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BRAVECTO®

Merck Animal Health

Fluralaner Chewable Tablet, 112.5 mg, 250 mg, 500 mg, 1000 mg, 1400 mg
Veterinary Use Only
DIN 02425068, 02425076, 02425084, 02425092, 02425106

DESCRIPTION:

BRAVECTO (Fluralaner Chewable Tablet) for dogs is a light to dark brown flavoured chewable tablet containing 112.5 mg, 250 mg, 500 mg, 1000 mg or 1400 mg of fluralaner respectively.

Each tablet is formulated to provide a minimum dose of 25 mg/kg body weight.

The chemical name of Fluralaner is 4-[5-(3,5-dichlorophenyl)-5-(trifluoromethyl)-4,5-dihydro-1,2-oxazol-3-yl]-2-methyl-N-{2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl}benzamide.

THERAPEUTIC CLASSIFICATION:

Antiparasitic

INDICATIONS:

BRAVECTO kills fleas and is indicated for the treatment and prevention of flea infestations *(Ctenocephalides felis)* and for the treatment and control of tick infestations with *Dermacentor variabilis* (American dog tick) for 12 weeks.

BRAVECTO is also indicated as an aid in the treatment and control of tick infestations with *Ixodes scapularis* (black-legged tick) and *Rhipicephalus sanguineus* (brown dog tick) for 12 weeks.

BRAVECTO is indicated for dogs and puppies 6 months of age and older and weighing 2 kg or greater.

DOSAGE AND ADMINISTRATION:

BRAVECTO should be administered orally as a single dose every 12 weeks according to the **Dosage Schedule** below to provide a minimum dose of 25 mg/kg body weight.

BRAVECTO should be administered with food.

Dosage Schedule

Body Weight Ranges (kg)	Chewable Tablet weight (g)	Fluralaner content (mg)	Chewable Tablets Administered	Package Colour
2 - 4.5	0.82	112.5	One	Yellow
> 4.5 - 10	1.83	250	One	Orange
> 10 - 20	3.67	500	One	Green
> 20 - 40	7.33	1000	One	Blue
> 40 - 56*	10.26	1400	One	Pink

* Dogs over 56 kg should be administered the appropriate combination of chewable tablets.

Treatment with BRAVECTO may begin at any time of the year. Due to climate variations across the country, Canada has highly variable distributions and abundance of flea and tick infestations. A comprehensive plan, based on regional risk assessment is recommended to determine an appropriate dosing interval.

CONTRAINDICATIONS:

This product should not be given to dogs with known or suspected allergy or intolerance to fluralaner or other components of this product.

CAUTIONS:

BRAVECTO has not been shown to be effective for 12-weeks duration in puppies less than 6 months of age. Fluralaner is a member of the isoxazoline class. This class has been associated with neurological adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurological disorders.

WARNINGS:

Not for human use. Keep out of the reach of children. 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.

ADVERSE REACTIONS:

Although all adverse reactions are not reported, the following information is based on voluntary post-approval drug experience reporting. It is generally recognized that this results in significant under-reporting. The adverse events listed here reflect reporting and not necessarily causality.

The following adverse events have been reported rarely[1] (reported in at least 1 but not more than 10 animals in 10,000 animals exposed) and very rarely [2] (reported in less than 1 in 10,000 animals exposed) and are listed by body system, in decreasing order of frequency:

Digestive tract disorders: vomiting[1], diarrhea[2], hypersalivation[2], hemorrhagic diarrhea[2]

Systemic disorders: lack of efficacy*,[1], lethargy[2], anorexia[2]

Skin and appendage disorders: pruritus[2], alopecia[2]

Neurological disorders: convulsions[2], ataxia[2], muscle tremor[2]

**Product efficacy requires that dosing and administration instructions be carefully followed. Failure to follow label directions could result in a real or perceived lack of efficacy. Several factors, including local parasite prevalence, consistent and compliant administration and environmental control measures can contribute to a perceived inefficacy.*

In a well-controlled US field study, which included 294 dogs (224 dogs were administered BRAVECTO every 12 weeks and 70 dogs were administered an oral active control every 4 weeks and were provided with a tick collar); there were no serious adverse reactions. All potential adverse reactions were

recorded in dogs treated with BRAVECTO over a 182-day period and in dogs treated with the active control over an 84-day period. The most frequently reported adverse reaction in dogs in the BRAVECTO and active control groups was vomiting.

Percentage of Dogs with Adverse Reactions in the Field Study

Adverse Reaction (AR)	BRAVECTO Group: Percentage of Dogs with the AR During the 182-Day Study (n=224 dogs)	Active Control Group: Percentage of Dogs with the AR During the 84-Day Study (n=70 dogs)
Vomiting	7.1	14.3
Decreased Appetite	6.7	0.0
Diarrhea	4.9	2.9
Lethargy	5.4	7.1
Polydipsia	1.8	4.3
Flatulence	1.3	0.0

In a well-controlled laboratory dose confirmation study, one dog developed edema and hyperemia of the upper lips within one hour of receiving BRAVECTO. The edema improved progressively through the day and had resolved without medical intervention by the next morning.

CLINICAL PHARMACOLOGY:

Peak fluralaner concentrations are achieved between 2 hours and 3 days following oral administration and the elimination half-life ranges between 9.3 to 16.2 days. Quantifiable drug concentrations can be measured (lower than necessary for efficacy) through 112 days. Due to reduced drug bioavailability in the fasted state, fluralaner should be administered with food.

