1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Bravecto 112.5 mg spot-on solution Veterinary Dogs
Bravecto 250 mg spot-on solution Veterinary Dogs
Bravecto 500 mg spot-on solution Veterinary Dogs
Bravecto 1000 mg spot-on solution Veterinary Dogs
Bravecto 1400 mg spot-on solution Veterinary Dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each ml contains 280 mg fluralaner.
Each pipette delivers:

	Pipette content (ml)	**Fluralaner (mg)**
for very small dogs 2 – 4.5 kg	0.4	112.5
for small dogs >4.5 – 10 kg	0.89	250
for medium-sized dogs >10 – 20 kg	1.79	500
for large dogs >20 – 40 kg	3.57	1000
for very large dogs >40 – 56 kg	5.0	1400

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Spot-on-solution.
Clear colourless to yellow solution.

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* and *Ctenocephalides canis*) killing activity for 12 weeks, and
- immediate and persistent tick (*Ixodes ricinus, Rhipicephalus sanguineus* and *Dermacentor reticulatus*) killing activity for 12 weeks.

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

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 listed in section 6.1.

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
Care should be taken to avoid contact with the eyes of the animal.
Do not use directly on skin lesions.
Do not wash or allow the dog to become immersed in water or swim in water courses within 3 days after treatment.
In the absence of available data, this 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 at shorter intervals has not been tested.
This product is for topical use and should not be administered orally.

Special precautions to be taken by the person administering the veterinary medicinal product to animals
Contact with the product should be avoided and disposable protective gloves must be worn when handling the product for the following reasons:
Hypersensitivity reactions have been reported in a small number of people, which can potentially be serious.
Persons with a hypersensitivity to fluralaner or to any of the excipients should avoid any exposure to the product.
The product binds to skin and may also bind to surfaces after spillage of the product. Skin rashes, tingling or numbness have been reported in a small number of individuals after skin contact.
If skin contact does occur, wash the affected area immediately with soap and water. In some cases, soap and water are not sufficient to remove the product spilled on the fingers.
Contact with the product may also occur when handling the treated animal.
Make sure that your animal's application site is no longer noticeable before resuming contact with the site of application. This includes cuddling the animal and sharing a bed with the animal. It takes up to 48 hours for the application site to become dry but it will be noticeable for longer.
If skin reactions occur, consult a physician and show them the product packaging.
People with a sensitive skin or known allergy in general e.g. to other veterinary medicinal products of this type should handle the veterinary medicinal product as well as treated animals with caution.
This product can cause eye irritation. In case of contact with the eyes, immediately rinse thoroughly with water.
This product is harmful after ingestion. Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product. A used pipette should immediately be disposed of. In case of accidental ingestion, seek medical advice and show the package leaflet or the label to the physician.
The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

In case of spillage onto, for example table or floor surfaces, remove excess product using paper tissue and clean the area with detergent.

4.6 Adverse reactions (frequency and seriousness)

Mild and transient skin reactions such as erythema or alopecia at the application site were commonly observed in clinical trials (1.2% of treated dogs).
Emesis, lethargy and anorexia have been reported very rarely in spontaneous reports after the use of this product.

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

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il

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 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 laboratory and clinical field testing, no interactions between Bravecto spot-on solution for dogs and routinely used veterinary medicinal products were observed.

4.9 Amounts to be administered and administration route

For spot-on use.

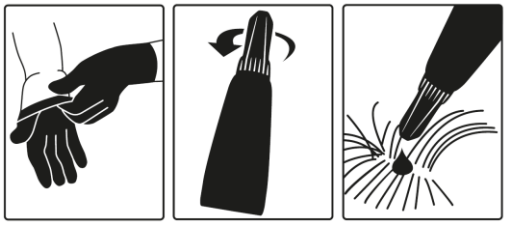
Bravecto should be administered in accordance with the following table (corresponding to a dose of 25-56 mg fluralaner/kg body weight):

Bodyweight of dog (kg)	**Strength and number of pipettes 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

