NexGard® (afoxolaner) Chewables

STUDY 1

Ability of *NexGard*® (afoxolaner) to prevent the transmission of *Borrelia burgdorferi* to dogs from infected *Ixodes scapularis* ticks.

Source: [1] Freedom of Information Summary. Supplemental NADA 141-406. *NexGard*. July 13, 2018. Study # 0377501

Group 1 Treated with ***NexGard***

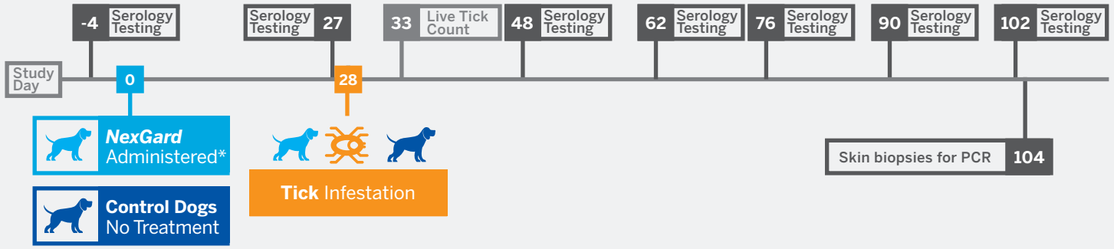
Group 2 Untreated **Control**

Tick Infestation:
- ✓ All dogs infested with ~50 adult, unfed, wild-caught *Ixodes scapularis* ticks on Study Day 28
- ✓ *B. burgdorferi* infection rate of ticks was determined to be 63.1%
- ✓ Ticks were removed and counted 5 days after infestation

Diagnostics:

Serology Testing: Dogs were tested for the presence of C6 *B. burgdorferi* antibody using the IDEXX SNAP®4Dx® test and Lyme Quant C6® test

PCR Testing: Dogs were tested for the presence of *B. burgdorferi* DNA by PCR testing of 4 skin biopsies per dog



*dosed as close as possible to minimum recommended dose of 2.5 mg/kg

Serology Test Results

Study Day	*NexGard*-treated Dogs Positive for *B. burgdorferi*	Control Dogs Positive for *B. burgdorferi*
-4	0/10	0/10
27	0/10	0/10
48	0/10	6/10
62	0/10	10/10
76	0/10	10/10
90	0/10	10/10
102	0/10	10/10

PCR Testing

- All dogs treated with *NexGard* were PCR negative for *B. burgdorferi* on all 4 skin biopsies.
- All control dogs were PCR positive for *B. burgdorferi* in at least 3 of the 4 skin biopsies.

100% **of dogs treated with *NexGard* were protected from *B. burgdorferi* infection.**

IMPORTANT SAFETY INFORMATION: *NexGard*® (afoxolaner) is for use in dogs only and is safe for dogs 8 weeks or older and weighing 4 pounds or more. The most frequently reported adverse reactions include vomiting, pruritus, lethargy, diarrhea, and lack of appetite. The safe use of *NexGard* in pregnant, breeding, or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures or neurologic disorders. For more information, see enclosed full prescribing information, call 888-637-4251 or visit NexGardClinic.com.

NexGard® (afoxolaner) Chewables

STUDY 2

Ability of *NexGard*® (afoxolaner) to prevent the transmission of *Borrelia burgdorferi* to dogs from infected *Ixodes scapularis* ticks.

Source: [2] Freedom of Information Summary. Supplemental NADA 141-406. *NexGard*. July 13, 2018 Study # 328901

[3] Baker CF, McCall JW, McCall SD, et al. Ability of an oral formulation of afoxolaner to protect dogs from *Borrelia burgdorferi* infection transmitted by wild *Ixodes scapularis* ticks. *Comp Immunol Microbiol Infect Dis*. 2016;49:65-69.

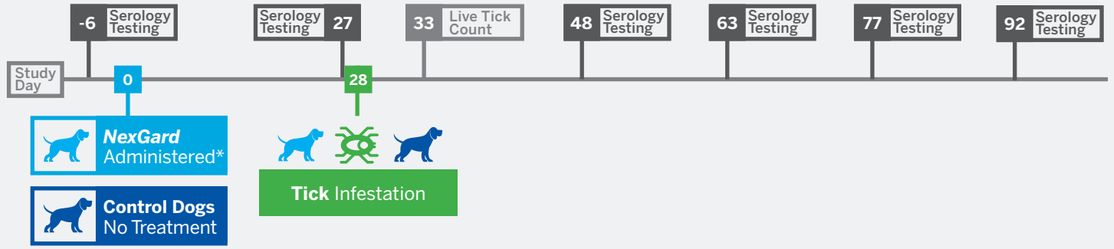
Group 1 Treated with ***NexGard***

Group 2 Untreated **Control**

Tick Infestation:
- ✓ All dogs infested with ~50 adult, unfed, wild-caught *Ixodes scapularis* ticks on Study Day 28
- ✓ *B. burgdorferi* infection rate of of ticks was determined to be 67%
- ✓ Ticks were removed and counted 5 days after infestation

