Fleas can cause considerable discomfort and health problems for pets, and infestations can be difficult to eliminate and frustrating for owners. At the same time, ticks are expanding in number and geographic range, putting dogs at greater risk for vector-borne diseases. Now, with NexGard, dog owners can effectively kill adult fleas, treat and prevent flea infestations, and treat and control ticks with the convenience of a palatable, soft, beef-flavored chew. This monthly flea and tick treatment contains afoxolaner, a molecule developed for veterinary medicine.

For the entire month, NexGard kills Ctenocephalides felis fleas before they can lay eggs, preventing subsequent flea infestations. This oral medication also provides sustained, month-long killing of black-legged ticks (Ixodes scapularis), American dog ticks (Dermacentor variabilis), and Lone star ticks (Amblyomma americanum).¹

NexGard is an FDA-approved product that has demonstrated safety and excellent efficacy in pivotal laboratory studies and in client-owned dogs.

IMPORTANT SAFETY INFORMATION: NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
NexGard Highlights

NexGard is indicated for the treatment and prevention of flea (*Ctenocephalides felis*) infestations and the treatment and control of black-legged tick (*Ixodes scapularis*), American dog tick (*Dermacentor variabilis*), and Lone star tick (*Amblyomma americanum*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 lbs of body weight or greater, for 1 month.\(^1\)

### Afoxolaner: A Molecule Developed for Veterinary Medicine
- NexGard contains afoxolaner, a novel member of the isoxazoline chemical class.
- Afoxolaner kills fleas and ticks by targeting a distinct binding site within nerve cell membrane GABA (gamma aminobutyric acid)—modulated chloride channels, resulting in uncontrolled hyperexcitation and death.\(^2\)

### Flea and Tick Control in a Palatable, Soft, Beef-Flavored Chew
- With braised-beef flavoring, each NexGard chew features a meaty appearance, chewy texture, and beefy aroma.
- The soft chew provides clients with ease of administration.

### Works Fast Against Flea Infestations\(^1\)
- Starts killing fleas within 4 hours after treatment.
- Kills adult fleas before they can lay eggs, reducing environmental flea biomass (eggs, larvae, and pupae).
- Prevents reinfestation with new fleas.

### Keeps Killing Adult Fleas All Month Long\(^1\)
- With new infestations, the majority of adult fleas are killed within 12 hours.
- In a well-controlled study, 100% of fleas were killed within 24 hours throughout the monthly treatment period.
- In a field study, NexGard reduced fleas by 98.0% to 99.9% over the course of 3 monthly treatments.

### Kills Ticks for 1 Month\(^1\)
- In studies, NexGard provided month-long killing power against *I. scapularis*, *D. variabilis*, and *A. americanum* ticks.

### No Need to Administer With Food
- Most dogs readily take the palatable chew, so there is no need to hide it in food.\(^3\)
- Afoxolaner plasma levels are the same regardless of whether NexGard is given with or without food.\(^3\)

**IMPORTANT SAFETY INFORMATION:** NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
Afoxolaner: Developed for the treatment of fleas and ticks in veterinary medicine

Afoxolaner is a novel member of the isoxazole class of compounds. This class of parasiticides was developed to deliver exceptional activity against a broad range of pests via potent blocking of nerve cell membrane GABA (gamma aminobutyric acid)–modulated chloride channels in fleas and ticks.

Isoxazolines comprise a wide array of naturally occurring and synthetic compounds. Some of these confer adaptive and protective capabilities, such as in certain sea sponges, in which isoxazoline alkaloids help protect them from a species of sea snails that feed on the sponges. Additionally, isoxazoline derivatives display significant therapeutic potential because of their antiparasitic, anti-inflammatory, antimicrobial, antitumor, anti-HIV, fibrinogen receptor antagonistic, caspase inhibitory, and antidepressant properties. Certain synthetically derived isoxazoline compounds also show activity against insects and acarines, including fleas and ticks.

Development of Afoxolaner: A Veterinary Prescription Drug for Treating Fleas and Ticks

A group of trisubstituted isoxazoline compounds that displayed excellent activity against the cat flea (Ctenocephalides felis) were identified. From these compounds, afoxolaner was selected for further evaluation.

Afoxolaner Safety

Safety evaluations of afoxolaner across multiple species demonstrated a general lack of systemic, dermal, ocular, neurologic, reproductive, or genetic toxicity. Laboratory animal studies in rodents evaluated oral doses up to 1,000 mg/kg in rats and 2,000 mg/kg in mice. No mortality was observed; the only effects reported in rats were reductions in food consumption and body weight. Afoxolaner is nonirritating to skin and only slightly irritating to the eyes. In specialized studies in rats and rabbits, afoxolaner was not found to be a reproductive toxicant.

Promising Proof-of-Concept Studies

Discovery studies in dogs demonstrated that afoxolaner was effective at controlling fleas and ticks on dogs for at least 1 month when administered orally at a dose of 2.5 mg/kg. A series of in vitro and in vivo proof-of-concept studies were performed using an experimental oral solution of afoxolaner. Results of these studies provided an indication for:

- The blood concentration of afoxolaner necessary to kill fleas
- In vivo safety and efficacy of afoxolaner against multiple flea and tick challenges
- The pharmacokinetic characteristics of afoxolaner
- The molecule’s unique insecticidal/acaricidal mode of action
- Unlikely potential for cross-resistance to commonly used insecticides
- Strong support for afoxolaner as an excellent choice for further development

Mode of Action: The GABA-Gated Chloride Channel

Afoxolaner kills fleas and ticks by binding to insect and acarine nerve cell membrane chloride channels, gated by the neurotransmitter GABA, thereby blocking the flow of chloride ions across cell membranes and inhibiting the firing of new action potentials. Binding to glutamate-gated chloride channels has also been noted. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines.

Important Safety Information: Nexgard is for dogs only and hasn’t been evaluated for use in pregnant, breeding, or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.

