NexGard® COMBO

(esafoxolaner, eprinomectin, and praziquantel topical solution)

Technical Monograph

FLEAS | TICKS | HEARTWORM DISEASE | ROUNDWORMS | HOOKWORMS | TAPEWORMS

The One You Want for One-and-Done Monthly Parasite Protection

Boehringer Ingelheim

Table of Contents

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The One You Want for One-and-Done Monthly Parasite Protection

FLEAS | TICKS | HEARTWORM DISEASE | ROUNDWORMS | HOOKWORMS | TAPEWORMS

Cats face an ever-present risk from endo- and ectoparasites that can have serious implications for the health and wellbeing of both animal and owner.[1] *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is the first and only topical treatment specifically formulated for cats that protects against fleas, ticks, heartworm disease, roundworms, hookworms, and tapeworms.

NexGard® COMBO Topical Solution is formulated with esafoxolaner, the purified, active (S)-enantiomer of afoxolaner, which was designed specifically for cats to provide powerful protection against fleas and ticks. This innovative ectoparasiticide is combined with eprinomectin and praziquantel, 2 ingredients proven to help protect against heartworm disease and gastrointestinal parasites (GI), including tapeworms.

The monthly topical is safe for use in cats and kittens 8 weeks of age and older, weighing 1.8 lb or more. *NexGard* COMBO Topical Solution was approved for use in several other countries in early 2021. Its unique product profile has led to it becoming a market leader in several of those markets since its launch.

Active ingredient	Associated indication
Esafoxolaner	• Kills adult *Ctenocephalides felis* fleas • Treats and prevents flea infestations • Treats and controls tick infestations: – *Ixodes scapularis* (black-legged tick) – *Amblyomma americanum* (lone star tick)
Eprinomectin	• Prevents heartworm disease caused by *Dirofilaria immitis* • Treats and controls roundworms: – *Toxocara cati* (4th-stage larval and adult) • Treats and controls hookworms: – *Ancylostoma tubaeforme* (4th-stage larval and adult) – *Ancylostoma braziliense* (adult)
Praziquantel	• Treats and controls tapeworms (*Dipylidium caninum*)

3 powerful ingredients provide broad-spectrum parasite control

NexGard® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) HIGHLIGHTS

Rapidly kills adult fleas and prevents flea infestations

- In laboratory studies, *NexGard*® COMBO Topical Solution killed fleas fast, before they could lay eggs.[2,3]
- In a field study, *NexGard* COMBO Topical Solution reduced fleas by ≥97.8% over the course of 3 monthly treatments and significantly improved signs of flea allergy dermatitis (FAD) through direct elimination of fleas.[2]

Kills the 2 most common tick species infesting cats in the US[4]

- *NexGard* COMBO Topical Solution demonstrated sustained efficacy against *Ixodes scapularis* and *Amblyomma americanum* for 1 month.[2]
- In well-controlled laboratory studies, *NexGard* COMBO Topical Solution demonstrated ≥95.1% effectiveness against *I. scapularis* 48 hours post-infestation for a month and an average ≥95.6% effectiveness against *A. americanum* 72 hours post-infestation for a month.[2]

Prevents heartworm disease in cats

- *NexGard* COMBO Topical Solution demonstrated 100% efficacy in prevention of heartworm disease caused by *Dirofilaria immitis* when administered once a month for 3 consecutive months.[2]

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Treats and controls the common GI parasites: Roundworms, hookworms, and tapeworms

- *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) demonstrated 98.8% and 100.0% efficacy against natural and induced infections, respectively, of adult *Toxocara cati* (roundworm).[2]
- In well-controlled laboratory studies using an early eprinomectin-containing formulation, the topical solution demonstrated >91% effectiveness against hookworms (adult and 4th-stage larval *Ancylostoma tubaeforme* and adult *Ancylostoma braziliense*).[5]
- *NexGard*® COMBO Topical Solution demonstrated an average 92.8% efficacy against the most common tapeworm species of cats (*Dipylidium caninum*), following both induced and natural infection.[2]

Safety of *NexGard* COMBO Topical Solution

- Over the course of a field study that included 244 cats treated with *NexGard* COMBO Topical Solution and 136 cats treated with an active control, there were no serious health abnormalities attributed to treatment. Concurrent administration of various medications and vaccines did not have an impact on the safety of *NexGard* COMBO Topical Solution.[2]
- Extensive safety testing was conducted in multiple laboratory target animal safety studies:
  - In a margin of safety study, *NexGard* COMBO Topical Solution was administered to kittens at 1X, 3X, and 5X the maximum exposure dose 6 times at 28-day intervals.[2]
  - In a safety study in heartworm-positive cats, using a similar eprinomectin-containing product, *NexGard* COMBO Topical Solution was administered to heartworm-positive cats at 1X or 3X the maximum exposure dose once every 28 days for 3 treatments.[2]
    - These studies support the safe use of *NexGard* COMBO Topical Solution in cats and kittens 8 weeks of age or older, weighing 1.8 lb or more, and in heartworm-positive cats.
  - In an oral administration study, *NexGard* COMBO Topical Solution was administered at 1X the maximum exposure dose. Hypersalivation occurred immediately after dosing but was no longer observed 1 hour after exposure.[2]

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Formulation

Esafoxalaner: Specifically Developed for Use in Cats

Esafoxolaner is the novel isoxazoline-class molecule used in *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) that is responsible for the product's properties against fleas and ticks. This active ingredient is the purified (S)-enantiomer of afoxolaner, the active ingredient used in *NexGard*® (afoxolaner) Chews for Dogs for flea and tick control. Esafoxolaner was engineered specifically for cats.

Afoxolaner is a racemate, made up of an equimolar (50:50) mixture of the (R)- and (S)-enantiomers (Figure 1). Previous studies evaluated the role of the 2 afoxolaner enantiomers, esafoxolaner and (R)-afoxolaner:

- In vitro efficacy studies demonstrated that esafoxolaner is responsible for the molecule's activity against fleas and ticks.[6]
- An in vivo exploratory study demonstrated that following administration of 1.25 mg/kg of either esafoxolaner, or the (R)-enantiomer, the efficacy against *Ctenocephalides felis* fleas was 100% in the esafoxolaner-treated group, while no efficacy was observed in the (R)-enantiomer-treated group.[6]
- Additional studies demonstrated that esafoxolaner did not significantly differ from afoxolaner in terms of safety, pharmacokinetic, and pharmacodynamic properties. The pharmacological properties of esafoxolaner, and efficacy and safety studies for *NexGard* COMBO Topical Solution, are discussed in the following sections.

Figure 1
Enantiomers of afoxolaner

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The advantage of using a purified and active enantiomer is that a lower dose of the active ingredient can be used, which can be beneficial when manufacturing a solution with multiple ingredients. In general, lowering the dose of the active ingredient is also associated with lowering the potential for side effects as well as chemical and pharmacological interactions.

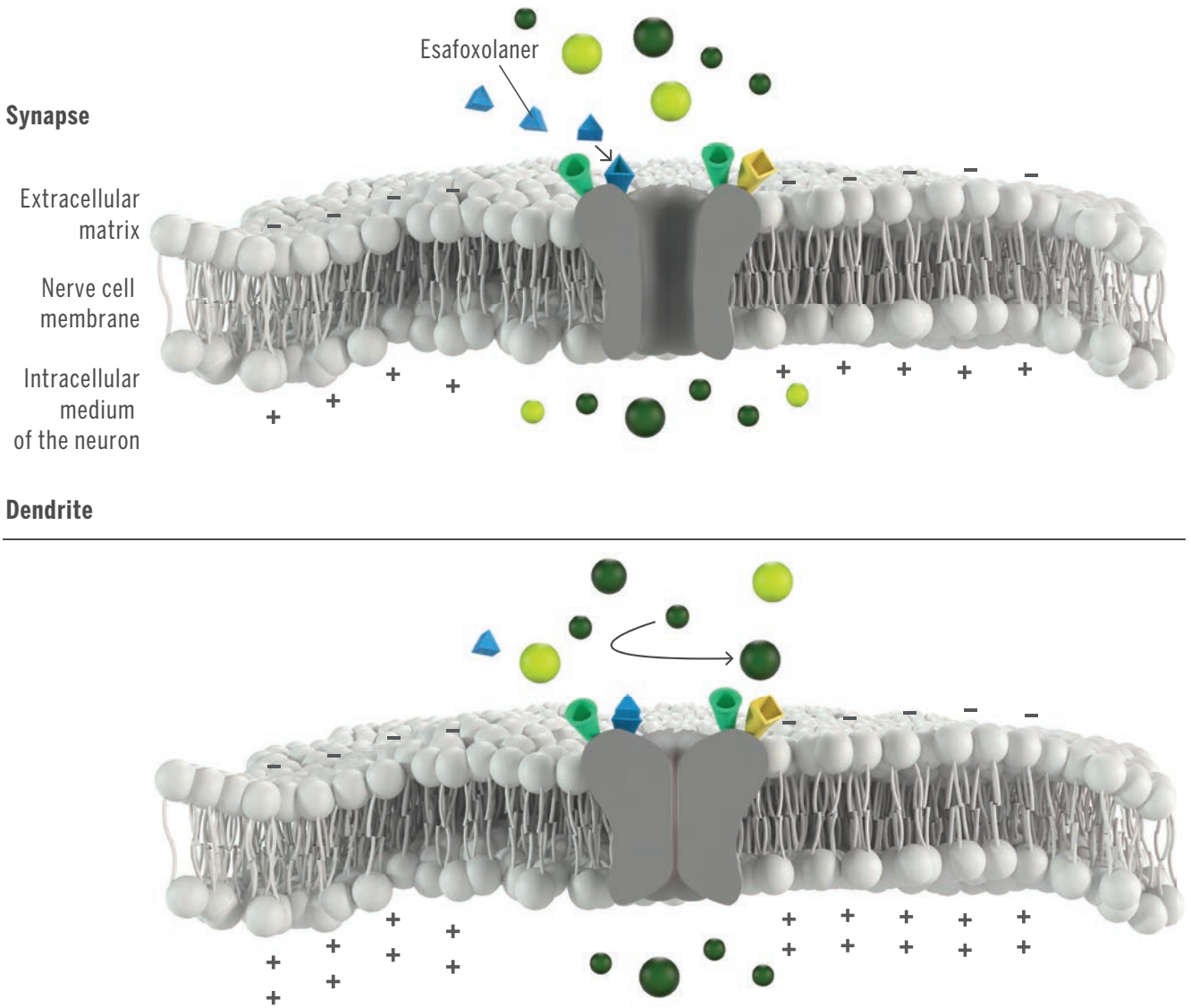
Because *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is a cat-specific topical with multiple ingredients, it is advantageous that the formulation includes a lower amount of this active ingredient per dose while still producing the same intended effect when all other factors (e.g., administration, species) are constant. The minimum dose of esafoxolaner (1.4 mg/kg) in *NexGard*® COMBO Topical Solution was selected based on laboratory efficacy studies (see the Efficacy Study section that starts on page 19). The safety of esafoxolaner was established in numerous exploratory and preclinical studies, as well as in the target animal safety studies described starting on page 61.

Esafoxolaner: Mechanism of Action

Esafoxolaner has an identical MOA as afoxolaner (Figure 2).

1. In fleas and ticks, the neurotransmitter gamma-aminobutyric acid (GABA) normally binds to nerve cell membranes, allowing the flow of chloride ions through the membrane channel.
2. Esafoxolaner binds to the GABA-gated chloride channels, blocking GABA and inhibiting the flow of chloride ions across the cell membrane.
3. This causes prolonged firing of neurons and uncontrolled hyperexcitation of the central nervous system, leading to the death of fleas and ticks.

