ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bravecto 150 mg/ml powder and solvent for suspension for injection for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder vial:

Active substance:
Fluralaner 2.51 g

White to pale yellow powder.

Solvent vial:

Each ml of solvent contains:

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl alcohol	22.3 mg
Carmellose sodium	
Poloxamer 124	
Disodium phosphate dihydrate	
Hydrochloric acid, concentrated	
Sodium hydroxide	
Water for injections	

Clear to opaque viscous solution.

Reconstituted suspension:

Each ml of reconstituted suspension contains:

Active substance:
Fluralaner 150 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl alcohol	20 mg
Carmellose sodium	

Poloxamer 124	
Disodium phosphate dihydrate	
Hydrochloric acid, concentrated	
Sodium hydroxide	
Water for injections	

3. CLINICAL INFORMATION

3.1 Target species

Dogs

3.2 Indications for use for each target species

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 3 days to 12 months after treatment for *Ixodes ricinus, Ixodes hexagonus,* and *Dermacentor reticulatus,*
- persistent tick killing activity from 4 days 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.

3.3 Contraindications

Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

Parasites need to start feeding on the host to become exposed to fluralaner; therefore, the risk of the transmission of parasite borne diseases (including *Babesia canis canis* and *D. caninum*) cannot be completely excluded.

Unnecessary use of antiparasitics, or use deviating from the instructions given, may increase the resistance selection pressure and lead to reduced efficacy. The decision to use the veterinary medicinal product should be based on confirmation of the parasitic species and burden, or of the risk

of infestation based on its epidemiological features (having regard to the duration of the effect of the product of 12 months), for each individual animal.

The possibility that other animals in the same household can be a source of re-infection with parasites should be considered, and these should be treated as necessary with an appropriate veterinary medicinal product.

3.5 Special precautions for use

Special precautions for safe use in the target species:
Safety of the product has not been assessed in dogs with pre-existing epilepsy. Therefore, use with caution in such dogs based on a benefit/risk assessment by the responsible veterinarian.
In the absence of available data, the veterinary medicinal product should not be used on dogs less than 6 months old.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
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.
This veterinary medicinal product is to be administered only by veterinarians or under their close supervision.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Dogs:

Common (1 to 10 animals / 100 animals treated)	Injection site swelling[1]
Uncommon (1 to 10 animals / 1,000 animals treated)	Decreased appetite Tiredness Hyperaemic mucous membranes
Very rare (<1 animal / 10 000 animals treated, including isolated reports)	Muscle tremor, Ataxia, Convulsion

[1]Palpable and/or visual swellings, non-inflammatory, non-painful, self-resolving over time

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
Use only according to the benefit-risk assessment by the responsible veterinarian.

3.8 Interaction with other medicinal products and other forms of interaction

Fluralaner is highly bound to plasma proteins and might compete with other highly bound active substances such as non-steroidal anti-inflammatory drugs (NSAIDs) and the coumarin derivative warfarin. Incubation of fluralaner in the presence of carprofen or warfarin in dog plasma at maximum expected plasma concentrations did not reduce the protein binding of fluralaner, carprofen or warfarin.
During clinical field testing, no interactions between the veterinary medicinal product and routinely used veterinary medicinal products were observed.

3.9 Administration routes and dosage

Subcutaneous use.

Administer 0.1 ml of reconstituted suspension per kg body weight (equivalent to 15 mg fluralaner per kg body weight) subcutaneously, e.g. between the shoulder blades (dorso-scapular region) of the dog.
The dog should be weighed at the time of dosing to calculate an accurate dose.
Underdosing could result in ineffective use and may favour development of resistance.