Although GABA-gated chloride channels are also target receptors of fipronil and cyclodienes (dieldrin), afoxolaner is unique because it targets a distinct site within the pentameric protein complex in which the chloride channel is situated. Cross-resistance studies using insects carrying the point mutation at the Rdl gene locus in GABA-gated chloride channels found no cross-resistance of afoxolaner with dieldrin, demonstrating that afoxolaner acts on a unique receptor site.
Afoxolaner Pharmacokinetics

After oral administration to dogs, afoxolaner is rapidly absorbed into the systemic circulation, where the drug becomes active against fleas and ticks upon a blood meal. Afoxolaner is highly protein bound (>99%), while unbound afoxolaner distributes moderately into tissues. The single exponential decay of afoxolaner in plasma during the terminal phase from Day 2 to 3 months suggests that no special tissue depots are present in the dog. This is consistent with the physical chemical properties of afoxolaner, which favor passive diffusion into and out of tissues.

Afoxolaner is slowly eliminated from the body via biliary excretion of free afoxolaner and via hepatic metabolism and subsequent biliary and renal clearance of afoxolaner metabolites. This slow clearance gives afoxolaner a long half-life in dogs and sustained ectoparasitic activity.

Pharmacokinetic Studies Demonstrated Rapid Absorption and Long Half-Life of Afoxolaner

In vivo studies were performed to evaluate the pharmacokinetics and oral bioavailability of afoxolaner in dogs.

In an oral bioavailability study, 12 fasted beagles were assigned to two groups of six dogs. One group was administered 1 mg/kg of afoxolaner intravenously delivered in ≈1 mL of a polyethylene glycol (PEG) 400:ethanol (8:2 v/v) solution, and another group was administered an oral chew with an afoxolaner dose of 2.83 mg/kg. Following oral administration, afoxolaner:

- Was rapidly absorbed (T_{max} = 2 to 4 hours)
- Achieved a maximum plasma concentration (C_{max}) of 1,655 ± 332 ng/mL
- Demonstrated a bioavailability of 73.9%
- Exhibited a terminal plasma half-life (T_{1/2}) of 15 days

In another study, 32 mongrel dogs were randomly assigned to four groups of eight dogs. Dogs in three of the groups were administered an oral chew with increasing doses of afoxolaner for each group (1.0, 2.5, and 4.0 mg/kg). The control group received an oral chew without afoxolaner.

**Pharmacokinetic Parameters for Afoxolaner Following Oral Administration of Afoxolaner in a Soft, Beef-Flavored Chew**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route of administration</td>
<td>Oral chew</td>
<td>Oral chew</td>
<td>Oral chew</td>
</tr>
<tr>
<td>Dose (mg/kg)</td>
<td>1.01 ± 0.01</td>
<td>2.54 ± 0.02</td>
<td>4.05 ± 0.03</td>
</tr>
<tr>
<td>T_{max} (hr)</td>
<td>2 to 6</td>
<td>2 to 4</td>
<td>2 to 6</td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>538 ± 85</td>
<td>1,384 ± 330</td>
<td>2,147 ± 575</td>
</tr>
<tr>
<td>T_{1/2} (day)</td>
<td>14.4 ± 3.6</td>
<td>15.2 ± 5.1</td>
<td>15.6 ± 9.0</td>
</tr>
</tbody>
</table>

Mean Afoxolaner Plasma Concentration Over Time

Mean afoxolaner plasma concentrations maintained dose proportionality throughout the measurement intervals. At all dose levels, afoxolaner plasma concentrations were proportional to the dose administered. Time to maximum concentration (T_{max}) and terminal plasma half-lives (T_{1/2}) were similar over the dose range evaluated.

**IMPORTANT SAFETY INFORMATION:** NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
A Pivotal Study Demonstrated Low Accumulation of Afoxolaner After Multiple Doses

The multiple-dose kinetics of afoxolaner were investigated in this study. Three male and three female beagle dogs were administered afoxolaner orally in a PEG 400:ethanol (8:2 v/v) solution via gavage once a month for 3 months (Days 0, 28, and 56). Blood was collected at regular intervals and through 28 days after the last dose.

Steady state was reached by the third monthly dose. There was low accumulation of afoxolaner, and the ratio for $C_{\text{max}}$ was 1.3 (a 30% increase from Dose 1 to Dose 3). The half-life was comparable after each of the three monthly doses. These parameters indicate that the clearance, distribution, and absorption processes are neither saturated nor induced after monthly dosing and the kinetics are linear.

The chewable formulation of afoxolaner was administered to five fed and five fasted dogs to determine whether food affects the pharmacokinetic characteristics of afoxolaner. Dogs in the first treatment group were fed before treatment, and dogs in the second treatment group were fasted overnight, before treatment, and for 4 hours after treatment. Blood samples were collected until Study Day 30. There was no difference in maximum plasma afoxolaner concentrations ($C_{\text{max}}$) between fed (1,366 ± 276 ng/mL) and fasted (1,453 ± 374 ng/mL) dogs, and the dogs’ overall afoxolaner exposure (AUC$_{0-\infty}$) was not affected by their preprandial state.

Because the pharmacokinetic characteristics of afoxolaner in fed and fasted dogs are essentially the same, there is no need to administer afoxolaner with food.

Plasma Concentration of Afoxolaner Over Time in Fed and Fasted Dogs

Experimental and Simulated Afoxolaner Plasma Concentration Over Time

IMPORTANT SAFETY INFORMATION: NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
Afoxolaner acts systemically, and a strong correlation was found between plasma concentration and efficacy.

A pharmacokinetic/pharmacodynamic model was used to describe the relationship between afoxolaner plasma concentration and percent efficacy. Data for flea efficacy at 24 hours and tick efficacy at 48 hours were compared with concurrent plasma afoxolaner levels using a sigmoidal $E_{\text{max}}$ model. The $EC_{90}$, or the afoxolaner plasma concentration estimated to provide 90% efficacy, was calculated using this model.