Figure 2
Esafoxolaner mechanism of action



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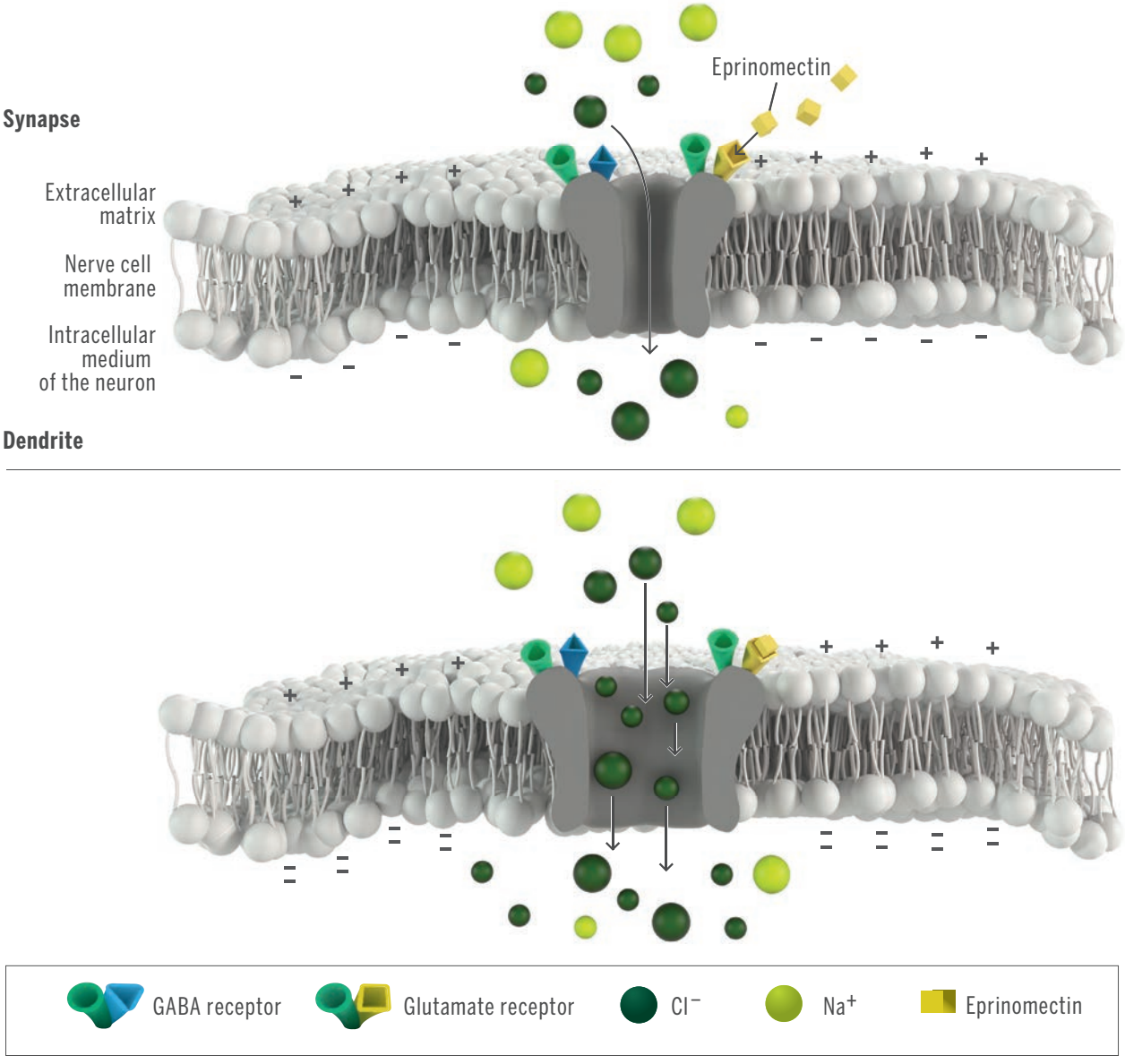
Eprinomectin

Eprinomectin is responsible for the prevention of heartworm disease as well as the treatment and control of roundworms and hookworms in *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution).

Eprinomectin is a macrocyclic lactone anthelmintic (Figure 3).

1. Eprinomectin binds to glutamate-gated chloride channels that are present in invertebrate nerve and muscle cells.
2. This causes the chloride channel to remain open, allowing chloride ions to more freely pass through the membrane.
3. The influx of chloride ions triggers hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite.

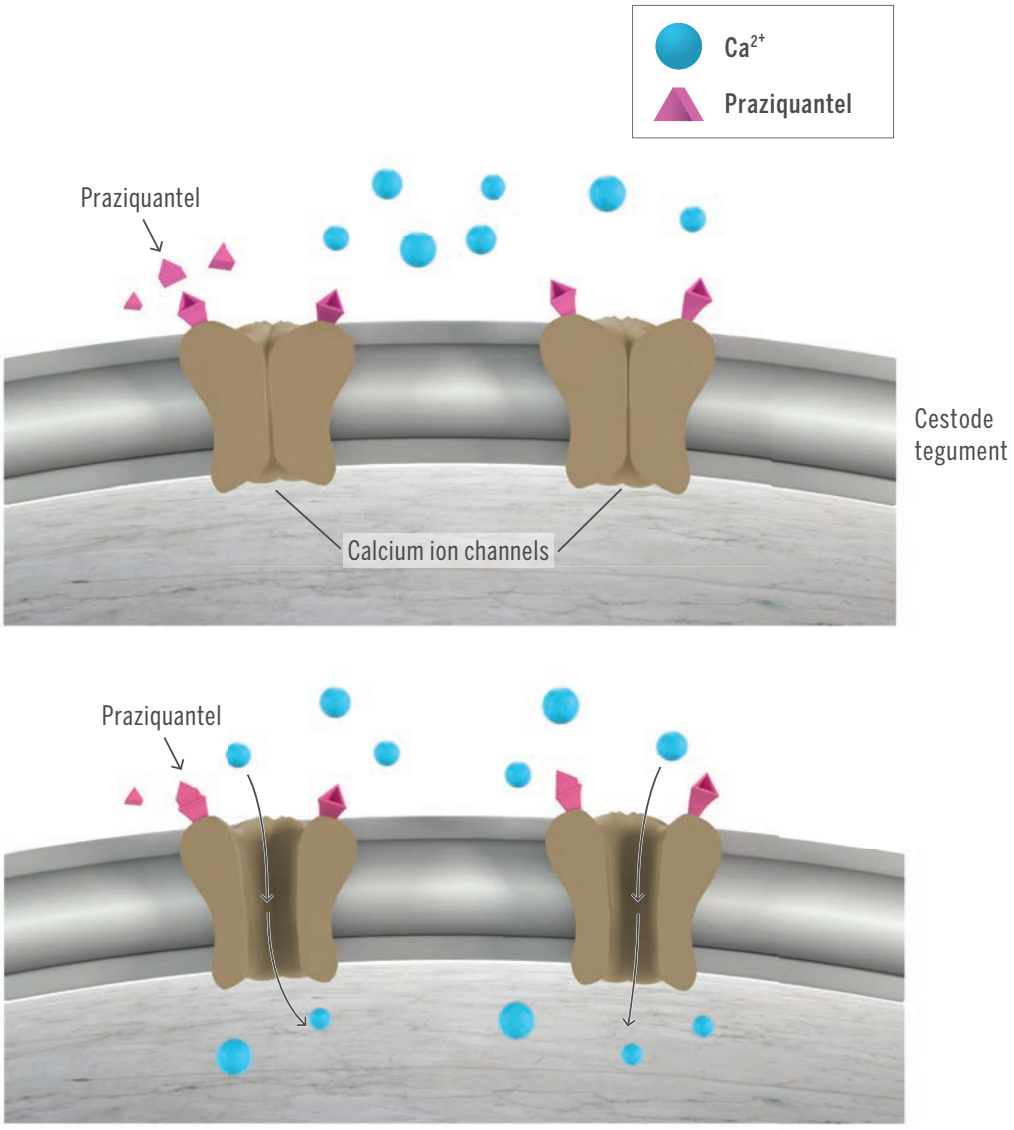
Figure 3
Eprinomectin mechanism of action



Praziquantel

The mechanism of action of praziquantel has not been fully elucidated, but it has been the standard for treatment for tapeworm infections in cats for decades. It is thought to act on cestode cell membranes to alter calcium ion permeability, resulting in spastic paralysis, detachment from the host, and eventual destruction by the host's immune system (Figure 4).

Figure 4
Praziquantel mechanism of action



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Conclusions

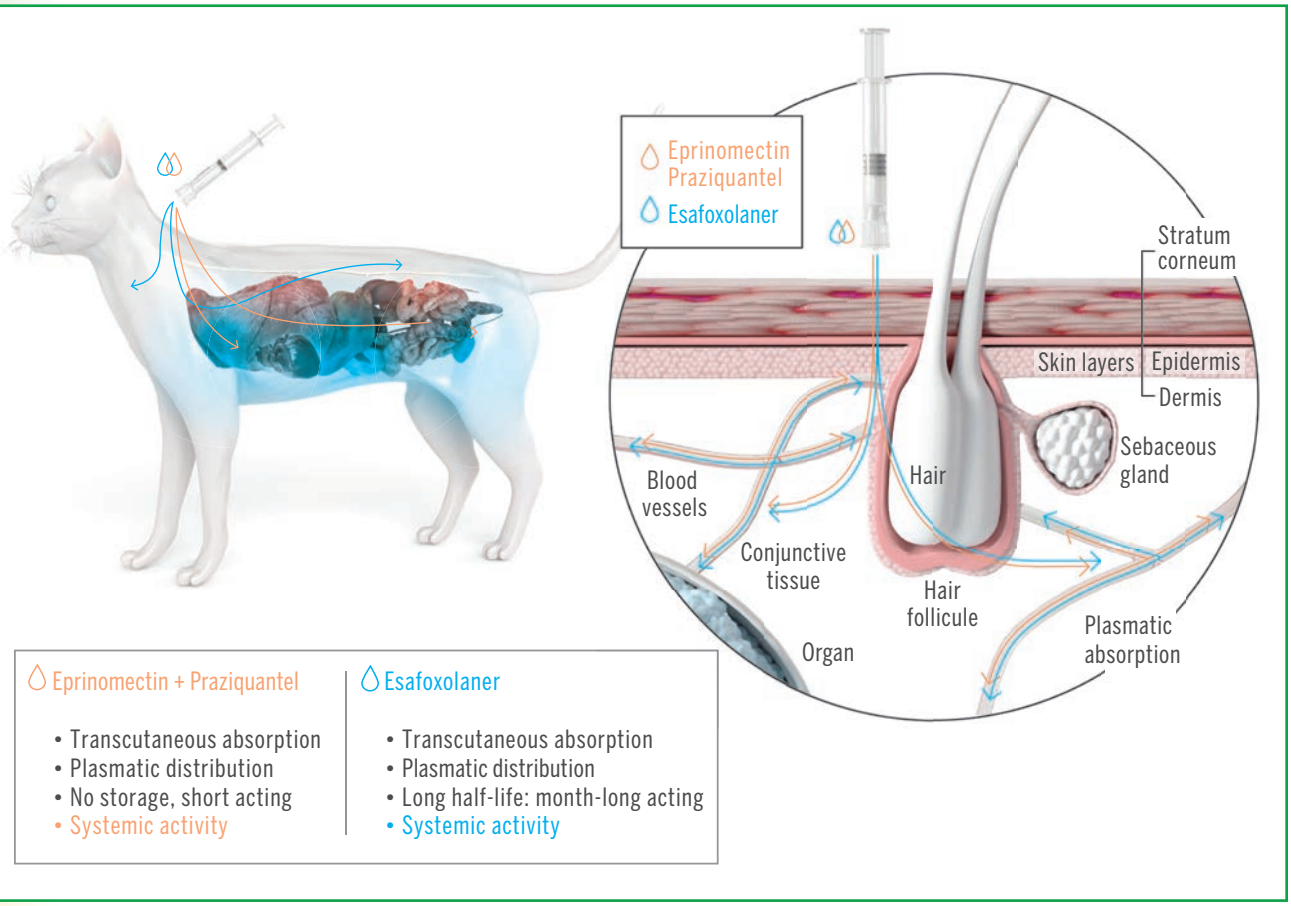
Esafoxolaner is a novel isoxazoline-class molecule derived from afoxolaner that effectively kills fleas and ticks. This molecule has been proven to be safe for use in cats and kittens. Together with 2 other active ingredients in *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution), this spot-on formulation protects cats and kittens from common endo- and ectoparasites for 1 month.

PHARMACOLOGICAL DATA

PHARMACOLOGICAL DATA

Mode of Diffusion

After topical administration of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) to cats, esafoxolaner, eprinomectin, and praziquantel are absorbed into the systemic circulation. Fleas and ticks are impacted upon a blood meal, while endoparasites are impacted through oral absorption or transcuticular/integument adsorption, depending on the worm species.



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Pharmacokinetics Following Topical Application

The pharmacokinetics of the individual enantiomers has been explored following administration of afoxolaner and its enantiomers. The activity of afoxolaner is due primarily to esafoxolaner, as demonstrated by in vitro assays and in vivo studies in dogs. Both afoxolaner enantiomers were demonstrated to be equivalent in rats, cats, and dogs from a pharmacokinetic standpoint. There is no in vivo conversion of esafoxolaner to the (R)-enantiomer, and the pharmacokinetic profile of esafoxolaner is not impacted by the presence of the (R)-enantiomer. Specific studies demonstrated that the metabolism of the racemic mixture is the same as the metabolism of the single enantiomer in cats.[6]

As a lipophilic compound, esafoxolaner exhibits solubility-limited absorption and a moderate volume of distribution into tissues. Esafoxolaner is highly bound to plasma protein (>99%) and is slowly eliminated from the body (slow clearance). The hepatic metabolism is limited. Free esafoxolaner and hydroxylated metabolites are mainly eliminated in the feces through biliary excretion (renal clearance accounts for less than 0.01% of the total clearance).

Eprinomectin and praziquantel also have a moderate volume of distribution into tissues, which indicates partitioning outside of the systemic circulation. Plasma protein binding is >99% for eprinomectin and 64% to 84% for praziquantel. Eprinomectin undergoes limited metabolism and is mainly excreted unchanged in the feces, while the hepatic metabolism of praziquantel is followed by renal excretion.

