

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.

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.

Precautions:
The safe use of NexGard in breeding, pregnant or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures (see **Adverse Reactions**).

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

¹Number of dogs in the afoxolaner treatment group with the identified abnormality.
²Number 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.

To report suspected adverse events, for technical assistance or to obtain a copy of the MSDS, contact Merial at 1-888-637-4251 or www.merial.com/NexGard. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VEITS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

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.

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.

NADA 141-406, Approved by FDA
Marketed by: Frontline Vet Labs™, a Division of Merial, Inc.
Duluth, GA 30096-4640 USA
Made in Brazil.

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1050-4493-03
Rev. 1/2015



**IT'S TICK SEASON.
The risk is real:
ticks are hunting
for your dog.**



Help protect your canine patients against:

- Ticks by using a flea and tick control product, such as **FRONTLINE® Gold for Dogs** or **NexGard® (afoxolaner)**
- Lyme disease by vaccinating with **RECOMBITEK® Lyme**



¹ Eisen RJ, Eisen L, Beard CB. County-scale distribution of *Ixodes scapularis* and *Ixodes pacificus* (Acari: Ixodidae) in the continental United States. *Journal of Medical Entomology*. 2016; 53(2):349-386.

² Dryden MW, Payne PA. Biology and control of ticks infesting dogs and cats in North America. *Veterinary Therapeutics*. 2004.

³ Freedom of Information Summary Supplement, NADA 141-406 (05/15/2014), NexGard.

⁴ Data on file.

⁵ Yabsley M. The forecasts are in: 2017 will be a big year for heartworm disease and Lyme disease. Pets & Parasites website. <http://www.petsandparasites.org/expert-insights/the-forecasts-are-in-2017-will-be-a-big-year-for-heartworm-disease-and-lyme/>. Accessed November 2, 2017.

⁶ Kahn C, ed. Lyme Borreliosis. In: *The Merck Veterinary Manual*. 10th ed. Whitehouse Station, NJ: Merck & Co., Inc. 10th ed. 2010:602.

⁷ Conlon JA et al. Efficacy of a non-adjuvanted, outer surface protein A, recombinant vaccine in dogs after challenge by ticks naturally infected with *Borrelia burgdorferi*. *Veterinary Therapeutics*. 2000;1:96-107.

⁸ Chang Y, et al. Recombinant OspA protects dogs against infection and disease caused by *Borrelia burgdorferi*. *Infection and Immunity*. 1995;63(9):3543-3549.

⁹ Probert WS, Crawford M, Cadiz RB, LeFebvre RB. Immunization with outer surface protein (Osp) A, but not OspC, provides cross-protection of mice challenged with North American isolates of *Borrelia burgdorferi*. *J Infect Dis*. 1997;175(2):400-405.

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IMPORTANT SAFETY INFORMATION: NexGard® is for use in dogs only. The most frequently reported adverse reactions included itching, vomiting, dry/flaky skin, diarrhea, lethargy, 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. For more information, see full prescribing information or visit www.NexGardForDogs.com.

TICKS NOW POSE A GREATER THREAT TO DOGS ACROSS THE COUNTRY THAN EVER BEFORE.^{1,2}

We offer a full range of easy-to-use topical and oral control products that kill both fleas and ticks.



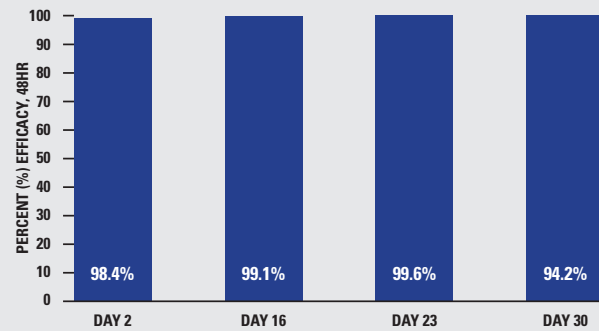
NexGard® (afoxolaner)

- The first prescription-only soft, beef-flavored monthly chewable that kills fleas AND ticks
- For dog owners who prefer to help protect their pets from fleas and ticks with an oral product that's easy to give
- Kills fleas and ticks all month long
- SATISFACTION PLUS GUARANTEE™ – ask for details.**

* Percent effectiveness of the treated group with respect to the control group was calculated using the formula $[(C - T)/C] \times 100$, where C = geometric mean live tick count for the control group and T = geometric mean live tick count for the treated group for each time point.