**Afoxolaner Pharmacodynamics**

The $EC_{90}$ value* for *C. felis* was determined to be 23 ng/mL.

The $EC_{90}$ value* for *D. variabilis* was determined to be 110 ng/mL.

**IMPORTANT SAFETY INFORMATION:** NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
The Goals of Flea Control

Effective flea control should provide relief to the pet and eliminate premise infestation.® Control of flea infestations is mainly based on the regular administration of flea adulticide products that accomplish these objectives through rapid speed of kill and killing fleas before they can lay eggs. Insect growth regulators and juvenile hormone analogues prevent development of flea eggs that are produced, but they do not provide relief to the pet or address other flea-related health issues.

Dogs are primarily infested by two flea species: the cat flea, *Ctenocephalides felis felis*, and the dog flea, *Ctenocephalides canis*. *C. felis* is the predominant flea species found on dogs and cats in the United States and worldwide.® Fleas are responsible for several clinical signs, including pruritus, alopecia, pale mucous membranes associated with anemia, and seborrhea. Flea saliva can also lead to the development of flea allergy dermatitis (FAD).

Fleas are the carrier of pathogens, including *Rickettsia felis*, *Bartonella henselae*, and *Mycoplasma* (hemoplasma), and the tapeworm *Dipylidium caninum*. In addition to infesting dogs and cats, *C. felis* readily infest numerous species of wild animals (canids, opossums, raccoons), domestic rabbits, and hedgehogs. *C. felis* will bite humans but will not establish a permanent infestation on people.

Sources of Flea Infestation

All of the animal species that are suitable hosts for the cat flea share habitats with people and their pets, and as a result, sites of flea development are ubiquitous. Part of what makes fleas so insidious is that they can infiltrate a pet owner’s home so easily:

- Once on a preferred host, cat fleas start feeding within minutes and begin breeding. A female flea can start laying eggs within 24 hours and can produce 40 to 50 eggs per day.®
- Feral cats and wildlife such as raccoons, opossums, and foxes can be heavily infested with cat fleas and are an important source of flea eggs. Newly emerged fleas from these eggs can jump on a pet when it explores areas where these animals have taken shelter.
- Fleas can hitch a ride inside on people’s clothing.
- Untreated, infested pets that are visiting a home can leave fleas and flea eggs behind.
- Dog parks, campsites, “doggy daycare,” and kennels can be hot spots for flea development. An untreated dog can become infested and seed its home with flea eggs.

Characteristics of a Flea Infestation

Development from eggs to larvae, pupae, and emerged fleas only takes about 3 weeks at 75°F.® By the time pet owners notice fleas on a pet and start treatment, they most likely have a flea infestation that has been developing under their feet for several weeks.

Key Factors in Successfully Treating and Preventing Flea Infestations

An effective parasiticide must:

- Start killing adult fleas quickly to minimize their feeding and reproductive abilities
- Disrupt the flea life cycle by killing fleas before they can lay eggs
- Continue providing flea-killing power for the entire treatment period to prevent new infestations

After a dog is treated with a flea adulticide, flea egg production is disrupted. An existing biomass of flea eggs, larvae, and pupae can still run its course, resulting in more fleas emerging into the environment until the biomass is exhausted. With monthly treatment with a long-lasting flea adulticide, new flea infestations will be prevented.
Studies Demonstrating NexGard Efficacy Against Fleas (Ctenocephalides felis)

In a Well-Controlled Laboratory Study, NexGard Began to Kill Fleas 4 Hours After Initial Administration and Demonstrated >99% Effectiveness at 8 Hours

An in vivo study was conducted to demonstrate the curative efficacy of NexGard against a pre-existing infestation of cat fleas (C. felis).

Study Design
Healthy beagles of either sex, 13.8 to 37.5 months of age and weighing 7.05 to 14.75 kg, were randomly assigned to the groups shown in the table at left.

Study Group | Number of Dogs | Treatment
--- | --- | ---
1 (Control) | 20 | None
2 | 20 | NexGard chew

All dogs were infested with ≈100 unfed C. felis fleas on Day –1. Treated dogs were administered a NexGard chew on Day 0 to achieve a minimum afoxolaner dose of 2.5 mg/kg of body weight.

Live fleas were counted upon removal at 4, 8, 12, and 24 hours after treatment. For each time point, flea counts were performed on 4 dogs from each of the control and treatment groups.

Four hours after treatment, flea counts were reduced 87.8% compared to flea counts on untreated dogs. NexGard demonstrated ≥99.5% efficacy against an existing flea infestation 8, 12, and 24 hours after treatment.

After Treatment, NexGard Kills Fleas Fast, Before They Can Lay Eggs

Flea egg counts were performed to assess the effectiveness of NexGard to reduce flea egg production on dogs that were pre-infested with C. felis the day before treatment. Flea egg counts were significantly reduced (P≤0.028) in comparison with the control group at 12 and 24 hours post-treatment, demonstrating that NexGard kills fleas fast, significantly reducing egg production from a flea infestation already established on the dog.

Counts of Flea Eggs Collected From Dogs 12 and 24 Hours After Treatment of a Pre-existing Flea Infestation

<table>
<thead>
<tr>
<th>Hours After Treatment</th>
<th>Control Group Geometric Mean (Range)</th>
<th>NexGard Group Geometric Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>15.5 (4–50)</td>
<td>1.7 (0–11)</td>
</tr>
<tr>
<td>24</td>
<td>27.2 (0–118)</td>
<td>3.9 (1–17)</td>
</tr>
</tbody>
</table>

Flea egg counts were performed to assess the effectiveness of NexGard to reduce flea egg production on dogs that were pre-infested with C. felis the day before treatment.

