ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bravecto 112.5 mg chewable tablets for very small dogs (2-4.5 kg)
Bravecto 250 mg chewable tablets for small dogs (>4.5-10 kg)
Bravecto 500 mg chewable tablets for medium-sized dogs (>10-20 kg)
Bravecto 1000 mg chewable tablets for large dogs (>20-40 kg)
Bravecto 1400 mg chewable tablets for very large dogs (>40-56 kg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each chewable tablet contains:

Bravecto chewable tablets	**Fluralaner (mg)**
for very small dogs (2-4.5 kg)	112.5
for small dogs (>4.5-10 kg)	250
for medium-sized dogs (>10-20 kg)	500
for large dogs (>20-40 kg)	1,000
for very large dogs (>40-56 kg)	1,400

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Chewable tablet.
Light to dark brown tablet with a smooth or slightly rough surface and circular shape. Some marbling, speckles or both may be visible.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the 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*) killing activity for 12 weeks,
- immediate and persistent tick killing activity for 12 weeks for *Ixodes ricinus, Dermacentor reticulatus* and *D. variabilis,*
- immediate and persistent tick killing activity for 8 weeks for *Rhipicephalus sanguineus*.

Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. The onset of effect is within 8 hours of attachment for fleas (*C. felis*) and 12 hours of attachment for ticks (*I. ricinus*).

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

4.3 Contraindications

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

4.4 Special warnings for each target species Parasites need to start feeding on the host to become exposed to fluralaner; therefore the risk of the transmission of parasite borne diseases cannot be excluded.

4.5 Special precautions for use

Special precautions for use in animals

In the absence of available data, the veterinary medicinal product should not be used on puppies less than 8 weeks old and /or dogs weighing less than 2 kg.

The product should not be administered at intervals shorter than 8 weeks as the safety for shorter intervals has not been tested.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product.

Do not eat, drink or smoke while handling the product.

Wash hands thoroughly with soap and water immediately after use of the product.

4.6 Adverse reactions (frequency and seriousness)

Commonly observed adverse reactions in clinical trials (1.6% of treated dogs) were mild and transient gastrointestinal effects such as diarrhoea, vomiting, inappetence, and drooling.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product in breeding, pregnant and lactating dogs has been demonstrated. Can be used in breeding, pregnant and lactating dogs.

4.8 Interaction with other medicinal products and other forms of interaction

None known.
Fluralaner is highly bound to plasma proteins and might compete with other highly bound drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and the cumarin 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 Bravecto chewable tablets for dogs and routinely used veterinary medicinal products were observed.

4.9 Amounts to be administered and administration route

For oral use.

Bravecto should be administered in accordance with the following table (corresponding to a dose of 25–56 mg fluralaner/kg bodyweight within one weight band):

Bodyweight of dog (kg)	**Strength and number of tablets to be administered**				
	Bravecto 112.5 mg	Bravecto 250 mg	Bravecto 500 mg	Bravecto 1000 mg	Bravecto 1400 mg
2-4.5	1				
>4.5-10		1			
>10-20			1		
>20-40				1	
>40-56					1

The chewable tablets should not be broken or divided.
For dogs above 56 kg bodyweight, use a combination of two tablets that most closely matches the bodyweight.

Method of administration:
Administer Bravecto chewable tablets at or around the time of feeding.
Bravecto is a chewable tablet and is well accepted by most dogs. If the tablet is not taken up voluntarily by the dog it can also be given with food or directly into the mouth. The dog should be observed during administration to confirm that the tablet is swallowed.

Treatment schedule:
For optimal control of flea infestation, the veterinary medicinal product should be administered at intervals of 12 weeks. For optimal control of tick infestation, the timing of retreatment depends on the tick species. See section 4.2.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

No adverse reactions were observed following oral administration to puppies aged 8–9 weeks and weighing 2.0–3.6 kg treated with overdoses of up to 5 times the maximum recommended dose (56 mg, 168 mg and 280 mg fluralaner/kg bodyweight) on three occasions at shorter intervals than recommended (8-week intervals).

There were no findings on reproductive performance and no findings of concern on offspring viability when fluralaner was administered orally to Beagle dogs at overdoses of up to 3 times the maximum recommended dose (up to 168 mg/kg bodyweight of fluralaner).

The veterinary medicinal product was well tolerated in Collies with a deficient multidrug-resistance-protein 1 (MDR1 -/-) following single oral administration at 3 times the recommended dose (168 mg/kg bodyweight). No treatment-related clinical signs were observed.

4.11 Withdrawal period

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Ectoparasiticides for systemic use.

ATCvet code: QP53BX.

5.1 Pharmacodynamic properties

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

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 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.