MODE OF ACTION:

Fluralaner is for systemic use and belongs to the class of isoxazoline-substituted benzamide derivatives. Fluralaner is an inhibitor of the arthropod nervous system. The mode of action of fluralaner is the antagonism of the ligand-gated chloride channels (gamma-aminobutyric acid (GABA) -receptor and glutamate-receptor). Fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance. For fleas *(C. felis)* and ticks *(I. ricinus)* the onset of effect (defined as ≥ 90% reduction in the number of fleas and ticks compared to control) is within 12 hours of infestation for 12 weeks.

EFFICACY:

BRAVECTO began to kill fleas within two hours after administration in a well-controlled laboratory study. In a European laboratory study, BRAVECTO killed fleas and *Ixodes ricinus* ticks and reduced the numbers of live fleas and *I. ricinus* ticks by > 96% within 12 hours for 12 weeks. In a well-controlled laboratory study, BRAVECTO demonstrated 100% efficacy against adult fleas 48 hours post-infestation for 12 weeks. In well-controlled laboratory studies, BRAVECTO demonstrated > 97% efficacy against *Dermacentor variabilis* 48 hours post-infestation for 12 weeks. BRAVECTO demonstrated > 96% efficacy against *Ixodes scapularis* and *Rhipicephalus sanguineus* 48 hours post-infestation for 8 weeks. However, ≥ 90% efficacy was not consistently demonstrated beyond 8 weeks.

Efficacy of BRAVECTO tablets against fleas and ticks in laboratory studies

	Study	% Efficacy*			
		2 days	4 weeks	8 weeks	12 weeks
Ctenocephalides felis	1	100 (100)	100 (100)	100 (100)	100 (100)
Dermacentor variabilis	1	100 (100)	100 (100)	100 (100)	97.7 (98.7)
	2	100 (100)	100 (100)	100 (100)	98.1 (99.0)
Ixodes scapularis	1	97.7 (98.9)	96.7 (97.7)	99.2 (99.4)	93.1 (96.6)
	2	100 (100)	100 (100)	100 (100)	87.6 (97.6)
Rhipicephalus sanguineus	1	100 (100)	100 (100)	99.5 (99.6)	89.4 (93.9)
	2	100 (100)	98.5 (98.9)	96.6 (98.6)	68.0 (87.6)
	3	100 (100)	100 (100)	99.5 (99.6)	88.0 (97.4)

* arithmetic mean (geometric mean). Note: the arithmetic mean was used to assess efficacy.

In a well-controlled U.S. field study, a single dose of BRAVECTO reduced fleas by ≥ 99.7% for 12 weeks. Dogs with signs of flea allergy dermatitis showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation as a direct result of eliminating flea infestations.

Palatability: In a well-controlled U.S. field study, which included 559 doses administered to 224 dogs, 80.7% of dogs voluntarily consumed BRAVECTO within 5 minutes, an additional 12.5% voluntarily consumed the product within 5 minutes when offered with food, and 6.8% refused the dose or required forced administration.

ANIMAL SAFETY:

Margin of Safety Study: In a margin of safety study, BRAVECTO was administered orally to 8- to 9-week-old puppies at 1, 3, and 5X the maximum labeled dose of 56 mg/kg three times at 8-week intervals. The dogs in the control group (0X) were untreated.

There were no clinically-relevant, treatment-related effects on physical examinations, body weights, food consumption, clinical pathology (hematology, clinical chemistries, coagulation tests, and urinalysis), gross pathology, histopathology, or organ weights. Diarrhea, mucoid and bloody feces were the most common observations in this study, occurring at a similar incidence in the treated and control groups. Five of the twelve treated dogs that experienced one or more of these signs did so within 6 hours of the first dosing. One dog in the 3X treatment group was observed to be dull, inappetant, with evidence of bloody diarrhea, vomiting, and weight loss beginning five days after the first treatment. One dog in the 1X treatment group vomited food 4 hours following the first treatment.

Reproductive Safety Study: BRAVECTO was administered orally to intact, reproductively-sound male and female Beagles at a dose of up to 168 mg/kg (equivalent to 3X the maximum treatment dose) on three to four occasions at 8-week intervals. The dogs in the control group (0X) were untreated.

There were no clinically-relevant, treatment-related effects on the body weights, food consumption, reproductive performance, semen analysis, litter data, gross necropsy (adult dogs) or histopathology findings (adult dogs and puppies). One adult treated dog suffered a seizure during the course of the study (46 days after the second treatment). Abnormal salivation was observed on 17 occasions: in six treated dogs (11 occasions) after dosing and four control dogs (6 occasions).

The following abnormalities were noted in 7 pups from 2 of the 10 dams in only the treated group during gross necropsy examination: limb deformity (4 pups), enlarged heart (2 pups), enlarged spleen (3 pups), and cleft palate (2 pups). During veterinary examination at Week 7, two pups from the control group had inguinal testicles, and two and four pups from the treated group had inguinal and cryptorchid testicles, respectively. No undescended testicles were observed at the time of necropsy (days 50 to 71).

In a well-controlled field study BRAVECTO was used concurrently with other medications, such as vaccines, anthelmintics, antibiotics, and steroids. No adverse reactions were observed from the concurrent use of BRAVECTO with other medications.

STORAGE CONDITIONS:

Do not store above 30°C.

HOW SUPPLIED:

BRAVECTO (Fluralaner Chewable Tablet) is available in five strengths (112.5 mg, 250 mg, 500 mg, 1000 mg, and 1400 mg fluralaner per tablet). Each tablet is packaged individually into aluminum foil blister packs sealed with a peelable paper backed foil lid stock. Product is packaged in 1 tablet per box.

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