Following topical administration of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution), the bioavailability of esafoxolaner, eprinomectin, and praziquantel was 47.2%, 31%, and 45%, respectively (Table 1).

Table 1

Summary of pharmacokinetic parameters of esafoxolaner, eprinomectin, and praziquantel in *NexGard*® COMBO Topical Solution when administered once at the recommended minimum dose

Component	$T_{½}$ (day)	T_{max} (day)	C_{max} (ng/mL)	AUC_{last} (day*ng/mL)	%F
Esafoxolaner (1.44 mg/kg)	21.7 (2.8)	7.13 ± 3.1	130 ± 36	4,411 ± 1,525	47.2%
Eprinomectin (0.5 mg/kg)	5.4 (2.7)	1.46 ± 0.47	23.6 ± 11	156 ± 94	31%
Praziquantel (10 mg/kg)	4.3 (1.9)	0.29 ± 0.08	107 ± 59	123 ± 25	45%

$T_{1/2}$, terminal plasma half-life; T_{max}, time from dosing to the maximum concentration; C_{max}, peak drug plasma concentration; AUC_{last}, area under the concentration versus time curve from the time of dosing to the time to the last quantifiable concentration; %F, bioavailability.

Values are means (N=3), with standard deviations in parentheses.

Bioavailability data for esafoxolaner were determined in a study of *NexGard* COMBO Topical Solution.[7]

Eprinomectin and praziquantel bioavailability was demonstrated in a separate study.[8]

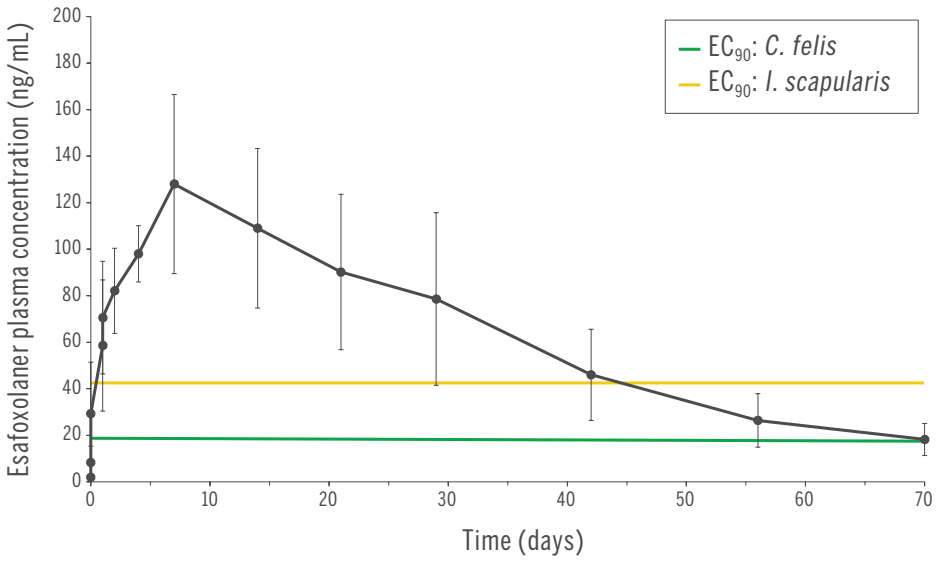
One study evaluated the main pharmacokinetics parameters (C_{max}, T_{max}, C_{last}, T_{last}, half-life, area under the curve [AUC], and bioavailability) of the 3 compounds administered in the formulation at the recommended minimum dose and the noninterference of the 3 compounds between each other. Another study evaluated the dose proportionality/linearity of esafoxolaner, eprinomectin, and praziquantel after a single administration of *NexGard* COMBO Topical Solution, as well as the time to steady state following repeated administrations.

Esafoxolaner in *NexGard* COMBO Topical Solution[7]

The plasma profile of esafoxolaner is relevant to a systemic ectoparasiticide compound with a sustained efficacy of 1 month for fleas and ticks. The EC_{90} for esafoxolaner is estimated to be 19.1 ng/mL for *Ctenocephalides felis* and 43.1 ng/mL for *Ixodes scapularis*.

After a single topical administration, esafoxolaner increased slowly up to a mean C_{max} of 130 ± 36 ng/mL, with a mean T_{max} of 7.13 ± 3.1 days (Figure 1). Concentrations then declined steadily and were quantifiable for 7 weeks, with a mean concentration of 18.2 ± 6.7 ng/mL 70 days after dosing. The mean $AUC_{0\text{-}Tlast}$ was 4,411 ± 1,525 day*ng/mL, and the mean plasma half-life of esafoxolaner in *NexGard* COMBO Topical Solution was 21.7 ± 2.8 days (see Table 1 at left).

Figure 1
Esafoxolaner average concentration—time curve



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Eprinomectin and Praziquantel

Eprinomectin and praziquantel plasma profiles are relevant to systemic endoparasiticide compounds for killing nematodes and cestodes, respectively.

After a single topical administration of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution), the maximum concentration of eprinomectin, C_{max} = 23.6 ± 11 ng/mL, was reached at T_{max} 35 hours (1.46 days), followed by a gradual decrease of concentration below the determination limit after 29 days (Figure 2). The mean half-life was 5.4 ± 2.7 days, and the mean $AUC_{0\text{-}Tlast}$ was 156 ± 94 day*ng/mL (see Table 1 on page 14).

Praziquantel concentration peaked quickly, indicating a rapid absorption. The maximum concentration was observed from 4 to 8 hours, and the mean C_{max} was 107 ± 59 ng/mL. Concentrations then declined steadily, with the last quantifiable plasma concentrations reached between 7 and 42 days following treatment (Figure 3). The mean half-life was 4.3 ± 1.9 days, and the mean $AUC_{0\text{-}Tlast}$ was 123 ± 25 day*ng/mL (see Table 1 on page 14).

Figure 2

Eprinomectin average concentration—time curve

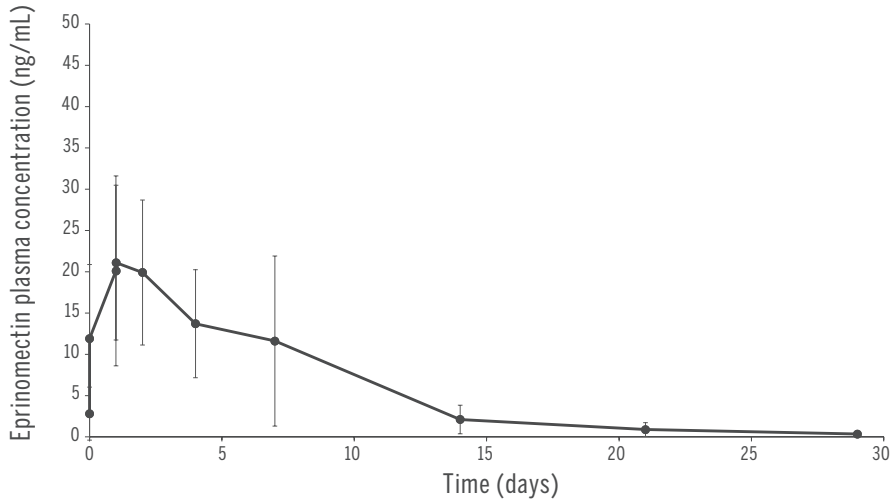
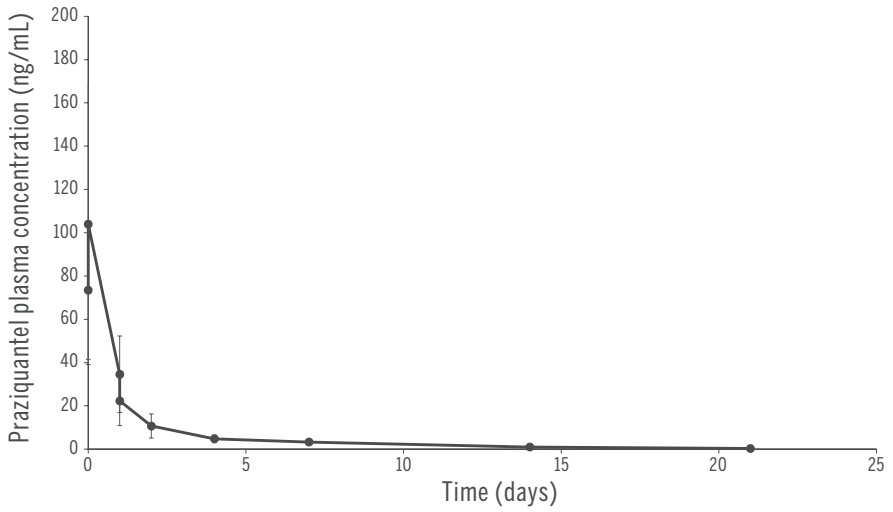


Figure 3

Praziquantel average concentration—time curve



Dose Linearity and Steady State[7]

Three groups of cats were treated once topically with *NexGard*® COMBO Topical Solution at 0.5X, 1X, and 2X the intended minimum label dose, respectively (0.72 to 2.88 mg of esafoxolaner/kg body weight, 5 to 20 mg of praziquantel/kg body weight, and 0.25 to 1.0 mg of eprinomectin/kg body weight). The study results showed that C_{max}, AUC_{Tlast}, and AUC_{inf} increased proportionally with dose for all active ingredients, indicating linear pharmacokinetics over the range of doses. The parameters for terminal plasma half-life and T_{max} were independent of dose, as expected.

A fourth group was treated topically with *NexGard* COMBO Topical Solution at the minimum dose, 5 times, at 28-day intervals. Based on the pre-dose drug plasma concentration comparison prior to the second, third, fourth, and fifth monthly doses, esafoxolaner and eprinomectin reached a steady state by the fifth monthly dose, while praziquantel reached it by the second monthly dose.

KEY POINTS

The pharmacokinetic profile of *NexGard* COMBO following topical application is characterized by:

- A long persistence of esafoxolaner (half-life, ~21 days), with quantifiable concentration for several weeks post administration, and efficacious plasma level maintained for a full month.
- Short persistence of eprinomectin and praziquantel (half-lives, ~4 to 5 days).

- No interaction affected the distribution, metabolism, or excretion of any of the 3 active ingredients. The addition of esafoxolaner did not impact the eprinomectin and praziquantel absorption profiles.
- Multiple dose kinetics were predictable for all active ingredients and resulted in steady-state drug plasma concentrations, which were reached between the second and fifth dose for all compounds.

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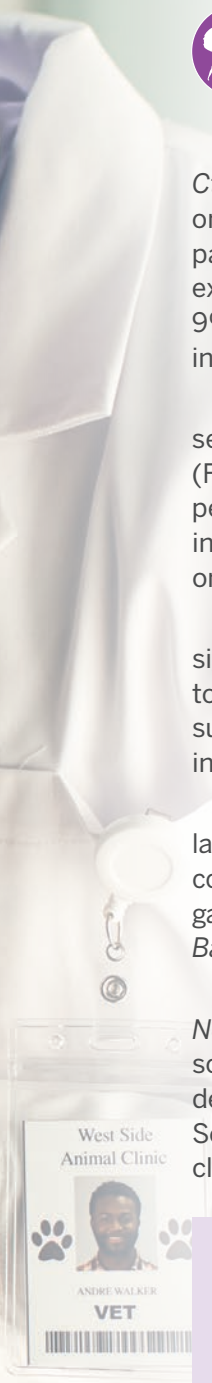
EFFICACY STUDIES



FLEAS

Ctenocephalides felis, the cat flea, is the most common external parasite found on dogs and cats in North America.[9] In surveys of free-roaming cats in warmer parts of the country, fleas were identified on more than half of the population examined, with virtually all cats infested in some locations. In temperate areas, 9% to 26% of pet cats presenting to veterinary clinics had evidence of flea infestations.[9,10]

Fleas are historically responsible for the majority of dermatologic issues seen in dogs and cats brought to veterinary practices. Flea allergy dermatitis (FAD) is a condition of dogs and cats characterized by pruritus (itching), persistent licking and chewing, hair loss, and secondary infection.[10,11] However, in some cats, miliary dermatitis and eosinophilic granuloma complex are the only signs associated with FAD.[10,11]

Fleas are obligatory blood feeders and can cause anemia associated with significant blood loss, which can be life-threatening in kittens and debilitating to some patients (unable to groom well). Alternatively, healthy cats can be such fastidious groomers that there may be no indication of an existing flea infestation (no visible fleas or flea dirt).

Fleas are an intermediate host of *Dipylidium caninum* tapeworms, because flea larvae will feed on *D. caninum* eggs in the environment. While grooming, a cat may consume *C. felis* fleas infected with *D. caninum* and can become infected with the gastrointestinal parasite. Fleas can also be infected with other pathogens, such as *Bartonella henselae*, the cause of cat scratch disease in humans.

The laboratory study in this section details the efficacy of topically applied *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) against direct infestations of adult *C. felis* fleas. This section also details a field study assessing effectiveness of *NexGard*® COMBO Topical Solution against natural flea infestations while also evaluating resolution of clinical signs of FAD in treated cats.