5.2 Pharmacokinetic particulars

Following oral administration, fluralaner is readily absorbed reaching maximum plasma concentrations within 1 day. Food enhances the absorption. Fluralaner is systemically distributed and reaches the highest concentrations in fat, followed by liver, kidney and muscle. The prolonged persistence and slow elimination from plasma ($t_{1/2}$ = 12 days) and the lack of extensive metabolism provide effective concentrations of fluralaner for the duration of the inter-dosing interval. Individual variation in C_{max} and $t_{1/2}$ was observed. The major route of elimination is the excretion of unchanged fluralaner in faeces (~90% of the dose). Renal clearance is the minor route of elimination.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pork liver flavour
Sucrose
Maize starch
Sodium lauryl sulfate
Disodium embonate monohydrate
Magnesium stearate
Aspartame
Glycerol
Soya-bean oil
Macrogol 3350

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.

6.4. Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

6.5 Nature and composition of immediate packaging

Cardboard box with 1 aluminium foil blister sealed with paper/PET aluminium foil lid stock containing 1, 2 or 4 chewable tablets.
Not all pack sizes may be marketed.

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

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The NETHERLANDS

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/158

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD/MM/YYYY}

10 DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Intervet GesmbH
Siemensstrasse 107
1210 Vienna
AUSTRIA

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Cardboard box

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bravecto 112.5 mg chewable tablets for very small dogs (2-4.5 kg)
Bravecto 250 mg chewable tablets for small dogs (>4.5-10 kg)
Bravecto 500 mg chewable tablets for medium-sized dogs (>10-20 kg)
Bravecto 1000 mg chewable tablets for large dogs (>20-40 kg)
Bravecto 1400 mg chewable tablets for very large dogs (>40-56 kg)

Fluralaner

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

Fluralaner 112.5 mg
Fluralaner 250 mg
Fluralaner 500 mg
Fluralaner 1000 mg
Fluralaner 1400 mg

3. PHARMACEUTICAL FORM

Chewable tablet

4. PACKAGE SIZE

1 chewable tablet
2 chewable tablets
4 chewable tablets

5. TARGET SPECIES

Dog

6. INDICATION(S)

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

Not applicable.

9. SPECIAL WARNING(S), IF NECESSARY

10. EXPIRY DATE

EXP: {month/year}

11. SPECIAL STORAGE CONDITIONS

Read the package leaflet before use.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Read the package leaflet before use.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, if applicable

For animal treatment only. To be supplied only on veterinary prescription.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The NETHERLANDS

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/13/158/001
EU/2/13/158/002
EU/2/13/158/003
EU/2/13/158/004
EU/2/13/158/005
EU/2/13/158/006
EU/2/13/158/007
EU/2/13/158/008
EU/2/13/158/009

EU/2/13/158/010
EU/2/13/158/011
EU/2/13/158/012
EU/2/13/158/013
EU/2/13/158/014
EU/2/13/158/015

17. MANUFACTURER'S BATCH NUMBER

Lot: {number}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bravecto 112.5 mg (2-4.5 kg)
Bravecto 250 mg (>4.5-10 kg)
Bravecto 500 mg (>10-20 kg)
Bravecto 1000 mg (>20-40 kg)
Bravecto 1400 mg (>40-56 kg)

Fluralaner

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Intervet International B.V.

3. EXPIRY DATE

EXP: (MM/YYYY)

4. BATCH NUMBER

Lot: {number}

5. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR
Bravecto chewable tablets for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
Intervet International B. V.
Wim de Körverstraat 35
5831 AN Boxmeer
The NETHERLANDS

Manufacturer responsible for batch release:
Intervet GesmbH
Siemensstrasse 107
1210 Vienna
AUSTRIA

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bravecto 112.5 mg chewable tablets for very small dogs (2-4.5 kg)
Bravecto 250 mg chewable tablets for small dogs (>4.5-10 kg)
Bravecto 500 mg chewable tablets for medium-sized dogs (>10-20 kg)
Bravecto 1000 mg chewable tablets for large dogs (>20-40 kg)
Bravecto 1400 mg chewable tablets for very large dogs (>40-56 kg)

Fluralaner

3. STATEMENT OF THE ACTIVE SUBSTANCE AND OTHER INGREDIENTS

Each chewable tablet of Bravecto contains:

Bravecto chewable tablets	**Fluralaner (mg)**
for very small dogs (2-4.5 kg)	112.5
for small dogs (>4.5-10 kg)	250
for medium-sized dogs (>10-20 kg)	500
for large dogs (>20-40 kg)	1,000
for very large dogs (>40-56 kg)	1,400

Light to dark brown tablet with a smooth or slightly rough surface and circular shape. Some marbling, speckles or both may be visible.