** For full details, visit www.nexgardfordogs.com.

Percent efficacy* against *Ixodes scapularis* 48 hours after treatment*** or reinfestation³



*** treatment was administered to the treated dogs on day 0

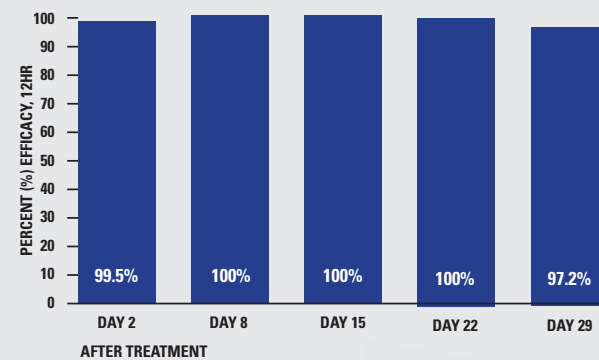
FRONTLINE® Gold

- The enhanced FRONTLINE formula that kills fleas and ticks, including the blacklegged (deer) tick that may transmit Lyme disease, lone star ticks, brown dog ticks and American dog ticks
- Easy-to-use applicator
- Kills fleas and ticks all month long
- SATISFACTION PLUS GUARANTEE™ – ask for details.**

* Percent effectiveness of the treated group with respect to the control group was calculated using the formula $[(C - T)/C] \times 100$, where C = geometric mean live tick count for the control group and T = geometric mean live tick count for the treated group for each time point.

** For full details, visit www.frontline.com.

Percent efficacy* against *Ixodes scapularis* 12 hours following weekly infestations⁴



COMFORTIS®, TRIFEXIS®, AND ADVANTAGE® DO NOT KILL TICKS. OUR PRODUCTS DO.

Grooming

REMAND YOUR PET OWNERS TO: Avoid wooded areas during tick season, brush their dogs frequently, and check for ticks. If they find a tick they should remove it promptly without crushing it and contact you if they have any concerns.

Using Flea and Tick Control

RECOMMEND A FLEA AND TICK CONTROL PRODUCT: **FRONTLINE® Gold for Dogs** and **NexGard® (afoxolaner)** kill ticks, including blacklegged ticks.



FRONTLINE Gold kills fleas, flea eggs, flea larvae and ticks including those that may transmit Lyme Disease.



NexGard is indicated for the treatment and prevention of flea infestations, and the treatment and control of tick infestations.



IMPORTANT SAFETY INFORMATION: NexGard is for use in dogs only. The most frequently reported adverse reactions included itching, vomiting, dry/flaky skin, diarrhea, lethargy, 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. For more information, see full prescribing information or visit www.NexGardForDogs.com.



RECOMBITEK® Lyme is the only nonadjuvanted Lyme vaccine.



THE COMPANION ANIMAL PARASITE COUNCIL (CAPC) SHOWS AREAS OF *Borrelia burgdorferi* TRANSMISSION HAVE EXPANDED BEYOND ENDEMIC REGIONS AND CASELOADS IN ENDEMIC REGIONS HAVE INCREASED.⁵

- Lyme disease is caused by *Borrelia burgdorferi*, which are bacteria that can be transmitted to dogs by infected blacklegged (deer) ticks.
- Lyme disease can damage canine joints, kidneys and other tissues.
- Infection can persist despite aggressive antibiotic therapy.⁶
- Areas of greatest incidence in the USA are regions in the Northeast (particularly the New England states), the upper Midwest and Pacific coast,⁶ but nearly half of U.S. counties have reported the ticks that carry the bacteria that can cause Lyme disease.¹

Vaccinating

VACCINATE AGAINST LYME DISEASE: **RECOMBITEK® Lyme** aids in the prevention of disease caused by *Borrelia burgdorferi*.



RECOMBITEK Lyme is recommended for vaccination of healthy dogs 9 weeks of age and older as an aid in the prevention of disease caused by *Borrelia burgdorferi*.

RECOMBITEK® Lyme

- The only nonadjuvanted Lyme vaccine
- Contains a unique formulation of OspA, the only antigen needed to stimulate immunity against Lyme disease in North America^{7,8,9}
- Customer Satisfaction Guarantee – ask for details.

In a study, 100% of dogs were protected from infection (as determined by isolation of *B. burgdorferi* after challenge).⁷