SUMMARY OF FLEA STUDIES

NexGard COMBO Topical Solution consistently killed adult fleas and was effective in the treatment and prevention of flea infestations for 1 month.

Under field conditions, *NexGard* COMBO Topical Solution effectively killed fleas and significantly improved signs of FAD through direct elimination of fleas.

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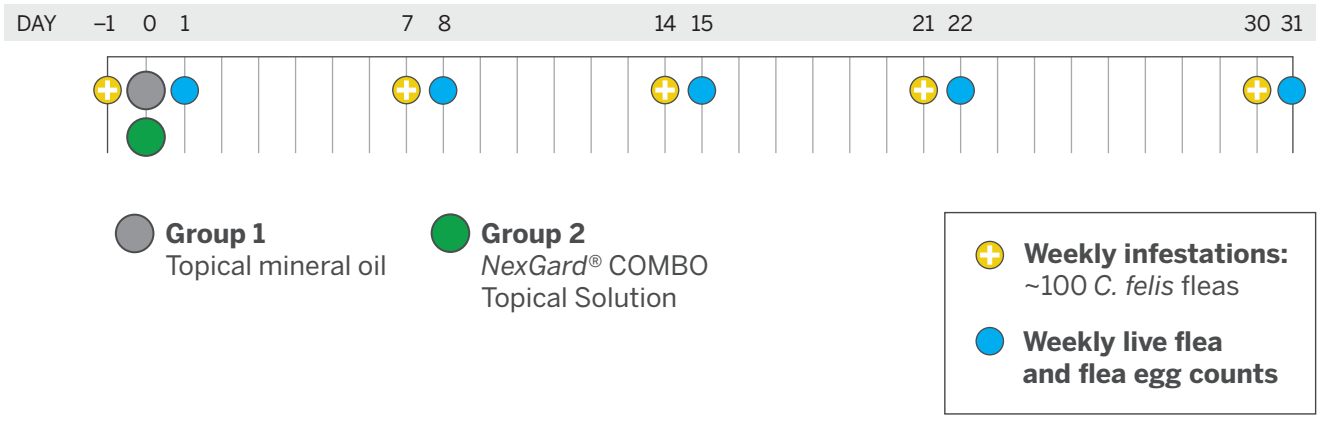
Efficacy Against Fleas

Efficacy Against Flea Infestations: Laboratory Study[2]

Objective	Confirm the efficacy of a single topical application of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) given at the recommended minimum dose for the treatment and control of induced infestations of adult *C. felis* on cats and for the inhibition of flea egg production
Study	A placebo-controlled laboratory study that followed a randomized block design based on pre-treatment flea counts
Treatment Groups	**Group 1** Treated with a **placebo control (mineral oil)**—10 cats **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—10 cats
Treatment	On Day 0, cats in the treatment group were administered *NexGard* COMBO Topical Solution (0.12 mL/kg), and cats in the control group were treated with topical mineral oil (0.12 mL/kg).
Flea Infestations	Cats were infested with ~100 unfed adult *C. felis* on Days –1, 7, 14, 21, and 30.
Assessment of Efficacy	• Live fleas were counted on Day 1 at 24 hours after treatment (to assess immediate efficacy) and on Days 8, 15, 22, and 31 at 24 hours after subsequent reinfestations (to assess sustained efficacy). • Flea eggs were collected from beneath each cage on Days 1, 8, 15, 22, and 31 and counted.

Flea Induced Infestation Model

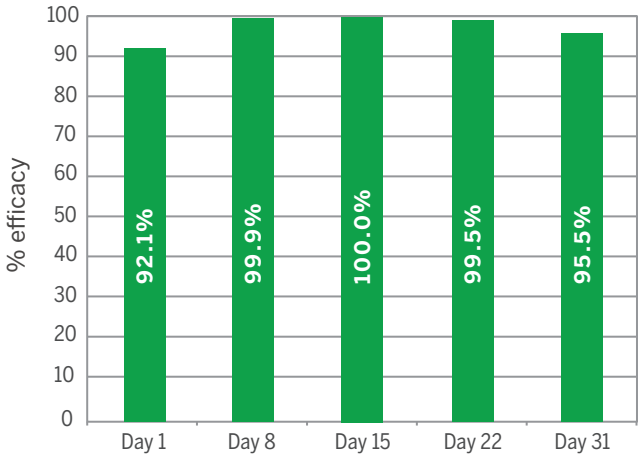


Results

- *NexGard* COMBO Topical Solution demonstrated >92% efficacy against adult fleas within 24 hours of treatment (Figure 1).
- During subsequent flea infestations, the efficacy of *NexGard* COMBO Topical Solution was ≥99.5% through Day 22 and 95.5% on Day 31 (Figure 1).
- On Day 1, a 60% reduction of flea egg production was observed. Because the cats had been infested with fleas on Day –1, the fleas were allowed to mate and produce eggs prior to being exposed to *NexGard* COMBO Topical Solution. After Day 1, inhibition of flea egg production was consistently >99% when compared to the control group (Table 1).

Figure 1

Percent efficacy[a] against adult *C. felis* 24 hours after treatment or reinfestation



[a] Percent efficacy was calculated as 100 × [(C – T)/C], where T and C are the arithmetic mean flea counts of the treated and control groups, respectively.

Table 1

Summary of efficacy against *C. felis* egg counts

Day	Percent efficacy[b]	*P* value
1	60.0	0.0073
8	99.8	0.0009
15	100.0	0.0045
22	100.0	0.0003
31	100.0	0.0017

[b] Percent efficacy was calculated as 100 × [(C – T)/C], where T and C are the arithmetic mean flea egg counts of the treated and control groups, respectively.

KEY POINTS

- A single application of *NexGard* COMBO Topical Solution was effective for the treatment and prevention of flea infestations for 1 month.
- Adult fleas were killed before they could lay eggs, resulting in effective control of flea egg production.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Efficacy Against Fleas

Effectiveness Against Natural Flea Infestations and Flea Allergy Dermatitis (FAD) Under Field Conditions on Client-Owned Cats[2]

Objective

Determine the effectiveness of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) against adult fleas and evaluate the effect of treatment on signs of FAD when administered topically 3 times at 1-month intervals

Study

A positive-controlled, blinded, multicenter field study using a randomized block design based on order of enrollment of 201 households with a total of 380 cats (208 females, 172 males), 167 of which were included in the final effectiveness assessment. The cats ranged in age from 8 weeks to 17 years and weighed between 1.8 and 23.9 lb (the safety component of this study can be found on pages 68 to 69)

Client-owned cats came from 11 veterinary clinics in 3 regions of the United States:
• Midwest (3) • Southeast (7) • West (1)

Experimental Design

Each household study unit had at least 1 cat naturally infested with ≥5 fleas. In households with >1 cat present, 1 sentinel cat that met the minimum flea infestation requirements and showed signs of FAD (if present) was chosen to represent the household for evaluations of effectiveness for this study.

Treatment Groups

Group 1
Treated with ***NexGard*® COMBO Topical Solution** at the intended label dose

Group 2
Treated with **selamectin (active control)** at the intended label dose

Treatment and Assessment of Effectiveness

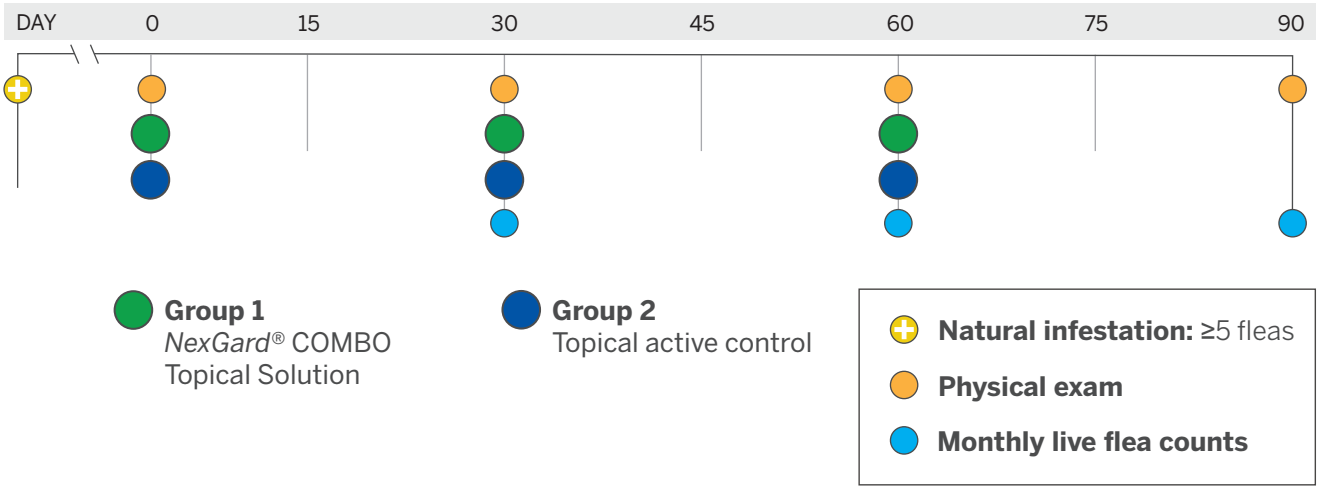
- Day 0: All cats in a household had a physical examination and were evaluated for fleas and signs of FAD at first visit.
- Days 0, 30, and 60: The treatment group received *NexGard* COMBO Topical Solution, and the active control group was administered topical selamectin (Table 1).
- Days 30, 60, and 90: Sentinel cats were examined at the veterinary clinic, live fleas were counted, signs of FAD were evaluated, and physical exams were performed on the sentinel cat from each household (Table 1).

Table 1
Number of cats evaluated at each visit for live flea counts

Visit day	*NexGard* COMBO Topical Solution	Active control (selamectin)
	Fleas (n)	Fleas (n)
Day 0	133	67
Day 30	127	60
Day 60	121	52
Day 90	117	50

n, the number of cats included in the flea count that did not have any protocol violations that disqualified them from that portion of the analysis.

Flea Natural Infestation Model



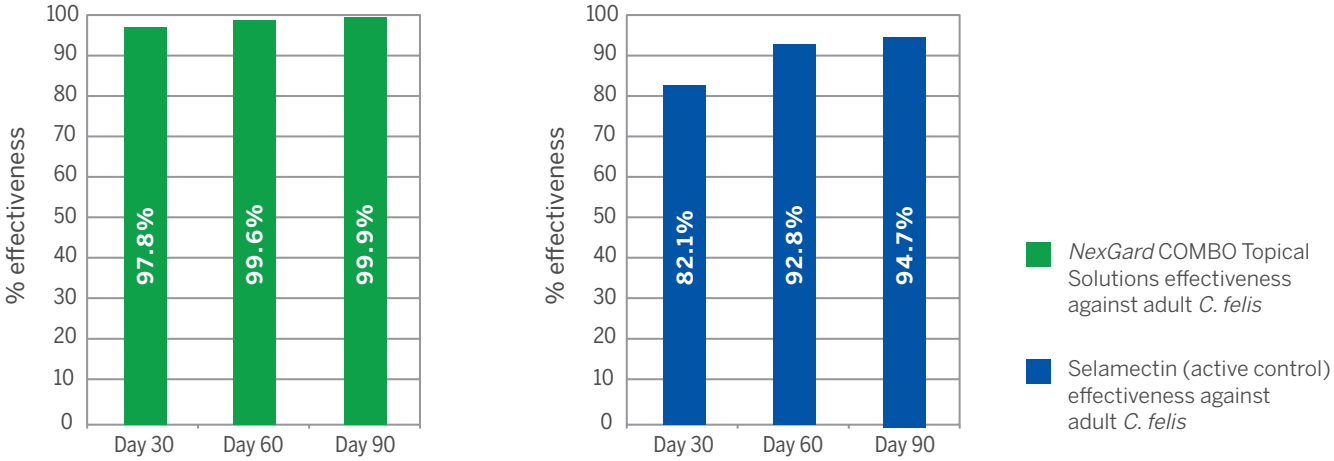
Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Results

- *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) demonstrated ≥97.8% effectiveness against live fleas under real-world conditions over the 3-month treatment period (Figure 1).
- Treatment with *NexGard*® COMBO Topical Solution significantly decreased multiple signs of FAD by Day 90 (Table 2).

Figure 1

Percent effectiveness[a] of *NexGard* COMBO Topical Solution or an active control (selamectin) against adult flea infestation



[a] Percent effectiveness refers to the percent reduction in flea count compared to the average baseline flea count. Percent effectiveness = 100 × [(C – T)/C], where T and C are the geometric mean flea counts of the treated and control groups, respectively.

Table 2

Number and percent improvement[b] in clinical signs of FAD at Day 90

FAD sign	*NexGard* COMBO Topical Solution		Active control (selamectin)	
	No. improved	Percent improved	No. improved	Percent improved
Alopecia	28 of 31	90.3	11 of 12	91.7
Miliary dermatitis	28 of 28	100	8 of 8	100
Excoriation	18 of 19	94.7	7 of 9	77.8
Erythema	23 of 25	92.0	12 of 12	100
Scaling	15 of 15	100	4 of 5	80.0

[b] Percent improvement = 100 × (C_1/C_2), where C_1 = number of cats improved after 90 days and C_2 = number of total cats in the treatment group.