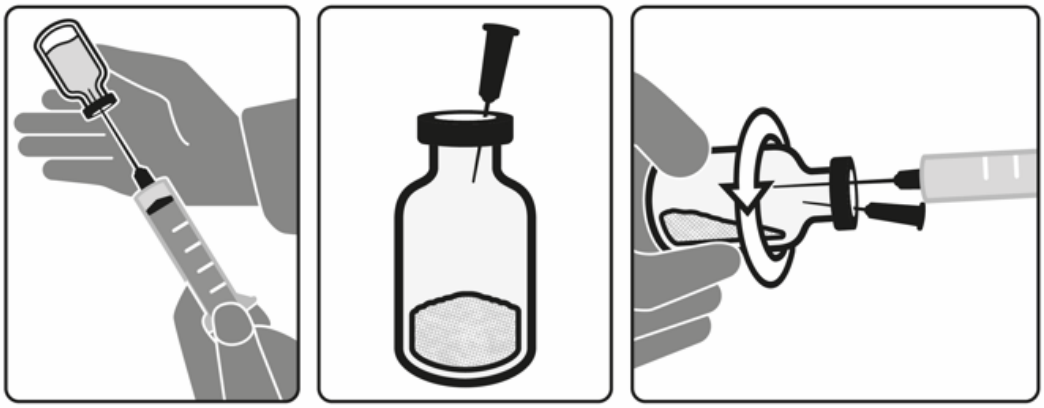
The following table may be used as a dosage guide:

Body weight (kg)	Volume of the reconstituted suspension (ml)
5	0.5
10	1
15	1.5
20	2
25	2.5
30	3
35	3.5
40	4
45	4.5
50	5
55	5.5
60	6

Calculate the dose accordingly for dogs weighing less than 5 kg or more than 60 kg.

Reconstitution of the suspension before first use:
Reconstitute 1 vial of powder with 15 ml of solvent. It is recommended to use an 18 G sterile transfer needle and a sterile 20 ml syringe for the reconstitution of the product.

1. Shake the fluralaner powder vial to break up any aggregates prior to reconstitution.
2. Invert the solvent vial at least 3 times until the content is visibly uniform.
3. First inject up to 14 ml of air into the solvent vial, then withdraw **15 ml** of the solvent from the vial (image A). **There is more solvent supplied in the vial than required for reconstitution.** Discard the vial with the rest of the solvent.
4. Insert the 25 G vent needle into the top of the fluralaner powder vial (image B).
5. **While rotating the vial horizontally in your hand,** slowly transfer the 15 ml of solvent into the fluralaner powder vial to ensure complete wetting of the powder (image C).



A B C

6. Once the solvent has been added, remove the vent needle and the transfer needle from the fluralaner powder vial. Discard the needles.
7. Shake the vial vigorously for at least 30 seconds until a thoroughly mixed suspension is formed. The reconstituted product is an opaque white to pale yellow slightly viscous suspension, practically free of aggregates.
8. The expiry date printed on the label of the glass vial refers to the powder as packaged for sale. After reconstitution, the suspension must be discarded within 3 months from the date of reconstitution. Write the discard date on the label of the glass vial.

Method of administration of the reconstituted suspension to the dog:

1. Determine the dose to be administered based on the dog's body weight.
2. Use a sterile syringe and a sterile 18 G needle for administration.
3. The fluralaner powder will separate out of suspension upon standing. Before every use, shake the reconstituted vial vigorously for 30 seconds to achieve a uniform suspension.
4. It may be necessary to inject air into the vial prior to dosing.
5. To maintain a uniform suspension and accurate dosing, the dose should be administered within approximately 5 minutes after drawing it into the dosing syringe.
6. Inject the product subcutaneously, e.g. in the dorso-scapular region.

Do not puncture the stopper of the vial containing the reconstituted suspension more than 20 times. For reconstitution after settling, shake the vial vigorously for at least 30 seconds to achieve a uniform suspension.