4. INDICATIONS

For the treatment of tick and flea infestations on dogs.

This veterinary medicinal product is a systemic insecticide and acaricide that provides
- immediate and persistent flea (*Ctenocephalides felis*) killing activity for 12 weeks,
- immediate and persistent tick killing activity for 12 weeks for *Ixodes ricinus, Dermacentor reticulatus* and *D. variabilis;*

- immediate and persistent tick killing activity for 8 weeks for *Rhipicephalus sanguineus*.

Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. The onset of effect is within 8 hours of attachment for fleas (*C. felis*) and 12 hours of attachment for ticks (*I. ricinus*).

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

5. CONTRAINDICATIONS

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

6. ADVERSE REACTIONS

Commonly observed adverse reactions in clinical trials (1.6% of treated dogs) were mild and transient gastrointestinal effects such as diarrhoea, vomiting, inappetence, and drooling.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)
- common (more than 1 but less than 10 animals in 100 animals)
- uncommon (more than 1 but less than 10 animals in 1,000 animals)
- rare (more than 1 but less than 10 animals in 10,000 animals)
- very rare (less than 1 animal in 10,000 animals, including isolated reports).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinary surgeon.

7. TARGET SPECIES

Dogs

8. DOSAGE FOR EACH SPECIES, ROUTE AND METHOD OF ADMINISTRATION

For oral use.

Bravecto chewable tablets should be administered in accordance with the following table (corresponding to a dose of 25–56 mg fluralaner/kg bodyweight within one weight band):

Bodyweight of dog (kg)	**Strength and number of tablets to be administered**				
	Bravecto 112.5 mg	Bravecto 250 mg	Bravecto 500 mg	Bravecto 1000 mg	Bravecto 1400 mg
2-4.5	1				
>4.5-10		1			
>10-20			1		
>20-40				1	
>40-56					1

For dogs above 56 kg bodyweight, use a combination of two tablets that most closely matches the bodyweight.

9. ADVICE ON CORRECT ADMINISTRATION

The chewable tablets should not be broken or divided.
Administer Bravecto chewable tablets at or around the time of feeding.

Bravecto is a chewable tablet and is well accepted by most dogs. If the tablet is not taken up voluntarily by the dog it can also be given with food or directly into the mouth. The dog should be observed during administration to confirm that the tablet is swallowed.

Treatment schedule:
For optimal control of flea infestation, the veterinary medicinal product should be administered at intervals of 12 weeks. For optimal control of tick infestation, the timing of retreatment depends on the tick species. See section 4.

10. WITHDRAWAL PERIOD

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.
Do not use this veterinary medicinal product after the expiry date stated on the blister after EXP. The expiry date refers to the last day of that month.

12. SPECIAL WARNINGS

Special warnings for each target species:
Parasites need to start feeding on the host to become exposed to fluralaner; therefore the risk of the transmission of parasite borne diseases cannot be excluded .

Special precautions for use in animals:
In the absence of available data, the product should not be used on puppies less than 8 weeks old and /or dogs weighing less than 2 kg.
The product should not be administered at intervals shorter than 8 weeks as the safety for shorter intervals has not been tested.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product.
Do not eat, drink or smoke while handling the product.
Wash hands thoroughly with soap and water immediately after use of the product.

Pregnancy, lactation and fertility:
The veterinary medicinal product can be used in breeding, pregnant and lactating dogs.

Interaction with other medicinal products and other forms of interaction:
None known.
Fluralaner is highly bound to plasma proteins and might compete with other highly bound drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and the cumarin 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 Bravecto chewable tablets for dogs and routinely used veterinary medicinal products were observed.

Overdose (symptoms, emergency procedures, antidotes):
Safety was demonstrated in breeding, pregnant and lactating animals treated with overdoses of up to 3 times the maximum recommended dose.
Safety was demonstrated in puppies aged 8–9 weeks and weighing 2.0–3.6 kg treated with overdoses of up to 5 times the maximum recommended on three occasions at shorter intervals than recommended (8-week intervals).
The veterinary medicinal product was well tolerated in collies with a deficient multidrug-resistance-protein 1 (MDR1 -/-) following single oral administration at 3 times the recommended dose.

Incompatibilities:
None known.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Medicines should not be disposed of via wastewater or household waste.
Ask your veterinary surgeon how to dispose of medicines no longer required. These measures should help to protect the environment.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

15. OTHER INFORMATION

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

Cardboard box with 1 aluminium foil blister sealed with paper/PET aluminium foil lid stock containing 1, 2 or 4 chewable tablets.

Not all pack sizes may be marketed.