studies show that the product is effective for the proposed indications as a systemic insecticide and acaricide that provides:

- immediate flea (*Ctenocephalides canis* and *C. felis*) killing activity for 1 month.
- immediate tick (*Dermacentor reticulatus*, *Ixodes hexagonus*, *I. ricinus* and *Rhipicephalus sanguineus*) killing activity for 1 month.
- For reduction of the risk of infection with *Babesia canis canis* via transmission by *D. reticulatus* for 1 month. The effect is indirect due to the product's activity against the vector.
- For reduction of the risk of infection with *Dipylidium caninum* via transmission by *C. felis* for 1 month. The effect is indirect due to the product's activity against the vector.

Tolerance in the target animal species

In the TAS study, fluralaner was well-tolerated at doses up to 3X the recommended dose. Even at higher doses, no intolerance signs considered related to Fluralaner Intervet were noted in most animals. Adverse events collected through the pharmacovigilance systems of this product in other non-EU countries where it is already authorised have been included accordingly in the SPC.

Field studies confirmed that fluralaner was well-tolerated at the recommended dose of 10 mg/kg bw.

Clinical trials

The results from two clinical field trials show that the product is effective for the proposed indication: as a systemic insecticide and acaricide that provides

- persistent flea (*Ctenocephalides canis* and *C. felis*) killing activity for 1 month.
- persistent tick (*Dermacentor reticulatus*, *Ixodes hexagonus*, *I. ricinus* and *Rhipicephalus sanguineus*) killing activity for 1 month.

The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD) at the proposed dose of 10 mg/kg in dogs.

Part 5 – Benefit-risk assessment

Introduction

Fluralaner Intervet chewable tablets is a veterinary medicinal product containing fluralaner. The active substance is well-known.

Fluralaner is a systemically acting ectoparasiticide belonging to the isoxazoline family. The product is intended for use in dogs for immediate and persistent flea (*Ctenocephalides canis* and *C. felis*) and tick (*Dermacentor reticulatus*, *Ixodes hexagonus*, *I. ricinus* and *Rhipicephalus sanguineus*) killing activity, as part of a treatment strategy for the control of flea allergy dermatitis (FAD), and for reduction of the risk of infection with *Babesia canis canis* via transmission by *D. reticulatus* and of infection with *Dipylidium caninum* via transmission by *C. felis*. The proposed dose is 10 – 22.5 mg/kg of fluralaner, via oral route, at 1-month intervals based on professional advice.

The application has been submitted in accordance with Article 8 of Regulation (EU) 2019/6 (full application).

Benefit assessment

Direct benefit

The benefit of Fluralaner Intervet is its efficacy for the treatment of tick and flea infestations in dogs, which was investigated in a large number of well-designed laboratory and field studies conducted to an acceptable standard. The CVMP is of the opinion that the claimed efficacy against target parasites has been adequately supported.

Additional benefits

Fluralaner Intervet has a long-lasting effect of a month and is easy to apply by the owner. The product increases the range of available treatment possibilities against tick and flea infestations in dogs.

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

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

Risks for the target animal

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

Risk for the user

The most severe risk is accidental ingestion by a child. The product is intended to be marketed in child-resistant packages, and the product information includes a warning advising of the potential for adverse effects in case of accidental ingestion and specific instructions to remove tablets from the packaging only when required, and to store the product out of the sight and reach of children.

The user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

Risk for the environment

Fluralaner Intervet 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

With respect to antiparasitic resistance, there is no evidence that use of the product has resulted in reduced susceptibility of the target pathogen to fluralaner.

Appropriate warnings regarding prudent use of antiparasitic products are already included in the SPC.

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 and environment and to provide advice on how to prevent or reduce these risks.

User safety

User safety risks have been identified, mainly the risks associated with exposure via oral route in children. These risks have been addressed by the safety warnings in the SPC and the presentation of the product in child-resistant packaging.

Environmental safety

No specific risks for the environment have been identified.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

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 canis and C. felis) killing activity for 1 month,*
- *immediate and persistent tick (Dermacentor reticulatus, Ixodes hexagonus, I. ricinus and Rhipicephalus sanguineus) killing activity for 1 month.*

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 D. reticulatus for 1 month. The effect is indirect due to the product's activity against the vector.

For reduction of the risk of infection with Dipylidium caninum via transmission by C. felis for 1 month. The effect is indirect due to the product's activity against the vector.

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Fluralaner Intervet is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.