Diagnostics:

Serology Testing: Dogs were tested for the presence of C6 *B. burgdorferi* antibody using the IDEXX SNAP®4Dx® test and Lyme Quant C6® test



*dosed as close as possible to minimum recommended dose of 2.5 mg/kg

Serology Test Results

Study Day	*NexGard*-treated Dogs Positive for *B. burgdorferi*	Control Dogs Positive for *B. burgdorferi*
-6	0/10	0/10
27	0/10	0/10
48	0/10	4/10
63	0/10	6/10
77	0/10	8/10
92	0/10	9/10

Lyme infection can lead to serious consequences in dogs. In addition to the consistent use of *NexGard*, a number of other preventive steps should be recommended to your clients, including:

- Avoid areas where ticks are common, if possible.
- Reduce areas that serve as ideal tick habitat in the yard.
- Check pets daily for ticks, and remove any that are found.
- Vaccinate dogs for Lyme disease.

NexGard **is FDA-approved to prevent Lyme infections by killing black-legged ticks.**

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Boehringer Ingelheim

NexGard®
(afoxolaner) Chewables

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Description:
NexGard® (afoxolaner) is available in four sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5-[3-chloro-5-(trifluoromethyl)-phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl.

Indications:
NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations *(Ctenocephalides felis),* and the treatment and control of Black-legged tick *(Ixodes scapularis),* American Dog tick *(Dermacentor variabilis),* Lone Star tick *(Amblyomma americanum),* and Brown dog tick *(Rhipicephalus sanguineus)* infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month. NexGard is indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Dosage and Administration:
NexGard is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

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 refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NexGard and resume a monthly dosing schedule.

Flea Treatment and Prevention:
Treatment with NexGard may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NexGard should continue the entire year without interruption.

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 Control:
Treatment with NexGard may begin at any time of the year (see **Effectiveness**).

Contraindications:
There are no known contraindications for the use of NexGard.

Warnings:
Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately.

Keep NexGard in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Precautions:
Afoxolaner is a member of the isoxazoline class. This class has been associated with neurologic 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 neurologic disorders.

The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated.

Adverse Reactions:
In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard. Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of >1% within any of the three months of observations are presented in the following table. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Table 1: Dogs With Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N[1]	% (n=415)	N[2]	% (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
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

[1] Number of dogs in the afoxolaner treatment group with the identified abnormality.

[2] Number of dogs in the control group with the identified abnormality.

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.

Post-Approval Experience (July 2018):
The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events reported for dogs are listed in decreasing order of reporting frequency for NexGard:

Vomiting, pruritus, lethargy, diarrhea (with and without blood), anorexia, seizure, hyperactivity/restlessness, panting, erythema, ataxia, dermatitis (including rash, papules), allergic reactions (including hives, swelling), and tremors.

Contact Information:
For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251 or www.nexgardfordogs.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or www.fda.gov/reportanimalae.

Mode of Action:
Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking 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 and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Effectiveness:
In a well-controlled laboratory study, NexGard began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was ≥93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NexGard was 81.1% 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 (0-11 eggs and 1-17 eggs in the NexGard treated dogs, and 4-90 eggs and 0-118 eggs 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 (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US 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 98.0%, 99.7%, and 99.9%, respectively.

Collectively, the data from the three studies (two laboratory and one field) demonstrate that NexGard kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NexGard demonstrated >97% effectiveness against *Dermacentor variabilis,* >94% effectiveness against *Ixodes scapularis,* and >93% effectiveness against *Rhipicephalus sanguineus,* 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days. In two separate, well-controlled laboratory studies, NexGard was effective at preventing *Borrelia burgdorferi* infections after dogs were infested with *Ixodes scapularis* vector ticks 28 days post-treatment.

Animal Safety:
In a margin of safety study, NexGard was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (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 four hours after treatment.

In a well-controlled field study, NexGard was used concomitantly with other medications, such as vaccines, anthelmintics, antibiotics (including topicals), steroids, NSAIDS, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NexGard with other medications.

Storage Information:
Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:
NexGard is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

Approved by FDA under NADA # 141-406

Marketed by: Frontline Vet Labs™, a Division of Boehringer Ingelheim Animal Health USA Inc. Duluth, GA 30096

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