KEY POINTS

- Under field conditions, *NexGard* COMBO Topical Solution effectively killed adult fleas arising from natural infestations.
- Treatment with *NexGard* COMBO Topical Solution over a 3-month period significantly decreased multiple clinical signs of FAD as a direct result of eliminating fleas.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Efficacy Against Fleas

Efficacy in Other Studies[3]

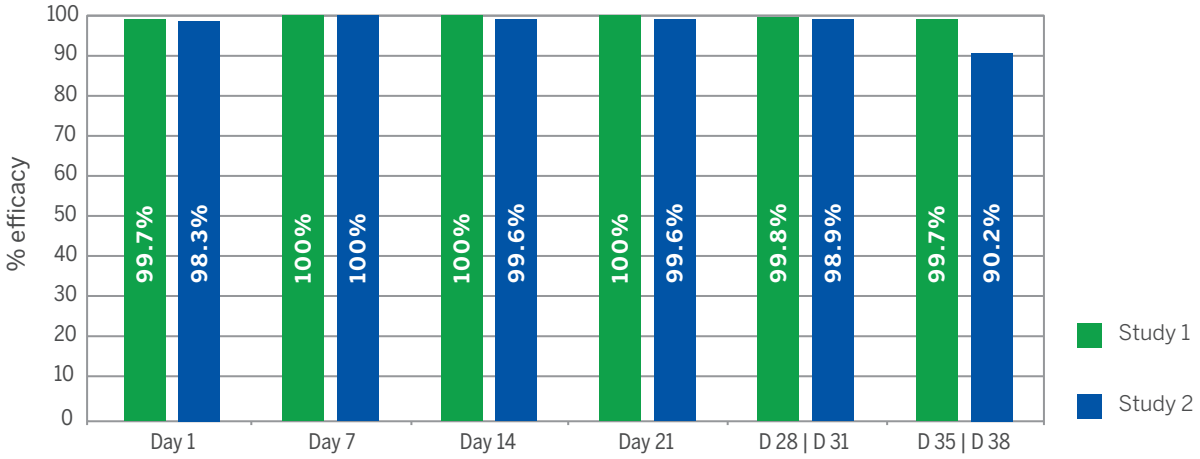
Laboratory studies following a similar design to the study on page 20 have been conducted in other countries to evaluate the efficacy of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) given at the recommended minimum dose for the treatment and control of adult flea (*C. felis*) infestations over a 1-month period.

Results

- Within 24 hours, *NexGard*® COMBO Topical Solution was highly effective against existing flea infestations (Figure 1).
- *NexGard* COMBO Topical Solution provided protection against reinfestations for at least 1 month (Figure 1).

Figure 1

Additional laboratory studies[a] evaluating percent efficacy[b] against adult fleas



[a] Studies 1 and 2 were additional laboratories studies conducted to assess the efficacy against adult fleas.[3]

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

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

TICKS

Ixodes scapularis (black-legged tick) and *Amblyomma americanum* (lone star tick) are the 2 most common ticks found on cats in the United States.[4] Cats can be at an ever-present risk of a tick infestation because certain ticks, depending on the species and life stage, may remain active in the environment throughout the entire calendar year. *I. scapularis*, for instance, can even be active throughout the winter whenever temperatures are above freezing.

Ticks typically feed on different hosts at each life stage, increasing the potential for transmitting disease-causing pathogens to new hosts. *A. americanum*, for example, can pick up *Cytauxzoon felis* when feeding on bobcats.[12] In the next life stage of the tick, it can transmit the pathogen as it feeds on a domestic cat.

The disease, called cytauxzoonosis, is a potentially life-threatening illness in cats, with clinical signs that include high fever, difficulty breathing, anorexia, pale gums, jaundice, coma, and even death. Tick bites can also cause skin irritation and secondary infection of the bite wound, or, in the case of a multi-tick infestation, anemia.

The laboratory studies in this section detail the efficacy of topically administered *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) against induced *I. scapularis* and *A. americanum* infestations.

SUMMARY OF TICK STUDIES

NexGard® COMBO Topical Solution was effective for the treatment and control of the 2 most common tick species found on cats in the United States[4], *I. scapularis* and *A. americanum*, for 1 month.

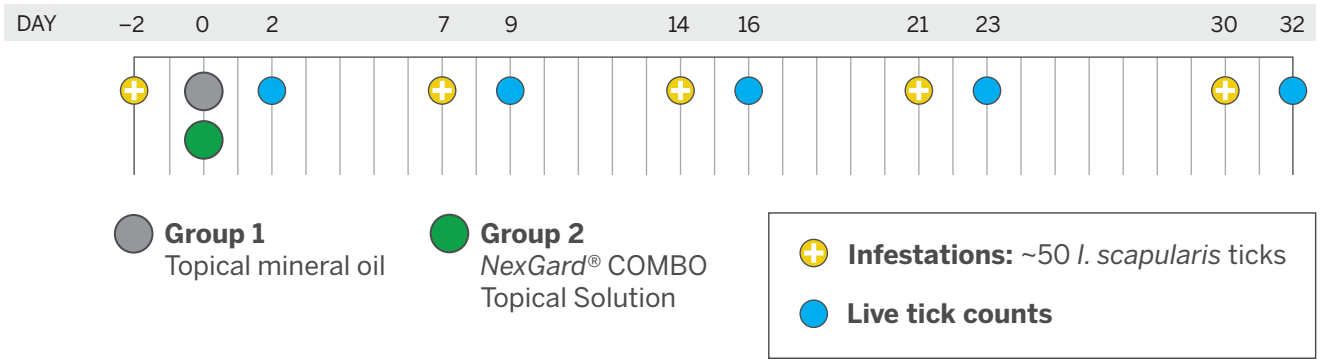
Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Efficacy Against Ticks

Efficacy Against *Ixodes scapularis*: 2 Laboratory Studies[2]

Objective	Confirm the efficacy of a single topical application of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) given at the recommended minimum dose for the treatment and control of induced infestations of *I. scapularis* on cats
Studies	2 placebo-controlled laboratory studies that followed a randomized block design based on pre-treatment live tick counts
Treatment Groups for Each Study	**Group 1** Treated with a **placebo control (mineral oil)**—10 cats **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—10 cats
Treatment	On Day 0, cats in the treatment group were administered *NexGard* COMBO Topical Solution (0.12 mL/kg), and cats in the control group were treated with topical mineral oil (0.12 mL/kg).
Tick Infestations	Cats were infested with ~50 live ticks on Days –2, 7, 14, 21, and 30.
Assessment of Efficacy	Days 2, 9, 16, 23, and 32: Live ticks were counted 48 hours post-treatment (to assess immediate efficacy) and 48 hours after each subsequent infestation (to assess sustained efficacy).

Ixodes scapularis Infestation Model

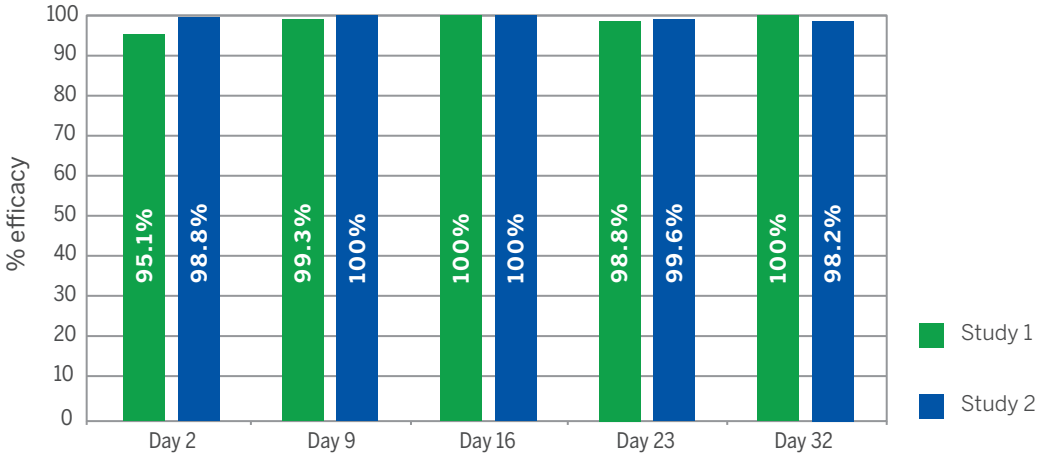


Results

- At 48 hours post-treatment, *NexGard* COMBO Topical Solution demonstrated ≥95.1% efficacy against *I. scapularis* (Figure 1).
- On subsequent days, the product demonstrated ≥98.2% efficacy against *I. scapularis* through Day 32 (Figure 1).

Figure 1

Percent efficacy[a] against *I. scapularis* 48 hours after treatment or reinfestation



[a] Percent efficacy = 100 × [(C – T)/C], where T and C are the arithmetic mean tick counts of the treated and control groups, respectively.

KEY POINT

NexGard COMBO Topical Solution was effective against *I. scapularis* ticks when assessed 48 hours after treatment and weekly against reinfestation for 32 days.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

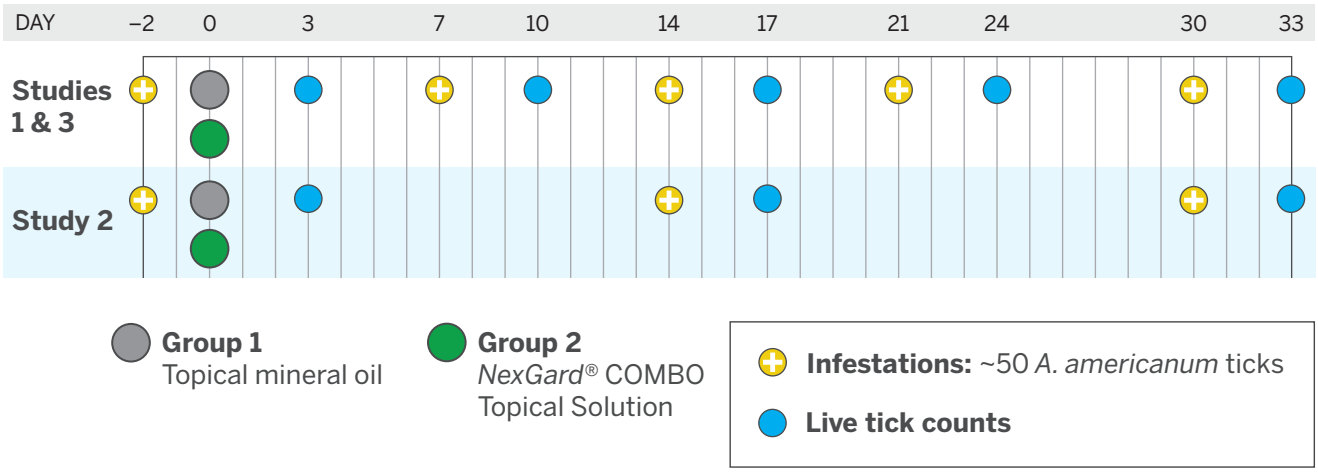
Efficacy Against Ticks

Efficacy Against *Amblyomma americanum*: 3 Laboratory Studies[2]

Objective	Confirm the efficacy of a single topical application of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) given at the recommended minimum dose for the treatment and control of *A. americanum* on cats
Studies	3 placebo-controlled laboratory studies that followed a randomized block design based on pre-treatment live tick counts
Treatment Groups for Each Study	 **Group 1** Treated with a **placebo control (mineral oil)**—10 cats  **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—10 cats
Treatment	On Day 0, cats in the treatment group were administered *NexGard* COMBO Topical Solution (0.12 mL/kg), and cats in the control group were treated with topical mineral oil (0.12 mL/kg).
Tick Infestations	• **Studies 1 & 3:** Cats were infested with ~50 live ticks on Days –2, 7, 14, 21, and 30. • **Study 2:** Cats were infested with ~50 live ticks on Days –2, 14, and 30.
Assessment of Efficacy	• **Studies 1 & 3:** Live ticks were counted on Days 3, 10, 17, 24, and 33 at 72 hours post-treatment (to assess immediate efficacy) and 72 hours after each subsequent infestation (to assess sustained efficacy). • **Study 2:** Live ticks were counted on Days 3, 17, and 33 at 72 hours post-treatment (to assess immediate efficacy) and 72 hours after each subsequent infestation (to assess sustained efficacy).