These results demonstrate that NexGard kills fleas fast after treatment. Because fleas can start laying eggs as soon as 24 hours after infestation, the fleas on these pre-infested dogs were competent to lay eggs at the time of treatment.

Percent Curative Efficacy of NexGard Against an Existing Cat Flea Infestation

![Graph showing percent curative efficacy of NexGard against existing cat flea infestation.]

Four hours after treatment, flea counts were reduced 87.8% compared to flea counts on untreated dogs. NexGard demonstrated ≥99.5% efficacy against an existing flea infestation 8, 12, and 24 hours after treatment.

Ctenocephalides felis Egg Count Reduction Efficacy 12 Hours After Treatment With NexGard in Dogs Pre-infested With Fleas the Day Before Treatment

![Graph showing egg count reduction efficacy of NexGard.]

IMPORTANT SAFETY INFORMATION: NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
In New Flea Infestations, NexGard Kills Adult Fleas Within 12 Hours for a Full Month

Even after existing flea infestations are eliminated, a dog can be exposed to several sources of continual reinfestation. Effective flea control requires treatments that continue to provide flea-killing power throughout the entire month.

Two in vivo studies were conducted to determine the efficacy of orally administered NexGard against repeated infestations with adult *C. felis* on dogs.

**Study Design**

The two studies used a total of 64 healthy beagles (34 males, 30 females) that were >6 months of age and weighed 8.2 to 19.6 kg. Within each study, the dogs were randomly assigned to the following groups:

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of Dogs</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>8</td>
<td>12-hour efficacy</td>
</tr>
<tr>
<td>NexGard chew</td>
<td>8</td>
<td>12-hour efficacy</td>
</tr>
<tr>
<td>None</td>
<td>8</td>
<td>24-hour efficacy</td>
</tr>
<tr>
<td>NexGard chew</td>
<td>8</td>
<td>24-hour efficacy</td>
</tr>
</tbody>
</table>

On Day 0, treated dogs were administered NexGard orally to achieve a minimum afoxolaner dose of 2.5 mg/kg of body weight.

All dogs were experimentally infested with 100 ± 5 unfed *C. felis* fleas on Days 7, 14, 21, 28, and 35. Live fleas were counted at 12 and 24 hours after infestations on Days 7, 14, 21, 28, and 35, according to count-by-time block assignments in each group.

**Results**

For all flea counts, the groups treated with NexGard had significantly lower flea counts than untreated control dogs in Study 1 (P<0.003) and Study 2 (P<0.0006).

For flea counts at 12 hours after infestation, NexGard efficacy was ≥95.2% through Day 21 in both studies. Efficacy continued at high levels and was ≥93.0% on Day 35 in Study 1 and ≥89.7% on Day 35 in Study 2.

**Percent Efficacy**

<table>
<thead>
<tr>
<th>Flea Infestation Day</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 7</td>
<td>95.2%</td>
<td>97.5%</td>
</tr>
<tr>
<td>Day 14</td>
<td>97.9%</td>
<td>97.7%</td>
</tr>
<tr>
<td>Day 21</td>
<td>98.4%</td>
<td>99.1%</td>
</tr>
<tr>
<td>Day 28</td>
<td>98.5%</td>
<td>99.5%</td>
</tr>
<tr>
<td>Day 35</td>
<td>98.9%</td>
<td>99.2%</td>
</tr>
</tbody>
</table>

According to flea counts at 24 hours after infestation, NexGard efficacy was 100% through Day 35 in both studies, except for one time point (99.9% on Day 21 in Study 2).

**SIGNIFICANCE**

With new flea infestations, NexGard kills the majority of adult fleas within 12 hours and provides 100% efficacy at 24 hours post-infestation throughout the monthly treatment period.
NexGard Kills Fleas Before They Can Lay Eggs All Month

Immature flea stages account for the vast majority of any flea infestation. Flea eggs can be difficult to eliminate because they can lodge deep in carpeting, upholstery, or floor cracks and crevices. An effective flea adulticide kills fleas before they can contaminate the environment with eggs.

In a study, flea egg counts were performed to evaluate the efficacy of orally administered NexGard in the prevention of flea egg production with repeated infestations of adult C. felis on dogs.

### Study Design

Thirty-two healthy beagles of either sex (22 males and 10 females) older than 12 months and weighing 9.1 to 19.1 kg were randomly assigned to the groups listed in the table at left.

All dogs were infested with 100 ± 5 unfed C. felis fleas on Day –1. Treated dogs were administered a NexGard chew on Day 0 to achieve a minimum afoxolaner dose of 2.5 mg/kg of body weight. Dogs were not fed before treatment. All dogs were repeatedly reinfested with unfed fleas on Days 7, 14, 21, 28, and 35.

To facilitate flea egg collection, the waste pans below the cages were cleaned and the pans were lined with paper. In Groups 1 and 2, shed flea eggs were collected and counted at 12 hours ± 30 minutes post-infestation. In Groups 3 and 4, eggs were collected and counted at 24 hours ± 1 hour post-infestation. Egg counts were performed on Days 0, 1, 7, 8, 14, 15, 21, 22, 28, 29, 35, and 36 according to count-by-time block assignments in each group.

### Results

For all flea egg counts, the groups treated with NexGard had significantly lower flea egg counts than untreated control dogs ($P<0.028$).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Number of Dogs</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: None</td>
<td>8</td>
<td>12-hour flea egg efficacy</td>
</tr>
<tr>
<td>2: NexGard chew</td>
<td>8</td>
<td>12-hour flea egg efficacy</td>
</tr>
<tr>
<td>3: None</td>
<td>8</td>
<td>24-hour flea egg efficacy</td>
</tr>
<tr>
<td>4: NexGard chew</td>
<td>8</td>
<td>24-hour flea egg efficacy</td>
</tr>
</tbody>
</table>

For the egg counts at 12 hours after infestation, no flea eggs were found on Days 7, 28, and 35, resulting in 100% efficacy. A single flea egg was collected from each of two dogs on Day 14, resulting in 99.1% efficacy, and a single flea egg was collected from one dog on Day 21, resulting in 99.5% efficacy.