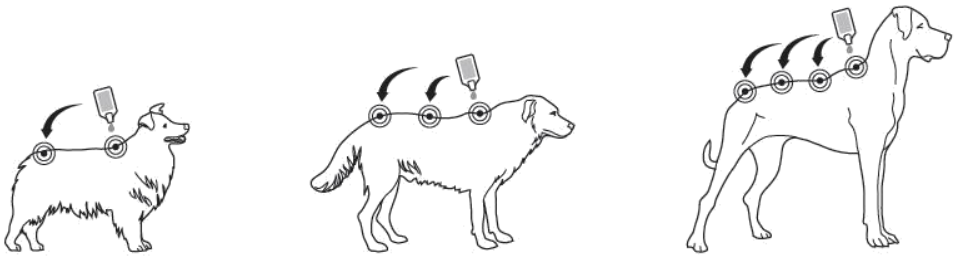
For dogs above 56 kg body weight, use a combination of two pipettes that most closely matches the body weight.

Method of administration:
Step 1: Immediately before use, open the sachet and remove the pipette. Put on gloves. The pipette should be held by the base or by the upper rigid portion below the cap in an upright position (tip up) for opening it. The cap should be rotated clockwise or counter clockwise one full turn. The cap will stay on the pipette; it is not possible to remove it. The pipette is open and ready for application when the breaking of the seal is felt.



Step 2 : The dog should be standing or lying with its back horizontal during application. Place the pipette tip vertically against the skin between the shoulder blades of the dog.

Step 3: Squeeze the pipette gently and apply the entire contents directly to the dog's skin in one (when volume is small) or several spots along the dog's dorsal line from the shoulder to the base of the tail. Avoid the application of more than 1 ml of solution at any one spot as it could cause some of the solution to run or drip off the dog.



Treatment schedule:
For optimal control of tick and flea infestation, the product should be administered at intervals of 12 weeks.

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

No adverse reactions were observed following topical administration to puppies aged 8–9 weeks and weighing 2.0–3.7 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).

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 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: QP53B E02.

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.

The onset of efficacy is within 8 hours for fleas (*C. felis*) and 12 hours for ticks (*I. ricinus*).

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

Fluralaner is readily absorbed from the topical administration site into the hair, skin and subjacent tissues, from where it is slowly absorbed into the vascular system. A plateau is seen in plasma between 7 and 63 days post administration, after which concentrations decline slowly. The prolonged persistence and slow elimination from plasma ($t_{1/2}$ = 21 days) and the lack of extensive metabolism provide effective concentrations of fluralaner for the duration of the inter-dosing interval. Unchanged fluralaner is excreted in feces and to a very low extent in urine.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethylacetamide
Glycofurol
Diethyltoluamide (DEET)
Acetone

6.2 Major incompatibilities

None known.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4. Special precautions for storage

Store below 25ºC.
The pipettes should be kept in the outer packaging to prevent solvent loss or moisture uptake.
The sachets should only be opened immediately prior to use.

6.5 Nature and composition of immediate packaging

Unit dose pipette made of laminated aluminium/polypropylene foil closed with an HDPE cap and packed in a laminated aluminium foil sachet. Each carton box contains 1 or 2 pipettes.
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 product should be disposed of as toxic waste, do not throw to sewer.

7. MANUFACTURER

Patheon Manufacturing Services LLC,
5900 Martin Luther King Jr. Highway,
Greenville, North Carolina (NC) 27834,

United States.

8. LICENSE HOLDER

Intervet Israel Ltd.
Industrial Zone Neve Ne'eman 2,
Hod Hasharon 45240,
Israel

9. LICENSE NUMBERS

Bravecto 112.5 mg spot-on solution Veterinary Dogs	160-69-35136-00
Bravecto 250 mg spot-on solution Veterinary Dogs	160-70-35137-00
Bravecto 500 mg spot-on solution Veterinary Dogs	160-71-35138-00
Bravecto 1000 mg spot-on solution Veterinary Dogs	160-72-35139-00
Bravecto 1400 mg spot-on solution Veterinary Dogs	160-73-35140-00

Revised in April 2021 according to MOHs guidelines.