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Amblyomma americanum Infestation Model

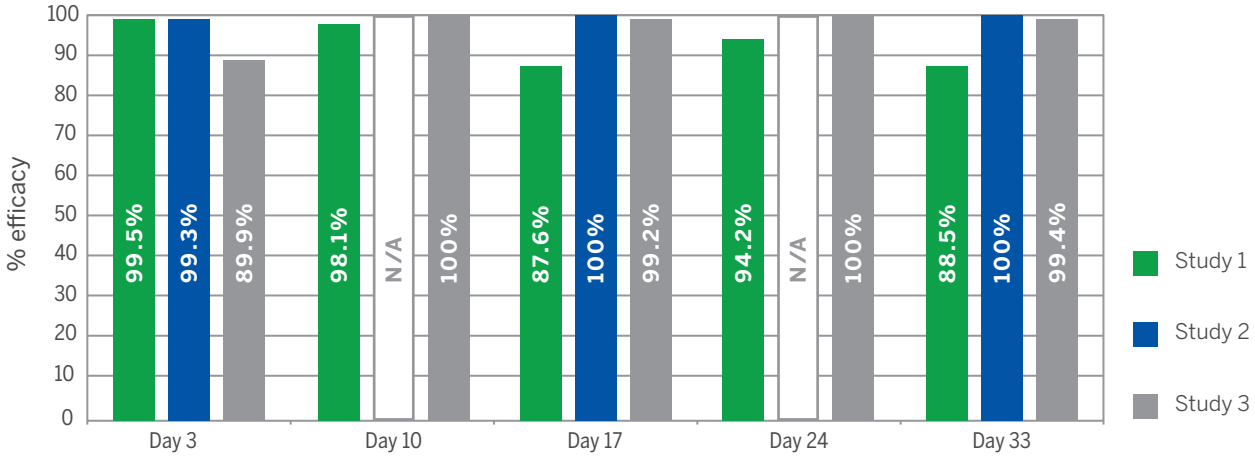


Results

- On average, *NexGard* COMBO Topical Solution demonstrated >95.6% efficacy against *A. americanum* at all time points (Figure 1).

Figure 1

Percent efficacy[a] against *A. americanum* 72 hours after treatment or reinfestation



[a] Percent efficacy = 100 × [(C – T)/C], where T and C are the arithmetic mean tick counts of the treated and control groups, respectively.

KEY POINT

NexGard COMBO Topical Solution was effective against *A. americanum* when assessed 72 hours after treatment and weekly reinfestation for 33 days.

FELINE HEARTWORM DISEASE

The nematode *Dirofilaria immitis*, heartworm, can cause unpredictable and potentially fatal disease in cats. *D. immitis* is passed to cats by the bite of an infected mosquito. Evidence of heartworm infection in cats has been identified in all 50 states.[13] In 1 study, more than 25% of confirmed heartworm-positive cats were described by pet owners as being solely indoor cats.[13,14]

The clinical signs of feline heartworm disease can range from mild respiratory distress and weight loss to seizures, severe respiratory distress, and sudden death. A common complication of a *D. immitis* infection in cats is heartworm-associated respiratory disease (HARD). HARD is tied to young heartworms reaching the pulmonary arteries of cats and dying. The death of these worms can cause clinical signs indistinguishable from those of allergies or bronchitis. These dead worms can also cause a severe inflammatory response and permanent lung damage. Unlike in dogs, there is currently no approved adulticide therapy for feline heartworm disease.

The laboratory studies in this section detail the efficacy of topically applied *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) against induced infections, using new isolates of *D. immitis*.

SUMMARY OF FELINE HEARTWORM DISEASE STUDIES

NexGard® COMBO Topical Solution was effective for the prevention of heartworm disease in cats caused by *D. immitis*.

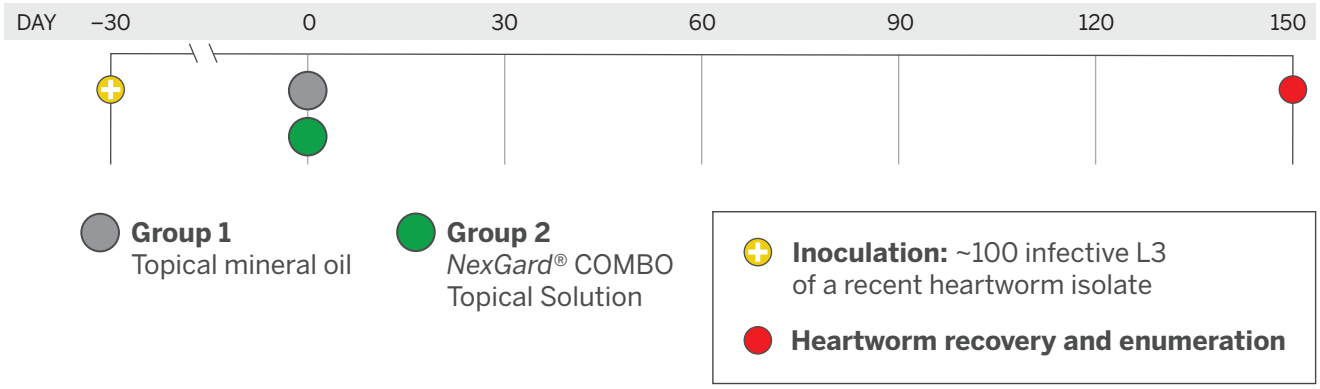
Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Efficacy Against Heartworm Disease Caused by *Dirofilaria immitis*

Prevention of Heartworm Disease in Cats: Laboratory Efficacy Study[2,15]

Objective	Confirm the efficacy of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) to prevent heartworm disease in cats when given at the recommended minimum dose 30 days after an induced infection with *D. immitis* 3rd-stage larvae (L3)
Study	A randomized, negative-controlled, blinded study using a recent heartworm isolate (Berkeley)
Treatment Groups	**Group 1** Treated with a **placebo control (mineral oil)**—10 cats **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—10 cats
Heartworm Infection	Day –30: Each cat was inoculated via subcutaneous injection in the inguinal area with ~100 *D. immitis* L3.
Treatment	Day 0: Cats in the treatment group were treated with *NexGard* COMBO Topical Solution (0.12 mL/kg), and cats in the control group were administered topical mineral oil (0.12 mL/kg).
Diagnostics	Day 150: All cats were necropsied for adult heartworm recovery and enumeration.

Heartworm Disease Prevention Model



Results

- 80% of cats in the control group harbored ≥2 adult *D. immitis* worms (Table 1).
- A single treatment of *NexGard* COMBO Topical Solution at the minimum recommended dose was 100% effective in the prevention of heartworm disease (Table 1).
- None of the cats treated with *NexGard* COMBO Topical Solution had evidence of adult heartworms (Table 1).

Table 1

Percent efficacy against the development of *D. immitis*

Treatment	*D. immitis* count on Day 150[a]	Geometric mean	Percent efficacy[b]	*P* value
Control	0, 1, 2, 5, 8, 8, 8, 14, 16, 16	5.1	—	—
NexGard COMBO Topical Solution	0 in each of the 10 cats	0.0	100%	<0.0001

[a] Total *D. immitis* counts in individual cats at necropsy.

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

KEY POINT

In this study, a single administration of *NexGard* COMBO Topical Solution was 100% effective in preventing *D. immitis* development in cats.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Efficacy Against Heartworm Disease Caused by *Dirofilaria immitis*

Efficacy Against Heartworm Disease: 4 Additional Laboratory Studies[2]

The US Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) is responsible for regulating animal drugs and for ensuring that they are safe and effective for their intended use. The FDA-recommended approach to demonstrate effectiveness of an investigational new animal drug intended for the prevention of heartworm disease in cats is for the efficacy of that product to be evaluated in 2 induced laboratory dose confirmation studies. The 2 studies are to be conducted at different laboratory facilities using *D. immitis* isolates that were isolated from the field within 5 years of study initiation. As part of the FDA's comprehensive approval process, several factors are considered for each study.

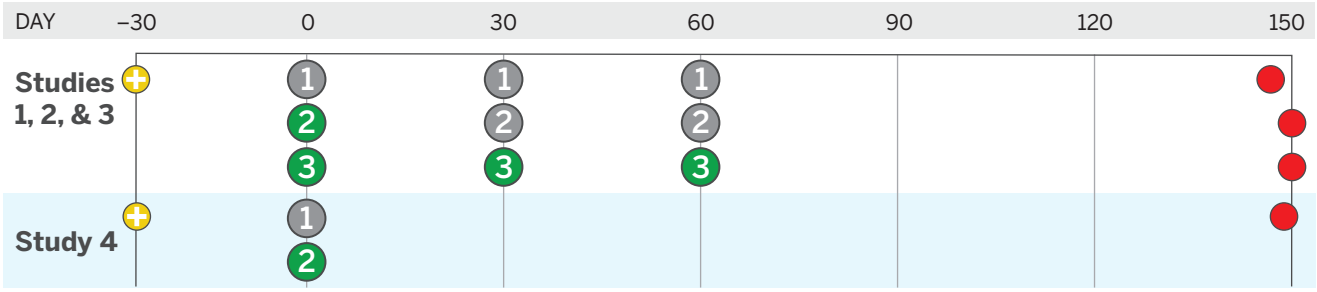
For a product to be indicated for the prevention of heartworm disease, the product must be 100% effective in preventing heartworm disease in both studies. In addition, the adequacy of infection is evaluated, and a minimum number of animals in the control group must be infected with a minimum number of worms during the study. In addition to the laboratory efficacy study described on page 36, 4 additional studies were performed to evaluate the efficacy of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) against a second heartworm isolate. However, these studies individually did not meet the FDA requirements for adequacy of infection: ≥60% of control cats (6 cats) infected with ≥2 heartworms.

When the 4 studies were evaluated together, the analysis confirmed that *NexGard*® COMBO Topical Solution is effective in the treatment of heartworm disease.

Objective	Confirm the efficacy of *NexGard* COMBO Topical Solution given at the recommended minimum dose once or 3 times at monthly intervals for the prevention of heartworm disease after an induced *D. immitis* infection
Studies	Randomized, negative-controlled, blinded studies using a second recently isolated heartworm isolate (Georgia II)
Treatment Groups	**Studies 1, 2, & 3** **Group 1** Treated with a **placebo control (mineral oil)**—10 cats **Group 2** Treated with ***NexGard* COMBO Topical Solution** for the first monthly treatment and **mineral oil** for 2 subsequent monthly treatments—10 cats **Group 3** Treated with ***NexGard* COMBO Topical Solution**—10 cats **Study 4** **Group 1** Treated with a **placebo control (mineral oil)**—10 cats **Group 2** Treated with ***NexGard* COMBO Topical Solution**—10 cats
Heartworm Infection	Day –30: Each cat was inoculated via subcutaneous injection to the inguinal area with ~100 *D. immitis* L3.

Treatment	**Studies 1, 2, & 3** In these studies, efficacy was evaluated after 1 monthly dose of *NexGard* COMBO Topical Solution (group 2) or after 3 monthly doses of *NexGard* COMBO Topical Solution (group 3). Days 0, 30, and 60 • Group 1 (control): Topical mineral oil (0.12 mL/kg) • Group 2: *NexGard* COMBO Topical Solution on Day 0 and topical mineral oil on Days 30 and 60 • Group 3: *NexGard* COMBO Topical Solution **Study 4** Day 0: Cats in the treatment group were treated with *NexGard* COMBO Topical Solution (0.12 mL/kg), and cats in the control group were administered topical mineral oil (0.12 mL/kg).
Diagnostics	Cats were necropsied for adult heartworm recovery and enumeration: • Day 147: Study 1 • Day 150: Studies 2 and 3 • Day 149: Study 4

Additional Heartworm Disease Prevention Studies Model



Studies 1, 2, & 3:

1 **Group 1**
Topical mineral oil

2 2 **Group 2**
NexGard® COMBO Topical Solution followed by topical mineral oil

3 **Group 3**
NexGard® COMBO Topical Solution

Study 4:

1 **Group 1**
Topical mineral oil

2 **Group 2**
NexGard® COMBO Topical Solution

Inoculation: ~100 infective L3 of a recent heartworm isolate

Heartworm recovery and enumeration
- Study 1: Day 147
- Studies 2 & 3: Day 150
- Study 4: Day 149

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Results

- The combined data from these 4 further studies substantiated the efficacy of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) in the prevention of heartworm disease in cats.
- No cat treated with *NexGard*® COMBO Topical Solution had evidence of adult heartworms (Table 1).

Table 1

Heartworm disease prevention efficacy when administered once in a monthly dose or in 3 consecutive monthly doses

			Number of heartworms observed in each individual animal	
Study	**Control group (n)**	***NexGard* COMBO Topical Solution (n)**	**Control group**	***NexGard* COMBO Topical Solution**
1	10	20	0, 0, 0, 0, 0, 0, 1, 2, 4, 7	All 0
2	10	20	0, 0, 0, 1, 1, 1, 3, 6, 6, 7	All 0
3	10	20	0, 0, 0, 0, 0, 0, 0, 0, 1, 1	All 0
4	10	10	0, 0, 0, 0, 0, 0, 1, 2, 4, 7	All 0

KEY POINTS

- *NexGard* COMBO Topical Solution consistently demonstrated 100% efficacy in preventing heartworm disease caused by *D. immitis*.
- Given that some of the heartworm disease prevention studies included cats that were dosed with 3 monthly doses, the product is labeled to be applied once monthly for at least 3 months after last exposure to mosquitoes for heartworm disease prevention.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

ROUNDWORMS

Roundworms are one of the most common intestinal parasites of cats, with some studies finding that 25% of cats test positive for *Toxocara cati.*[16,17] Clinical signs of a *T. cati* infection may include vomiting, diarrhea, and poor growth, with kittens having a higher chance of experiencing severe signs than adult cats because of their increased susceptibility to infection.