### Percent Efficacy* in Flea Egg Reduction at 12 Hours After Infestation for Dogs Treated With NexGard

For egg counts performed 24 hours after infestation, no flea eggs were found on any day, resulting in 100% efficacy, with the exception of Day 14, when a single flea egg was collected on one dog, resulting in 99.8% efficacy at that time point.

### Percent Efficacy* in Flea Egg Reduction at 24 Hours After Infestation for Dogs Treated With NexGard

*Percent efficacy = 100 × [ (C – T)/C], where T and C are the geometric mean flea egg counts of the treated and control groups, respectively.

**IMPORTANT SAFETY INFORMATION:** NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
In a Field Study, NexGard Was Effective at Killing Adult Fleas on Client-Owned Dogs

Field studies demonstrate how a flea product works in the "real world," where dogs may be exposed to newly emerged fleas from environments contaminated with flea eggs, larvae, and pupae.

A 90-day, multicenter, clinical field study was conducted to evaluate the safety and efficacy of NexGard chews. The blinded, positive-control study used a randomized block design based on order of household enrollment.

The efficacy component of this study, which focused on activity against fleas in a single sentinel (index) dog in each household, is described below. Although tick counts were performed, the number of dogs with ticks was too low to assess tick efficacy.

The safety portion of this study, which included the index dogs as well as all treated dogs in the households, can be found on page 32.

**Efficacy Assessment Study Design**

A total of 282 index dogs from 282 households were enrolled at veterinary clinics in 14 sites across the United States. Participating households were selected based on the following inclusion criteria:

- Ownership of healthy dog(s) with up to five dogs and cats in the household.
- At least one dog in the household had to harbor ≥10 fleas and was designated the index dog.
- In households where more than one dog had at least 10 fleas, the index dog was randomly selected.

For each study site, blocks of three households were formed based on order of enrollment. Within blocks, households were assigned to the treatment groups listed in the table below.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Number of Dogs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>186</td>
<td>NexGard chew</td>
</tr>
<tr>
<td>2</td>
<td>96</td>
<td>Oral active control product</td>
</tr>
</tbody>
</table>

Treatments were dispersed at the veterinary clinics on Visit 1 (Day 0), Visit 2 (≈Day 30), and Visit 3 (≈Day 60). Owners were instructed to administer the treatment within 4 days of the visit in each household:

- All dogs were treated with NexGard or an oral active control product.
- All cats were treated with a topical flea—tick product.

On Days 0, 30, 60, and 90, index dogs were evaluated at the veterinary clinics for ectoparasites:

- Flea counts were performed by systematically using a fine-toothed flea comb for at least 5 minutes.
- Live fleas and ticks were removed, counted, and recorded.

**Results**

At the start of the trial, initial flea counts on dogs subsequently treated with NexGard averaged 26.5. From baseline (Visit 1, pretreatment), NexGard-treated dogs showed a significant reduction in fleas at all visits (P<0.001). There was a 98% effectiveness in reduction in fleas 1 month after the first treatment, 99.7% effectiveness after Month 2, and 99.9% effectiveness after Month 3.

**SIGNIFICANCE**

In households with existing flea infestations of varying severity, NexGard reduced fleas by 98.0% to 99.9% over the course of 3 monthly treatments.

**Percent Reduction in Fleas for NexGard Treatment Group, Geometric Mean**

![Percent Reduction in Fleas for NexGard Treatment Group, Geometric Mean](image)

**IMPORTANT SAFETY INFORMATION**: NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
Today, ticks pose a greater threat to dogs across the country than ever before. Several tick species are following the growing population of white-tailed deer, their preferred hosts, into new areas. Other wildlife hosts, such as coyotes, raccoons, wild turkeys, and even feral cats and dogs are moving into suburban and urban areas, bringing ticks with them. And in many areas, climate fluctuations are extending the tick season.

All of this adds up to more ticks, distributed across a broader geographic range, often with prolonged tick questing activity, putting canine patients at greater risk of tick-borne diseases.

Dogs May Be Co-infected With Multiple Pathogens

Ticks can transmit a wide range of bacterial, rickettsial, viral, protozoan, and fungal organisms. To complicate matters, ticks can be co-infected with multiple infectious microbes, and dogs can also be infested with more than one species of tick; this means canine patients are at increased risk of becoming infected with multiple tick-borne pathogens.

Co-infection with more than one tick-borne pathogen can complicate the clinical presentation and make diagnosis more difficult.

With the expansion of ticks into more places, veterinarians should be on the lookout for signs of tick-borne diseases in their patients.

Because ticks are expanding into new geographic areas, veterinary practitioners may encounter infectious diseases that were once uncommon in the area.

### Ticks of Veterinary Importance May Be Infected With More Than One Pathogen

<table>
<thead>
<tr>
<th>Vector</th>
<th>Organism or Agent</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ixodes scapularis (black-legged tick)</td>
<td><em>Borrelia burgdorferi</em>[^25,26]</td>
<td>Lyme disease</td>
</tr>
<tr>
<td></td>
<td><em>Anaplasma phagocytophilum</em>[^27]</td>
<td>Anaplasmosis</td>
</tr>
<tr>
<td>Dermacentor variabilis (American dog tick)</td>
<td><em>Rickettsia rickettsii</em>[^26,27]</td>
<td>Rocky Mountain spotted fever</td>
</tr>
<tr>
<td></td>
<td><em>Ehrlichia canis</em>[^28,29]</td>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td></td>
<td><em>Ehrlichia chaffeensis</em>[^30,31]</td>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td></td>
<td>Salivary neurotoxins[^26]</td>
<td>Tick paralysis</td>
</tr>
<tr>
<td>Amblyomma americanum (Lone star tick)</td>
<td><em>Ehrlichia ewingii</em>[^27]</td>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td></td>
<td><em>Ehrlichia chaffeensis</em>[^30,31]</td>
<td>Ehrlichiosis</td>
</tr>
<tr>
<td></td>
<td>Salivary neurotoxins[^32]</td>
<td>Tick paralysis</td>
</tr>
<tr>
<td></td>
<td>Possibly <em>Rickettsia rickettsii</em>[^26]</td>
<td>Rocky Mountain spotted fever</td>
</tr>
</tbody>
</table>

[^25]: Experimental infections have been documented with this vector.

