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NEXGARD®

Boehringer Ingelheim

(afoxolaner)

Soft, Beef-Flavoured Chewable Tablets for Dogs

Flea and tick treatment and control

VETERINARY USE ONLY

INDICATIONS: For the treatment and control of flea *(Ctenocephalides felis)* infestations and the treatment and control of adult *Dermacentor variabilis* (American Dog Ticks), adult *Ixodes scapularis* (Blacklegged Ticks), and adult *Amblyomma americanum* (Lone Star Ticks), in dogs and puppies 8 weeks of age or older. **NEXGARD** is indicated for the reduction of *Borrelia burgdorferi* infections as a direct result of killing adult *Ixodes scapularis* vector ticks.

DOSAGE AND ADMINISTRATION: NEXGARD Chewable Tablets are given orally once a month, at the dosage of 2.5 to 6.3 mg/kg based on body weight.

Body Weight (kg)	Afoxolaner per chewable tablet (mg)	Chewable tablets administered
1.8-4.5	11.3	One
4.6-10.9	28.3	One
11.0-27.2	68.0	One
27.3-54.4	136.0	One
Over 54.4	Administer the appropriate combination of chewable tablets	

NEXGARD can be administered with or without food.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, or vomiting occurs within 2 hours of administration, redose with another full dose. If a dose is missed, administer **NEXGARD** and resume a monthly dosing regimen. To be effective, **NEXGARD** should be administered every 30 days.

Flea Treatment and Prevention:

For prevention of flea infestation, **NEXGARD** should be administered ideally just before fleas become active. To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Prevention:

Administration of **NEXGARD** should coincide with the time of year the ticks are active in the warmer weather.

CAUTIONS: The safety of **NEXGARD** Chewable Tablets has not been evaluated in breeding, pregnant or lactating dogs. The safety of **NEXGARD** in puppies less than 8 weeks of age has not been evaluated.

Afoxolaner 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: Keep out of reach of children. In case of accidental ingestion, contact a physician immediately.

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. Adverse events are listed by body system, in decreasing order of frequency:

Digestive tract disorders: vomiting, diarrhea, hemorrhagic diarrhea, hypersalivation

Systemic disorders: lethargy, anorexia, panting

Neurological disorders: seizures, ataxia, tremors

Behavioural disorders: hyperactivity/restlessness

Skin and appendage disorders: pruritus, dermatitis, erythema, allergic reactions

In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 treated with **NEXGARD** Chewable Tablets, 200 treated with an active control) no serious adverse reactions were attributed to **NEXGARD**. Evaluation of safety was completed over the 90-day period through in-clinic physical examinations. Adverse reactions with an incidence of >1% over the course of the study are provided in the following table. The most frequently reported adverse reaction in the **NEXGARD** and active control groups was vomiting. The occurrence of vomiting nonetheless was generally self-limiting and of short duration. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Reported Adverse Reactions

Adverse Reaction	Treatment Group			
	Afoxolaner		Active Control	
	N[1]	% (n=415)	N[1]	% (n=200)
Vomiting with and without blood	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea with and without blood	13	3.1	7	3.5
Pruritus	10	2.4	2	1.0
Seborrhea	8	1.9	3	1.5
Erythema	7	1.7	3	1.5
Lethargy	7	1.7	4	2.0

Skin disorders NOS	6	1.4	1	0.5
Anorexia	5	1.2	9	4.5
Dermatitis and eczema	5	1.2	4	2.0

[1]Number of dogs treated with the identified adverse reaction

NOS = Not Otherwise Specified.

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of **NEXGARD**. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of **NEXGARD**. The dog remained enrolled and completed the study. A third dog with a history of seizures received **NEXGARD** and experienced no seizures throughout the study.

CLINICAL PHARMACOLOGY:

Description: Afoxolaner is a new molecule and a member of the isoxazoline family.

Mode of Action: Afoxolaner binds to flea and tick nerve cell chloride channels activated by the neurotransmitter GABA (gamma-aminobutyric acid), which blocks pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects/acarines and mammals may be inferred by the differential sensitivity of the insects/acarines' GABA receptors versus mammalian GABA receptors.

