

MICHAEL W. DRYDEN, DVM, MS, PHD
Kansas State University



KEY POINTS

- ▶ The tenacity of fleas in the environment presents challenges for a control program.
- ▶ Flea control programs often include both host-targeted and environmental insecticides or mechanical means of eliminating various flea stages.
- ▶ Two monthly doses of afoxolaner reduced on-animal flea counts by 100% on study days 40-45 and 54-60.⁴
- ▶ A dramatic shift from a female- to male-dominated flea population suggested that afoxolaner killed fleas rapidly, likely before female fleas could produce viable eggs.

Next Generation Flea & Tick Protection

Fleas are one of the most important ectoparasites of dogs in the United States. When assessing flea control products, several criteria are often used to determine the convenience and practical application for a pet owner. These factors include speed of action, duration and spectrum of activity, route of administration, and systemic versus topical action of the product.¹ Other important factors include owner compliance with administration and dosing recommendations as well as excessive bathing or swimming.² All of these are important characteristics for veterinarians to consider when recommending a flea and tick control product for a patient.

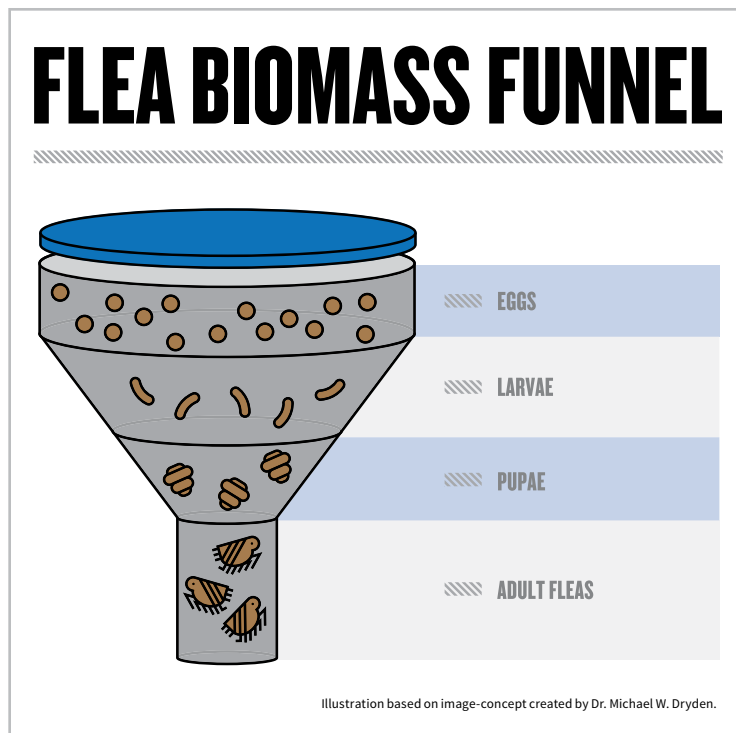
Animal health companies must also address these issues when developing flea and tick control products for pets. In January 2014, Merial launched **NexGard®** (afoxolaner), the first oral flea and tick control product for dogs. The development of NexGard has provided a convenient, easy-to-use monthly flea and tick control product for dogs in a chewable form that is highly palatable.³

Flea Tenacity

The most commonly encountered flea in North America is the “cat flea,” or *Ctenocephalides felis felis*.² Although the name can be misleading, *C. felis* is the most important flea species of dogs.¹ The tenacity of *C. felis* in the environment of the host presents challenges for a control program. The life cycle depends on the temperature and humidity of the microenvironment and can be as short as 12-14 days or as long as 174 days.² The pre-emergent adult can subsist as a pupa for weeks to months waiting for a suitable host to arrive.²

IMPORTANT SAFETY INFORMATION:

NexGard is for use in dogs only. The most frequently reported adverse reactions include 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. Visit www.nexgardfordogs.com or see the prescribing information located on page 12.