### Canine Tick-Borne Diseases and Their Clinical Signs

The growing list of tick-borne infections that can harm dogs in the United States includes:

- **Lyme disease (borreliosis)**[^25]:—Fever, lameness, joint swelling, or lymphadenomegaly may be the only signs in the early stages of this disease. Lyme disease can also be subclinical. Infection has been associated with a severe and fatal form of protein-losing glomerulonephritis.

- **Rocky Mountain spotted fever**[^28]:—The short incubation period of this disease (2 to 14 days) means clinical signs, such as fever and edema of the extremities, lips, pinnae, and scrotum, can occur relatively soon after transmission. Petechial or ecchymotic hemorrhage are also common findings. Lab results often reveal thrombocytopenia.

- **Ehrlichiosis**[^29]:—Subtle signs, such as anorexia, bleeding diatheses, fever, lethargy, and lymphadenomegaly, are common with this disease. Dogs may then enter into a subclinical stage, and show no outward signs, but exhibit thrombocytopenia on laboratory analysis. In the chronic stages, impaired bone marrow production may lead to pancytopenia and a poor prognosis.

- **Anaplasmosis**[^30,31]:—The causative agent for anaplasmosis is transmitted by the same ticks that carry the pathogen for Lyme disease. The result is that dogs may be co-infected with both *A. phagocytophilum* and *B. burgdorferi*. Similar to other tick-borne diseases, signs of anaplasmosis may include anorexia, fever, lameness, and lethargy. Thrombocytopenia may also occur.

- **Tick paralysis**[^26]:—Salivary neurotoxins from feeding female ticks cause tick paralysis. The first clinical signs are weakness and hindlimb incoordination, followed by paralysis in the forelimbs, neck, and respiratory muscles. Once ticks are removed, affected dogs will usually recover.
Six studies with a total of 108 dogs were conducted to evaluate the efficacy of NexGard against three species of ticks of veterinary importance in the United States (Ixodes scapularis, Dermacentor variabilis, and Amblyomma americanum). The FDA Center for Veterinary Medicine requires at least two studies demonstrating effectiveness against each species of tick.

**Study Design**

Although each study used a single species of tick, all studies followed the same randomized block design. In each study, 16 to 20 beagles ranging from 6.1 to 46.2 months of age were randomly assigned to two groups, as shown in the table.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Number of Dogs</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Control)</td>
<td>8 to 10</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>8 to 10</td>
<td>NexGard chew</td>
</tr>
</tbody>
</table>

On Day –1, all dogs were infested with ≈50 unfed adult ticks. On Day 0, dogs in Group 2 were administered a NexGard chew to achieve a minimum afoxolaner dose of 2.5 mg/kg of body weight.

All dogs were reinfested with 50 ticks on Days 7, 14, 21, and 28. Forty-eight hours after treatment, live and dead ticks were collected from all dogs. After re-infestation on Days 7, 14, 21, and 28, live and dead ticks were removed and counted from individual animals at 48 hours after infestation in the I. scapularis and D. variabilis studies. In the A. americanum studies, live and dead ticks were removed and counted from individual animals at 72 hours after infestation.

Percent effectiveness of the treated group with respect to the control group was based on live tick counts on the animals and was calculated using the formula 

\[
\frac{(C – T)}{C} \times 100
\]

where \( C \) = geometric mean of live ticks on the control group dogs and \( T \) = geometric mean of live ticks on the treated group dogs for each time point.

Dead ticks in the collection pans under the cages were counted and removed 24 and 48 hours after treatment in all studies. After infestation on Days 7, 14, 21, and 28, dead ticks were counted and removed from collection pans 24 and 48 hours after infestation (I. scapularis and D. variabilis studies) or 24, 48, and 72 hours after infestation (A. americanum studies).

**Results: Ixodes scapularis**

NexGard was ≥94.2% effective against live I. scapularis ticks through Day 30. Live tick counts were significantly reduced (\( P \leq 0.002 \) and \( P < 0.001 \) for Studies 1 and 2, respectively), and dead tick counts were significantly increased (\( P < 0.001 \) and \( P < 0.007 \) for Studies 1 and 2, respectively) in the treated group compared to the control group at all time points.

### Percent Efficacy Against Ixodes scapularis

48 Hours After Treatment or Reinfestation

<table>
<thead>
<tr>
<th></th>
<th>Day 2</th>
<th>Day 9</th>
<th>Day 16</th>
<th>Day 23</th>
<th>Day 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>98.4%</td>
<td>98.9%</td>
<td>98.4%</td>
<td>99.6%</td>
<td>98.6%</td>
</tr>
<tr>
<td>Study 2</td>
<td>99.1%</td>
<td>99.1%</td>
<td>99.1%</td>
<td>99.6%</td>
<td>99.2%</td>
</tr>
</tbody>
</table>

*A minimum of 25% of the original ticks used to infest the animal at each time point evaluated was considered to be an adequate infestation, and a minimum of six adequately infested control dogs was required for the study to be considered valid. These conditions were not met for the tick infestations on Day 7 of Study 1 and Day 21 of Study 2.