Afoxolaner acts systemically to kill fleas and ticks. The time of exposure needed for the flea or tick to die depends on the time it takes the flea or tick to attach and exchange fluids with the host dog as well as the drug dose needed to kill fleas or a specific species of tick and the dog's drug plasma concentration at the time of attachment. Once feeding begins for fleas *(C. felis)*, the onset of effect is within 8-24 hours. For ticks, *Dermacentor variabilis,* and *Ixodes scapularis* >90% are killed within 48 hours and for *Amblyomma americanum* >90% are killed within 72 hours.

Pharmacokinetics: The pharmacokinetic profile of afoxolaner was studied following oral administration of **NEXGARD** in dogs, and was shown to have high systemic absorption following administration. The absolute bioavailability was 74%. The mean maximum concentration (C_{max}) was 1655 ± 332 ng/mL in plasma found 2-4 hours (T_{max}) after a 2.5 mg/kg afoxolaner dose.

Afoxolaner distributes into tissues with a volume of distribution of 2.6 ± 0.6 L/kg and a systemic clearance value of 5.0 ± 1.2 mL/hr/kg. The terminal plasma half-life is approximately 2 weeks in dogs.

EFFICACY:

In a well-controlled speed of kill laboratory study, NEXGARD Chewable Tablets started to kill adult fleas 30 minutes after initial administration, with 99.7-100% effectiveness achieved between 8 and 24 hours.

In another well-controlled laboratory, **NEXGARD** demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days. On day 7 **NEXGARD** was 83.3% effective, 12 hours post infestation. Dogs in both the treated and control groups that were infested with fleas on Day-1 generated flea eggs at 12 and 24 hours post treatment (mean count of 2.8 and 5.4 eggs in **NEXGARD** treated dogs and a mean of count of 22.9 and 51.8 in the control dogs at 12 and 24 hours respectively). At subsequent evaluations post-infestation fleas from dogs in the treated group were essentially unable to produce any eggs (mean count of 0.1-0.3 eggs) while fleas from dogs in the control group continued to produce eggs (means 14-54.8).

In a 90-day U.S. field study conducted in households with existing flea infestations of varying severity, the effectiveness of **NEXGARD** against fleas on the Day 30, 60 and 90 visits compared with baseline was 96.4%, 99.4% and 99.8%.

Collectively, the data from the two studies (laboratory and field study) demonstrate that **NEXGARD** kill fleas before they can lay eggs, thus preventing subsequent flea infestations after the initial treatment of existing flea infestations.

In well-controlled laboratory studies, **NEXGARD** demonstrated > 90% effectiveness for 30 days against *Ixodes scapularis,* and *Dermacentor variabilis,* 48 hours post-infestation, and against *Amblyomma americanum* 72 hours post-infestation.

In two separate, well-controlled laboratory studies, **NEXGARD** was effective at preventing *Borrelia burgdorferi* infections after dogs were infested, at room temperature, with adult *Ixodes scapularis* vector ticks 28 days post-treatment.

In palatability trials, **NEXGARD** was shown to be a palatable oral dosage form, which was consumed at first offering by the majority of dogs.

ANIMAL SAFETY:

In a margin of safety study, **NEXGARD** Chewable Tablets were administered orally to Beagle puppies 8 to 9 weeks old at 1, 3, and 5 times the maximum exposure dose of 6.3 mg/kg for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistries, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited 4 hours after treatment.

STORAGE: Store at room temperature between 15 - 30°C. Brief exposure (not to exceed 24 hours) up to 40°C is permitted.

PRESENTATION: NEXGARD Chewable Tablets are available in four soft, beef-flavoured chewable tablets strengths: 11.3, 28.3, 68.0 or 136.0 mg afoxolaner per chewable tablet. Each strength is available in colour-coded packages of 1, 3 or 6 chewable tablets. Not all pack sizes may be marketed.

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