Indoor cats and outdoor cats are both at risk of exposure to infection, either from roundworm eggs or prey (paratenic hosts) containing infective larvae.[18] Roundworm eggs also pose a zoonotic threat: Accidental ingestion of infective roundworm eggs by humans may lead to serious infections involving ocular and visceral migrans of roundworm larvae.

The laboratory studies in this section detail the efficacy of topically applied *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) against both induced and natural *T. cati* infections.

SUMMARY OF ROUNDWORM STUDIES

NexGard® COMBO Topical Solution was proven effective for treatment and control of adult *T. cati* infections.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

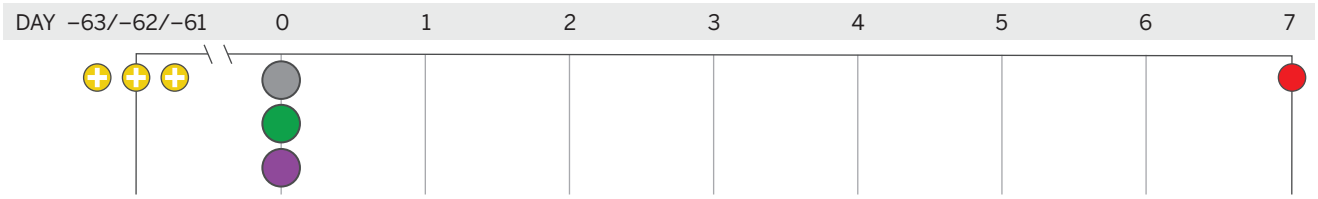
Efficacy Against Roundworms

Efficacy Against Induced *T. cati* Infection: Laboratory Study[2]

Objective	Confirm the efficacy of a single topical application of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) given at the recommended minimum dose for the treatment and control of adult *T. cati* on cats while also confirming the ineffectiveness of esafoxolaner alone at treating an existing roundworm infection
Study	A randomized, negative-controlled, blinded study
Treatment Groups	**Group 1** Treated with a **placebo control (mineral oil)**—10 cats  **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—10 cats  **Group 3** Treated with esafoxolaner—10 cats 
Roundworm Infection	• Before inoculation: All cats were confirmed negative for *T. cati* eggs. • Days –63, –62, and –61: Each cat was inoculated orally with ~34 infective larvated *T. cati* eggs.
Treatment	• Before treatment, all cats were diagnosed positive for *T. cati* eggs, indicating the presence of adult worms. • On Day 0, cats in the control group were treated with topical mineral oil (0.12 mL/kg), cats in group 2 were treated with 0.12 mL/kg of *NexGard* COMBO Topical Solution at the minimum recommended dose, and cats in group 3 were treated topically with esafoxolaner at a volume of 0.12 mL/kg, which delivered 1.4 mg/kg of esafoxolaner.
Diagnostics	Day 7: All cats were necropsied for *T. cati* recovery and enumeration.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Toxocara cati Induced Infection Model



Group 1
Topical mineral oil

Group 2
NexGard® COMBO Topical Solution

Group 3
Esafoxolaner

Inoculation: ~34 infective larvated *T. cati* eggs followed by a positive diagnosis

Parasite recovery and enumeration

Results

- *NexGard* COMBO Topical Solution demonstrated 100% efficacy against adult *T. cati* (Table 1).
- Esafoxolaner alone was not effective against adult *T. cati*, demonstrating the need for eprinomectin in the combination product (Table 1).

Table 1
Efficacy against induced *T. cati* infection

Treatment	Geometric mean worm count	Percent efficacy[a]	*P* value
Mineral oil	29.5	—	—
NexGard COMBO Topical Solution	0.00	100%	<0.0001
Esafoxolaner	30.5	−3.2%	0.8858

[a] Percent efficacy = 100 × [(C − T)/C], where T and C are the geometric mean worm counts of the treated and control groups, respectively.

KEY POINT

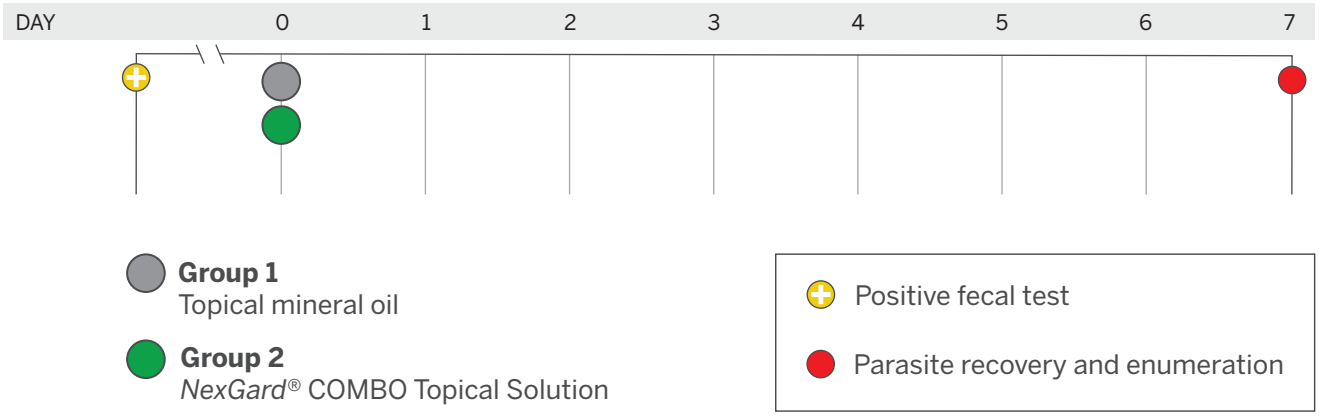
A single administration of *NexGard* COMBO Topical Solution was effective for the treatment of an induced adult roundworm infection.

Efficacy Against Roundworms

Efficacy Against Natural *T. cati* Infection[2]

Objective	Confirm the efficacy of a single topical application of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) given at the recommended minimum dose for the treatment and control of a natural infection with adult *T. cati*
Study	A randomized, negative-controlled, blinded study
Treatment Groups	**Group 1** Treated with a **placebo control (mineral oil)**—10 cats **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—10 cats
Roundworm Infection	Before treatment, all cats were confirmed positive for infection by the presence of *T. cati* eggs in feces (100 to 5,800 eggs per gram of feces).
Treatment	On Day 0, cats in the control group were treated with topical mineral oil (0.12 mL/kg), and cats in the treatment group received 0.12 mL/kg of *NexGard* COMBO Topical Solution at the minimum recommended dose.
Diagnostics	Day 7: All cats were necropsied for *T. cati* recovery and enumeration.

Toxocara cati Natural Infection Model



Results

- *NexGard* COMBO Topical Solution demonstrated 98.8% efficacy against *T. cati* (Table 1).

Table 1
Efficacy against natural *T. cati* infection

Treatment	Geometric mean worm count	Percent efficacy[a]	*P* value
Mineral oil	12.14	—	—
NexGard COMBO Topical Solution	0.14	98.8%	<0.0001

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

KEY POINT

A single administration of *NexGard* COMBO Topical Solution was effective for the treatment of a natural *T. cati* roundworm infection.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Efficacy Against Roundworms

Roundworms: Additional Studies[2]

Additional studies to support the substantial evidence of effectiveness for the eprinomectin dose used in *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) for the treatment and control of roundworms (4th-stage larval and adult *Toxocara cati)* were conducted with another formulation that uses the same dose and dosing recommendations as *NexGard*® COMBO Topical Solution (Table 1).

Table 1
Summary of results

Parasite	Infection	Geometric mean worm count control group (range)	Geometric mean worm count treated group (range)	Percent efficacy[a]
T. cati	N	5.1 (1-16)	0.1 (0-1)	98.6%
T. cati	I	70.9 (37-150)	0.1 (0)	100%
T. cati	I	17.4 (1-131)	0.1 (0-2)	99.4%
T. cati (4th-stage larvae)	I	3.3 (0-10)	0.0 (0)	100%
T. cati (adult and 4th-stage larvae)	I	4.2 (0-21)	0.0 (0)	100%
T. cati (adult and 4th-stage larvae)	I	7.2 (0-38)	1.2 (0-9)	83.2%
T. cati (4th-stage larvae)	I	56.4 (29-89)	0.5 (0-3)	99.2%

N, natural infection; I, induced infection.

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

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

HOOKWORMS

Hookworm infections are common in cats throughout the United States, with up to 20% of ownerless (community) cats infected with *Ancylostoma* spp. (e.g., *A. tubaeforme* and *A. braziliense*) and the highest infection rates occurring in warm coastal regions.[19]

Hookworms can live in the small intestine of cats and kittens, where the parasites graze on the intestinal mucosa, leaving bleeding wounds, and siphon blood from the host cat. A severe hookworm infection can result in anemia or death. *A. braziliense* larvae can also penetrate the skin of humans and can cause cutaneous larva migrans, a highly pruritic (itchy) condition.

SUMMARY OF HOOKWORM STUDIES

NexGard® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) contains the same dose of eprinomectin as CENTRAGARD® (eprinomectin and praziquantel transdermal solution). The FDA has allowed claims of efficacy against 4th-stage larval and adult *A. tubaeforme* and adult *A. braziliense* to be bridged for *NexGard*® COMBO Topical Solution without the requirement for further studies.[2]

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Efficacy Against Hookworms

Hookworm Studies[2]

Additional studies to support the substantial evidence of effectiveness for the eprinomectin dose used in *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) for the treatment and control of hookworms (4th-stage larval and adult *Ancylostoma tubaeforme* and adult *Ancylostoma braziliense*) were conducted with another formulation that uses the same dose and dosing recommendations as *NexGard*® COMBO Topical Solution (Table 1).

Table 1
Summary of results

Parasite	Infection	Geometric mean worm count control group (range)	Geometric mean worm count treated group (range)	Percent efficacy[a]
A. tubaeforme	N	19.0 (2-71)	0.2 (0-2)	99.0%
A. braziliense	N	13.3 (10-114)	2.8 (0-25)	91.0%
A. tubaeforme (adult and 4th-stage larvae)	I	45.1 (2-129)	0.0 (0)	100%
A. tubaeforme (adult and 4th-stage larvae)	I	69.1 (3-152)	0.0 (0)	100%
A. tubaeforme (adult and 4th-stage larvae)	I	105.1 (11-338)	0.2 (0.1)	99.8%
A. braziliense	I	137.0 (49-339)	0.6 (0-2)	99.5%
A. tubaeforme	I	54.8 (21-125)	0 (0)	100%

N, natural infection; I, induced infection.

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

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

TAPEWORMS

The cestode *Dipylidium caninum* is estimated to infect between 1.8% to 52.7% of cats; however, obtaining accurate prevalence data has been a challenge due to complications with testing methods.[20]

Although infection in cats and kittens rarely causes severe clinical signs, pet owners are taken aback when seeing the proglottids near the anus of their cats. Additionally, *D. caninum* tapeworms can pose a zoonotic risk because humans (typically children) can become infected through accidental ingestion of an adult *C. felis* flea harboring infective *D. caninum* tapeworms.

The laboratory studies in this section detail the efficacy of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) against both induced and natural *D. caninum* infections.