Treatment schedule

For infestations with fleas and ticks, the need for and frequency of re-treatment(s) should be based on professional advice and should take into account the local epidemiological situation and the animal's lifestyle. Treatment with this veterinary medicinal product may begin at any time of the year and can continue without interruption. See section 3.4.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Following the subcutaneous administration of 3 and 5 times the recommended dose of 15 mg fluralaner/kg body weight every 4 months for a total of 6 doses (Days 1, 120, 239, 358, 477 and 596) to 6 months old puppies, the only treatment-related finding was limited to injection site swellings that resolved over time.

The active substance fluralaner was well tolerated in Collies with a deficient multidrug-resistance-protein 1 (MDR1 -/-) following single oral administration at 3 times the maximum recommended dose (168 mg/kg body weight). Since the peak systemic exposure to fluralaner after subcutaneous

administration is not higher compared to oral administration, the subcutaneous injection of the veterinary medicinal product is considered safe in MDR1(-/-) dogs.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QP53BE02

4.2 Pharmacodynamics

Fluralaner is an acaricide and insecticide. It is efficacious against ticks (*Ixodes* spp., *Dermacentor* spp. and *Rhipicephalus sanguineus*) and fleas (*Ctenocephalides* spp.) on dogs.

Fluralaner reduces the risk of infection with *Babesia canis canis* via transmission by *Dermacentor reticulatus* by killing the ticks within 48 hours, before disease transmission occurs.

Fluralaner reduces the risk of infection with *Dipylidium caninum* via transmission by *Ctenocephalides felis* by killing the fleas before disease transmission occurs.

I. ricinus and *D. reticulatus* ticks already present on the dog prior to administration of the veterinary medicinal product are killed within 72 hours. *R. sanguineus* ticks already present on the dog prior to administration of the veterinary medicinal product are killed within 96 hours. Ticks newly infested are killed within 48 hours from one week through 12 months after treatment.

Fleas already present on the dog prior to administration of the veterinary medicinal product are killed within 48 hours. Fleas newly infested are killed within 24 hours from one week through 12 months after treatment.

Fluralaner has a high potency against ticks and fleas by exposure via feeding, i.e., it is systemically active on target parasites.

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).

In molecular on-target studies on insect GABA receptors of flea and fly, fluralaner is not affected by dieldrin resistance.

In *in vitro* bio-assays, fluralaner is not affected by proven field resistances against amidines (tick), organophosphates (tick, mite), cyclodienes (tick, flea, fly), macrocyclic lactones (sea lice), phenylpyrazoles (tick, flea), benzophenyl ureas (tick), pyrethroids (tick, mite) and carbamates (mite).

The veterinary medicinal product contributes towards the control of the environmental flea populations in areas to which treated dogs have access.

Newly emerged fleas on a dog are killed before viable eggs are produced. An *in vitro* study also demonstrated that very low concentrations of fluralaner stop the production of viable eggs by fleas. The flea life cycle is broken due to the rapid onset of action and long-lasting efficacy against adult fleas on the animal and the absence of viable egg production.

4.3 Pharmacokinetics

Fluralaner is systemically absorbed from the injection site, with median T_{max} observed on day 37 (range day 30 – day 72). The half-life in blood ranges from 92 to 170 days in 6 months old puppies. The 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.
Unchanged fluralaner is excreted in faeces and to a very low extent in urine.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years
Shelf life after reconstitution according to directions: 3 months

5.3 Special precautions for storage

This veterinary medicinal product as packaged for sale does not require any special temperature storage conditions.
After reconstitution, store below 30 °C.

5.4 Nature and composition of immediate packaging

Type I glass vials closed with bromobutyl rubber stoppers and sealed with aluminium flip-off caps.

Each cardboard box contains 1, 2, 5 or 10 sets of a fluralaner powder vial (2.51 g fluralaner), a solvent vial (16 ml solvent), and a sterile 25 G vent needle.
Not all pack-sizes may be marketed.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

The veterinary medicinal product should not enter water courses as fluralaner may be dangerous for aquatic invertebrates.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Intervet International B.V.

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/158/032-035

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD month YYYY}

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

{DD month YYYY}

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).