



## Summary

- In a study, NexGard<sup>®</sup> (afoxolaner) was administered to dogs every 28 days for three consecutive doses, and efficacy was determined every 7 days from day 42 through day 84.<sup>1</sup>
- At 6 hours after infestation with 100 fleas, efficacy ranged from 62.8% to 97.3%. NexGard efficacy was 94% to 100% 12 hours after flea infestations and 100% 24 hours after each infestation.
- Sustained speed of kill against fleas was demonstrated for NexGard with consecutive monthly dosing.

## IMPORTANT SAFETY INFORMATION:

For use in dogs only. The most common adverse reaction is vomiting. Other adverse reactions reported are dry/flaky skin, diarrhea, lethargy, and anorexia. 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.

## References

- <sup>1</sup> Beugnet F, Liebenberg J, Halos L. Comparative speed of efficacy against *Ctenocephalides felis* of two oral treatments for dogs containing either afoxolaner or fluralaner. *Vet Parasitol.* 2015;207:297–301.
- <sup>2</sup> Letendre L, Harriman J, Huang R, Kvaternick V, et al. The intravenous and oral pharmacokinetics of afoxolaner, a novel isoxazoline, used as a monthly chewable antiparasitic for dogs. *Vet Parasitol.* 2014;201:190–197.
- <sup>3</sup> Kunkle BN, Drag M, Chester TS, Larsen DL. Assessment of the onset of action of afoxolaner against existing adult flea (*Ctenocephalides felis*) infestations on dogs. *Vet Parasitol.* 2014;201:204–206.
- <sup>4</sup> Shoop WL, Hartline EJ, Gould BR, Waddell ME, et al. Discovery and mode of action of afoxolaner, a new isoxazoline parasiticide for dogs. *Vet Parasitol.* 2014;201:179–189.



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NEX15TECHALERT1 (07/15).

## NexGard starts killing fleas fast for the entire treatment period

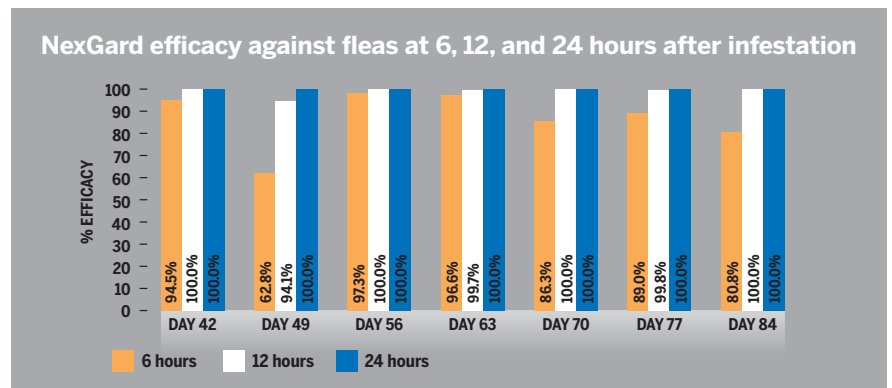
### Introduction

Immediate and sustained speed of kill are important characteristics of flea control products, because these can affect the comfort of the dog and whether the pet owner observes fleas on the dog; their primary determination of effectiveness. The effectiveness of a systemically active drug like afoxolaner is affected by the dose administered and its pharmacokinetic properties, including the peak plasma levels achieved after ingestion, plasma protein binding, and the drug's terminal plasma half-life ( $15.5 \pm 7.8$  days for afoxolaner).<sup>2</sup> A decrease in the speed of kill over time is typically observed with systemic or topical flea control products, during the time when plasma or hair coat concentrations of active ingredient decline.

In a previous study,<sup>3</sup> the immediate speed of kill after treatment of flea-infested dogs with NexGard was 87.8% four hours and 100% eight hours after treatment.

### Methodology

8 dogs were treated with NexGard by body weight on Days 0, 28 and 56. Treated and untreated control dogs were infested with 100 unfed adult cat fleas (*Ctenocephalides felis*) on days 42, 49, 56, 63, 70, 77, and 84. Flea counts were conducted by combing at 6, 12, and 24 hours after infestation. On Day 56, the flea infestation was performed after the administration of NexGard.



## Results and Discussion

After three consecutive treatments with NexGard, efficacy at 6 hours after infestation remained greater than 80% for 28 days. Studies examining multiple dose kinetics of afoxolaner in dogs showed low accumulation, with a ratio of  $AUC_{0-\text{Inf}}$  (Dose #3) to  $AUC_{0-\text{Inf}}$  (Dose #1) of approximately 1.0,<sup>2</sup> and achievement of steady state after the second or third dose.<sup>4</sup>

The results reported for the study highlighted here<sup>1</sup> demonstrate that NexGard provides consistently rapid speed of kill through the dosing period after consecutive dosing.

# NexGard<sup>®</sup>

## (afoxolaner) Chewables

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

### Description:

NexGard<sup>®</sup> (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-[2,2,2-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 <sup>1</sup>	% (n=415)	N <sup>2</sup>	% (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

<sup>1</sup>Number of dogs in the afoxolaner treatment group with the identified abnormality.

<sup>2</sup>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.

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](http://www.merial.com/nexgard). For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS 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.

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