**IMPORTANT SAFETY INFORMATION:** NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
Results: *Amblyomma americanum*\(^1\)
NexGard was 100% effective against live adult *A. americanum* ticks when measured 48 hours after treatment and was ≥97.8% effective when measured at 72 hours post-infestation for 31 days. Live tick counts were significantly reduced (\(P \leq 0.001\)) and dead tick counts were significantly increased (\(P \leq 0.018\)) in the treated group compared to the control group at all time points.

**SIGNIFICANCE**
The increased number of dead ticks and the reduction of live ticks across all studies support the treatment and control indications of NexGard for black-legged ticks (*I. scapularis*), American dog ticks (*D. variabilis*), and Lone star ticks (*A. americanum*).

**IMPORTANT SAFETY INFORMATION:** NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.

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Results: *Dermacentor variabilis*\(^4\)
NexGard was ≥97.3% effective against live *D. variabilis* ticks through Day 30. There were significant differences in live tick counts (\(P \leq 0.006\)) and dead tick counts (\(P \leq 0.002\)) between treated and control dogs at all time points.

---

**Percent Efficacy Against *Dermacentor variabilis***
48 Hours After Treatment or Infestation

<table>
<thead>
<tr>
<th>Time</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 9</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 16</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 23</td>
<td>97.7%</td>
<td>97.3%</td>
</tr>
<tr>
<td>Day 30</td>
<td>98.5%</td>
<td>98.5%</td>
</tr>
</tbody>
</table>

---

**Percent Efficacy Against *Amblyomma americanum***
48 Hours After Treatment and 72 Hours After Infestation

<table>
<thead>
<tr>
<th>Time</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 10</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 17</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 24</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 31</td>
<td>98.9%</td>
<td>98.9%</td>
</tr>
</tbody>
</table>

---

**Percent Efficacy Against *Dermacentor variabilis***
48 Hours After Treatment or Infestation

<table>
<thead>
<tr>
<th>Time</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 10</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 17</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 24</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Day 30</td>
<td>98.9%</td>
<td>98.9%</td>
</tr>
</tbody>
</table>
Initial Probe Studies Demonstrated the Safety of Afoxolaner in Dogs

Before developing the final formulation of NexGard, numerous probe studies were conducted with an experimental oral solution of afoxolaner designed to provide high bioavailability and accurate dosing. During the entire length of the study, all dogs were evaluated by veterinary physical exams, weight, and serum chemistry and hematology, as well as clinical observations for adverse reactions.

In initial safety studies, oral administration of 25 mg/kg afoxolaner every other week for 3 months resulted in no clinically significant effects. Toxicology studies with afoxolaner in dogs demonstrated no clinically relevant effects following two oral doses of 100 mg/kg.

A 5-month in vivo study also evaluated the safety of the test compound when administered to dogs at an afoxolaner dose of 2.5 mg/kg at 30-day intervals. No clinical signs of adverse reactions were observed during the study. Group means for hematology and serum chemistry parameters were within normal limits. Weight variation was minimal, with no discernable difference between the afoxolaner-treated group and the control group.

SIGNIFICANCE
These findings confirmed the potential for afoxolaner as a safe ectoparasiticide for dogs and led the way to additional target animal safety studies.

In a Margin of Safety Study, NexGard Was Demonstrated to Be Well Tolerated in Dogs as Young as 8 Weeks of Age

A 4.5-month in vivo study was conducted to evaluate the safety of afoxolaner formulated as a soft, beef-flavored chew in dogs.

Study Design
Thirty-two healthy puppies (16 males and 16 females) 8 to 9 weeks of age were randomly allocated into four groups. Dogs were dosed at 1×, 3×, and 5× multiples of the highest afoxolaner exposure level for the product weight ranges (6.3 mg/kg).

All dogs were observed for general health twice daily beginning on at least Day –14. Feed consumption was monitored daily beginning on Day –1.

Treatments were administered at:
- 4-week dose intervals through Day 84 (Days 0, 28, 56, and 84)
- Followed by 2-week intervals (Days 98 and 112)

Physical examinations including body weights were performed three times pretreatment and biweekly throughout the study period. Blood for clinical pathology analysis was collected twice pretreatment and biweekly throughout the study period. Urine for urinalysis examination was collected once pretreatment and on Days 27 and 126.

All dogs were weighed and humanely euthanized, and a full necropsy with tissue collection was performed 2 weeks after the last treatment (Day 126).

Results
Throughout the study, no clinically or statistically significant abnormalities related to the administration of NexGard were observed. At all sampling periods, no afoxolaner-related changes were observed in:
- Daily food consumption
- Body weight
- Physical examination variables
- Hematology parameters
- Coagulation profiles
- Urinalysis parameters
- Plasma chemistry values
- Gross observation at necropsy
- H&E-stained microscopic tissue sections
- Terminal body or organ weights

Vomiting and diarrhea were observed sporadically across all groups, including the controls. There were no afoxolaner-related changes in:
- Gross observation at necropsy
- H&E-stained microscopic tissue sections
- Terminal body or organ weights

SIGNIFICANCE
NexGard was demonstrated to be well tolerated in dogs as young as 8 weeks of age.

IMPORTANT SAFETY INFORMATION: NexGard is for dogs only and has not been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.
Any health abnormalities observed in the dogs treated with NexGard were regarded as mild. There was a similar prevalence of abnormal health observations reported for both the NexGard and oral active control product groups, with the exception of emesis. The prevalence of emesis in dogs treated with the oral active control product was ≈3 times higher than those treated with NexGard and was 4 times higher on the day of treatment.

Both NexGard and the oral active control product were administered in conjunction with anthelmintics, antibiotics, vaccines, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and other frequently used veterinary products. Concurrent medications administered during the study did not appear to impact the safety or efficacy of NexGard.

**SIGNIFICANCE**

NexGard has been demonstrated to be safe in dogs when administered by pet owners at the recommended dose over a 3-month period.