▲ Afoxolaner kills fleas before they can lay eggs.

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Flea infestations are common in the United States. A well-developed flea control program often includes host-targeted and environmental insecticides or mechanical means of eliminating various flea stages, such as vacuuming carpets and other infested fabrics and washing pet bedding and bed sheets.²

Speed of Kill & Residual Activity

Afoxolaner has rapid, month-long residual effectiveness in the dog. Client-owned dogs with flea infestations in Tampa, Florida, were included in a recent study to evaluate flea control within their private residences. The dogs were treated with 2 monthly doses of afoxolaner. On-animal flea counts 7 days after the first administration were reduced by 99.3% and were reduced by 99.9% when evaluated 28-30 days after administration. Additionally, 97.3% (or 36 out of 37) of participating dogs were found to be flea free after one month.⁴ After the second administration of afoxolaner,

given between days 28-30 of the study, the on-dog flea burden was reduced by 100% on study days 40-45 and 54-60.⁴

It has been previously demonstrated that if flea reproduction is inhibited, a gender shift will occur from a female-dominated, or at least gender-neutral population, to a male-dominated population. If the product fails to stop reproduction, there will be no gender shift.⁵ In this study, a dramatic shift from a female-dominated population to a male-dominated population suggested that afoxolaner not only acted as an excellent form of flea control, but also that its residual speed of kill was so rapid that it likely killed female fleas before they could produce viable eggs.

Client Appeal & Suitability

Oral flea control appeals to the consumer who prefers a safe and effective product that is easy to administer and does not involve physical contact with liquids, sprays, or collars. It also benefits the dog with dermal sensitivity to such products. Afoxolaner is an excellent addition to the existing market of topicals, sprays, and spot-on insecticides, and is a safe and effective way to treat and prevent flea infestations.

References

1. Perrins N, Hendricks A. Recent advances in flea control. *In Practice*. 2007;29:202-207.
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3. Data on file at Merial.
4. Dryden MW, Smith V, Chwala M, et al. Evaluation of afoxolaner chewables to control flea populations in naturally infested dogs in private residences in Tampa FL, USA. *Parasites & Vectors* 2015;8:286.
5. Dryden MW, Carithers D, McBride A, et al. A comparison of flea control measurement methods for tracking flea populations in highly infested private residences in Tampa FL, following topical treatment of pets with Frontline® Plus (fipronil/(S)-methoprene). *Intern J Appl Res Vet Med*. 2011; 9(4):356-567.



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NATALIE ISAZA, DVM, is clinical associate professor and clinical service chief for the Veterinary Community Outreach Program clerkship at University of Florida. On graduating from University of Florida, Dr. Isaza completed a rotating internship in small animal medicine and surgery at Cornell University. After 4 years of small animal private practice in southern California, she returned to academia, first at Kansas State University, then at University of Florida.

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MATTHEW JOHNSON, DVM, MVSc, DACVS (Small Animal), is clinical instructor of small animal surgery at University of Florida. A graduate of University of Florida, he spent 3 years in general practice before completing a rotating internship and several surgical internships, followed by a surgical residency at Western College of Veterinary Medicine in Saskatoon, Saskatchewan. Postresidency experience included orthopedic- and sports medicine-exclusive practice as well as private referral practice.

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AMY KNOLLINGER, DVM, DACVO, is in practice at Eye Care for Animals in Salt Lake City, Utah. Dr. Knollinger earned her DVM with honors from North Carolina State University. She completed a 3-year residency program with Eye Care for Animals. Dr. Knollinger's interests include corneal disease and surgery as well as cosmetic blepharoplasty.

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JESSICA MCDONALD, DVM, is a second-year ophthalmology resident at Eye Care for Animals in Salt Lake City, Utah. Dr. McDonald earned her DVM from University of Wisconsin. Her clinical interests include glaucoma and ophthalmic diseases of exotic animals.

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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-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 chemistry, 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, antihelmintics, antibiotics (including topical), 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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