**Dogs With Adverse Reactions**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Afoxolaner (n=415)</th>
<th>Oral active control product (n=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting (with and without blood)</td>
<td>4.1%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Dry/flaky skin</td>
<td>3.1%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Diarrhea (with and without blood)</td>
<td>3.1%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>1.7%</td>
<td>4.5%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.2%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

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.

**IMPORTANT SAFETY INFORMATION:** NexGard is for dogs only and hasn’t been evaluated for use in pregnant, breeding or lactating dogs. Reported side effects include vomiting, dry/flaky skin, diarrhea, lethargy, and lack of appetite. Use with caution in dogs with a history of seizures.

---

**Multicenter Field Study Confirmed the Safety of NexGard in Client-Owned Dogs**

A 90-day, multicenter, clinical field study was conducted to evaluate the safety and efficacy of NexGard.

**Study Design**

The basic design of this study is described under the field efficacy study listed on page 22. In this well-controlled U.S. 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 by the 15 veterinary clinics that completed the study.

**Results**

The most frequent reactions reported at an incidence of >1% within any of the 3 months of observations are presented in the table on the next page.

The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting, 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. Two dogs with a history of seizures experienced seizures during the study.
NexGard: Product Composition and Packaging

Product Composition
Each NexGard chew is formulated to provide a minimum afoxolaner dosage of 2.5 mg/kg (1.14 mg/lb). Each chew contains 2.27% w/w of afoxolaner.

Chew Sizes
NexGard is available in four flavored chew sizes:

<table>
<thead>
<tr>
<th>Chew Size (g)</th>
<th>Quantity of Afoxolaner (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 g (11.3 mg)</td>
<td>11.3</td>
</tr>
<tr>
<td>1.25 g (28.3 mg)</td>
<td>28.3</td>
</tr>
<tr>
<td>3 g (68 mg)</td>
<td>68</td>
</tr>
<tr>
<td>6 g (136 mg)</td>
<td>136</td>
</tr>
</tbody>
</table>

Packaging
Each chew is packaged individually in a foil-backed blister card that contains one, three, or six chews. To remove a chew from the foil-backed blister, peel back the foil, starting at the arrow in the corner, as shown below.

NexGard: Administration

Frequency of Administration and Directions for Use
NexGard is given orally once a month at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

To give NexGard, first remove a chew from the foil-backed blister card by peeling back the foil from the inner corner, as shown by the arrow. The pack is designed so that the foil must be peeled back in three steps.

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 2 hours of administration, redose with another full dose. If a dose is missed, administer NexGard and resume a monthly dosing schedule.

NexGard Dosing and Administration

<table>
<thead>
<tr>
<th>Body Weight of Dog</th>
<th>NexGard 1.14 mg/lb (2.5 mg/kg) Minimum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chew Size (g)</td>
</tr>
<tr>
<td>Small</td>
<td>0.5</td>
</tr>
<tr>
<td>Medium</td>
<td>1.25</td>
</tr>
<tr>
<td>Large</td>
<td>3</td>
</tr>
<tr>
<td>Extra Large</td>
<td>6</td>
</tr>
</tbody>
</table>

Administer the appropriate combination of chewables.
Each chewable size is available in color-coded packages of three or six chews.

For dogs over 12.1 lbs, administer the appropriate combination of chewables.

| Small | For dogs 4.0 to 10.0 lbs |
| Large | For dogs 24.1 to 60.0 lbs |
| Medium | For dogs 10.1 to 24.0 lbs |
| Extra Large | For dogs 60.1 to 121.0 lbs |

Back Panel

**Indications:** NEXGARD is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg) as determined by a 20 mg afoxolaner tablet in three or six chews.

**Dosage and Administration:** NEXGARD is given orally once a month to provide adequate control of flea infestations (for tick infestations, see following table). The treatment and prevention of flea infestations (for tick infestations, see following table) is recommended and should be administered for at least two months to ensure that the dose is not lost or refused. It is recommended that the dose be administered every month during the tick season.

**Treatments:** NEXGARD should be administered at the same time of the day and in the same manner to ensure that the dose is not lost or refused. It is recommended that the dose be administered every month during the tick season.

**Storage Information:** NEXGARD should be stored at or below 30°C (86°F) with excursions permitted up to 40°C (104°F). NEXGARD should be stored at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

**Additional Information:** Contact your veterinarian if tick infestations are suspected.

**Not for Use in Human: Keep out of reach of children. In case of accidental ingestion, contact a veterinarian immediately.

**Warranty:** NexGard Chewables are covered by a 1-year warranty. See the warranty information for complete details.

**Precautions:** For additional information about adverse drug reactions reporting for animals, visit the U.S. Department of Health and Human Services, Food and Drug Administration's web site: www.fda.gov/animalvet.

**Adverse Reactions:** NEXGARD is expected to cause some adverse reactions in the dog. The most common adverse reactions to NEXGARD are vomiting and anorexia.

**Effectiveness:** In a well-controlled laboratory study, NEXGARD demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days. In another study, NEXGARD demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days. In a well-controlled field study, NEXGARD demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days.

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**Not for Use in Human: Keep out of reach of children. In case of accidental ingestion, contact a veterinarian immediately.

**Warranty:** NexGard Chewables are covered by a 1-year warranty. See the warranty information for complete details.

**Precautions:** For additional information about adverse drug reactions reporting for animals, visit the U.S. Department of Health and Human Services, Food and Drug Administration's web site: www.fda.gov/animalvet.

**Adverse Reactions:** NEXGARD is expected to cause some adverse reactions in the dog. The most common adverse reactions to NEXGARD are vomiting and anorexia.

**Effectiveness:** In a well-controlled laboratory study, NEXGARD demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days. In another study, NEXGARD demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days. In a well-controlled field study, NEXGARD demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days.

**Additional Information:** Contact your veterinarian if tick infestations are suspected.

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References