SUMMARY OF TAPEWORM STUDIES

NexGard® COMBO Topical Solution was effective for treatment of the most common tapeworm species in cats, *D. caninum*.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

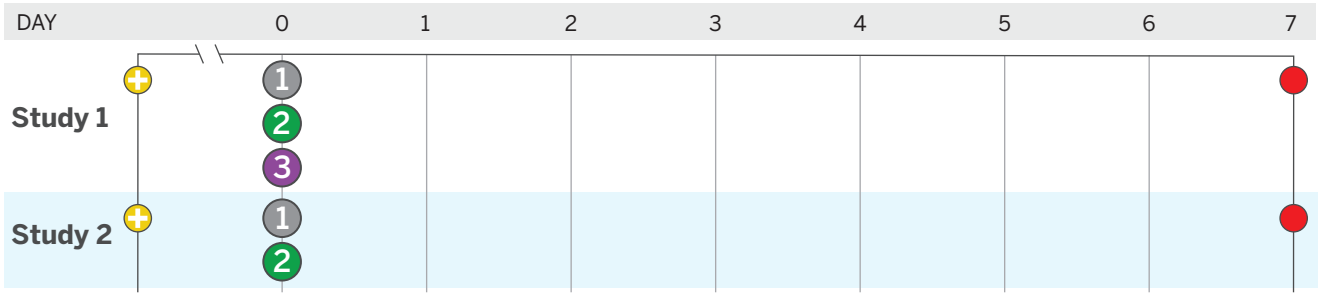
Efficacy Against Tapeworms

Efficacy Against Induced *D. caninum* Infection: 2 Laboratory Studies[2,21]

Objective	Confirm the efficacy of a single topical application of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) given at the recommended minimum dose after an induced infection with *D. caninum* while also confirming the ineffectiveness of esafoxolaner alone in treating an existing *D. caninum* infection
Studies	2 randomized, negative-controlled, blinded laboratory studies
Treatment Groups	**Study 1** **Group 1** Treated with a **placebo control (mineral oil)**—8 cats **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—8 cats **Group 3** Treated with **esafoxolaner**—8 cats **Study 2** **Group 1** Treated with a **placebo control (mineral oil)**—8 cats **Group 2** Treated with ***NexGard* COMBO Topical Solution**—8 cats
Tapeworm Infection	• Cats were experimentally infected using the intermediate host, *C. felis*, with ~100 to 150 adult fleas harboring *D. caninum*. • Before treatment, all cats were diagnosed positive for infection by the presence of *D. caninum* proglottids in feces.
Treatment	On Day 0, cats in the control group were treated with topical mineral oil (0.12 mL/kg), cats in group 2 were treated with 0.12 mL/kg of *NexGard* COMBO Topical Solution at the minimum dose, and for study 1, cats in group 3 were treated topically with esafoxolaner at a volume of 0.12 mL/kg, which delivered 1.4 mg/kg of esafoxolaner.
Diagnostics	Day 7: All cats were necropsied for tapeworm recovery and enumeration.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Dipylidium caninum Induced Infection Model



Study 1

1. **Group 1** Topical mineral oil
2. **Group 2** *NexGard*® COMBO Topical Solution
3. **Group 3** Esafoxolaner

Study 2

1. **Group 1** Topical mineral oil
2. **Group 2** *NexGard*® COMBO Topical Solution

Inoculation: ~100 to 150 *C. felis* fleas harboring *D. caninum* followed by a positive fecal test

Parasite recovery and enumeration

Results

- *NexGard* COMBO Topical Solution demonstrated an average 90% efficacy against induced *D. caninum* infection (Table 1).
- Esafoxolaner alone was not an effective treatment for an existing *D. caninum* infection, demonstrating the need for praziquantel in the combination product (Table 1).

Table 1
Efficacy against induced *D. caninum* infection

Treatment		Geometric mean worm count	Percent efficacy[a]	*P* value
Study 1	Mineral oil	28.9	—	—
	NexGard COMBO Topical Solution	0.6	98.0%	0.0018
	Esafoxolaner	56.5	–95.8%	—
Study 2	Mineral oil	3.3	—	—
	NexGard COMBO Topical Solution	0.6	81.4%	0.024

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

KEY POINT

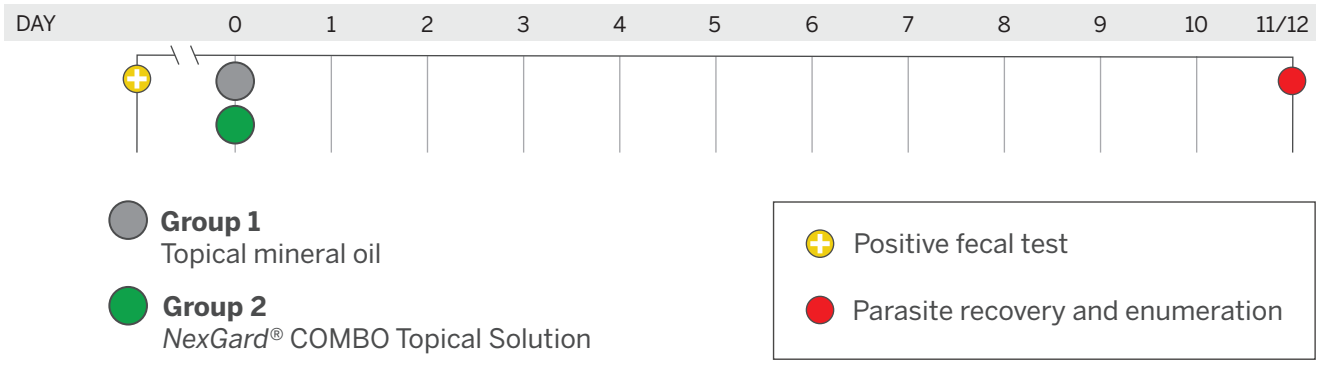
A single administration of *NexGard* COMBO Topical Solution was effective for the treatment of an induced *D. caninum* infection.

Efficacy Against Tapeworms

Efficacy Against Natural *D. caninum* Infection[2]

Objective	Confirm the efficacy of a single topical application of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) given at the recommended minimum dose for the treatment and control of a natural *D. caninum* infection
Study	A randomized, negative-controlled, blinded study
Treatment Groups	**Group 1** Treated with a **placebo control (mineral oil)**—10 cats **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—10 cats
Tapeworm Infection	Before treatment, all cats were diagnosed positive for infection by the presence of *D. caninum* proglottids in feces.
Treatment	Day 0: Cats in the control group were treated with topical mineral oil (0.12 mL/kg), and cats in the treatment group were administered *NexGard* COMBO Topical Solution (0.12 mL/kg).
Diagnostics	Day 11/12: All cats were necropsied for tapeworm recovery and enumeration.

Dipylidium caninum Natural Infection Model



Results

- *NexGard* COMBO Topical Solution demonstrated >99% efficacy against a natural *D. caninum* infection (Table 1).

Table 1
Efficacy against natural *D. caninum* infection

Treatment	Geometric mean worm count	Percent efficacy[a]	*P* value
Mineral oil	68.1	—	—
NexGard COMBO Topical Solution	0.6	99.1%	<0.0001

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

KEY POINT

A single administration of *NexGard* COMBO Topical Solution was effective for the treatment of a natural *D. caninum* infection.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

SAFETY AND TOLERANCE STUDIES

SAFETY AND TOLERANCE STUDIES

The safety of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) has been evaluated extensively in numerous studies. The following pages highlight the target animal safety and tolerance studies conducted for approval of the product in the United States.

Summary of Studies

Studies on the safety and tolerance of *NexGard*® COMBO Topical Solution confirmed that it was safe and well-tolerated, with minimal adverse side effects when applied at the recommended label dose.

NexGard COMBO Topical Solution was demonstrated to be safe for use in heartworm-positive cats.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Target Animal Safety Study[2]

Objective

Evaluate the safety of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) when administered topically to kittens at 1X, 3X, and 5X the maximum exposure dose 6 times at 4-week intervals

Study

A placebo-controlled, blinded safety study with a total of 32 kittens (16 male, 16 female) ranging in age from 8 to 9 weeks and weighing between 0.7 and 1.2 kg

Treatment Groups

Group 1
Treated with a **placebo control (mineral oil)**
—8 kittens

Group 3
Treated with ***NexGard* COMBO Topical Solution (3X)**
—8 kittens

Group 2
Treated with ***NexGard*® COMBO Topical Solution (1X)**
—8 kittens

Group 4
Treated with ***NexGard* COMBO Topical Solution (5X)**
—8 kittens

Treatment

Days 0, 28, 56, 84, 112, and 140: Kittens were dosed with either mineral oil or the appropriate dose of *NexGard* COMBO Topical Solution (Table 1).

Table 1
Dose per treatment for each group

Group	*NexGard* COMBO Topical Solution dose	Dose volume (mL/kg)	Esafoxolaner dose (mg/kg)	Eprinomectin dose (mg/kg)	Praziquantel dose (mg/kg)
1	0X	1	0	0	0
2	1X	0.375	4.5	1.5	31.1
3	3X	1.125	13.5	4.5	93.4
4	5X	1.875	22.5	7.5	155.6

Assessment of Safety

Clinical Observations

- Clinical observations were performed twice daily on nondosing days.
- On dosing days, kittens were observed prior to dosing and 10 minutes after dosing of the last animal and at 1, 2, 3, 4, 6, and 8 hours after dosing of the last animal.
- On Days 84, 112, and 140, additional clinical observations were conducted on all kittens at 9 and 10 hours after dosing of the last animal.
- At each clinical observation, the eyes were examined and scored for pupillary dilation light reflex.
- More detailed physical observations were performed before treatment, weekly during the study, and at necropsy.

Assessment of Safety *(cont.)*

- The condition of the dosing application site was also documented.
- Detailed veterinary physical examinations were conducted before treatment, on the day after each treatment, on the day of necropsy, and as needed to assess adverse events.

Further Clinical Observations

- **Body weights:** Animals were weighed before dosing and weekly during the study period, including the day before each dose administration, and before necropsies.
- **Food and water consumption:** Food and water consumption were quantitatively measured daily starting on Day –1.
- **Clinical pathology:** Samples were obtained for hematology, serum biochemistry profiles, coagulation parameters, and urinalysis testing before dosing, on the day after each dosing, and before necropsy.
- **A complete necropsy** with organ weights and microscopic examinations was completed at the end of the study.

Results

- *NexGard* COMBO Topical Solution was well-tolerated when administered at 4-week intervals for 6 treatments at 1X and 3X the maximum exposure dose.
- 1 reversible adverse event was observed in a male cat (5X group) after administration of the third dose on Day 56. Nine hours after treatment, the cat exhibited recumbency, slight tremors, hypothermia, ataxia, disorientation, and pupil dilation (responsive to light). This kitten received supportive care, including washing of the application site, and recovered within 48 hours post-dose. He had no adverse reaction after the next three 5X doses (Days 84, 112, and 140), and he had a normal growth rate and no abnormal clinical or anatomical pathology observed throughout the study.
- No significant changes related to *NexGard* COMBO Topical Solution were observed for physical examination, body weight, clinical pathology (hematology, coagulation, and serum biochemistry), histopathology, or organ weights.
- No further treatment-related effects were detected in any of the cats in this study.

KEY POINT

NexGard COMBO Topical Solution was demonstrated to be safe for use in cats and kittens 8 weeks of age and older, weighing 1.8 lb or more, when dosed according to label directions.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Oral Tolerance Study[2]

Objective	Determine the safety of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) when given orally at the maximum exposure dose of 0.375 mL/kg
Study	A placebo-controlled, blinded safety study with a total of 16 kittens (8 males, 8 females) ranging in age from 7 to 9 weeks and weighing between 0.6 and 1.0 kg
Treatment Groups	 **Group 1** Treated with a **placebo control (sterile water)**—8 kittens  **Group 2** Treated with ***NexGard*® COMBO Topical Solution**—8 kittens
Treatment	Day 0: Kittens were orally dosed with either sterile water (0.375 mL/kg) or *NexGard* COMBO Topical Solution (0.375 mL/kg).
Assessment of Tolerance	• Days –4, 0, 1, 7, and 14: Physical examinations were performed by a veterinarian to assess any adverse clinical signs. – Day 0 physical examinations were performed by veterinarians 6 hours after dose administration, followed by kittens being observed by qualified technicians 1, 2, 3, 4, 8, and 12-hours post-treatment. • Days –7 to 14: Kittens were observed twice daily by qualified technicians. • Days –4, 0, 1, 7, and 14: Body weight of all kittens was measured. • Days –7 to 14: Individual kitten daily food consumption was measured. • Days –1 and 14: Blood and urine samples were taken for hematology, plasma biochemistry profiles, and urinalysis. • Throughout the study, oral tolerance was evaluated to assess the effects of accidental oral ingestion in cats, including from licking or grooming the application site.

Results

- All kittens orally administered *NexGard* COMBO Topical Solution salivated profusely immediately after dosing. Salivation was no longer visible at the first hourly post-dose observation and afterward.
- There were no clinically relevant differences between the 2 groups in food consumption, body weight, or clinical pathology (hematology, serum biochemistry, and urinalysis).

KEY POINTS

- Other than hypersalivation immediately after dosing, *NexGard* COMBO Topical Solution did not cause any adverse side effects, and there were no clinically relevant signs of toxicity.
- Correct application of *NexGard* COMBO Topical Solution will minimize accidental oral ingestion in cats.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Safety of an Eprinomectin-Containing Formulation in Cats Infected With Heartworms[2]

The concentration of eprinomectin in *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is identical to the concentration of eprinomectin in CENTRAGARD® (eprinomectin and praziquantel transdermal solution). Therefore, the safety of *NexGard*® COMBO Topical Solution when used in cats infected with adult *D. immitis* is established based on the study supporting the safety of CENTRAGARD® Transdermal Solution in this animal population.

Objective	Determine the safety of an eprinomectin-containing topical solution with identical eprinomectin dosing as used for *NexGard* COMBO Topical Solution when given at monthly intervals for 3 months at 1X (0.375 mL/kg) and 3X (1.125 mL/kg) the maximum exposure dose to heartworm-infected cats
Study	A randomized, negative-controlled, blinded study
Treatment Groups	**Group 1** Treated with a **placebo control (mineral oil)**—12 cats **Group 2** Treated with an **eprinomectin-containing solution (1X)**—12 cats **Group 3** Treated with an **eprinomectin-containing solution (3X)**—12 cats
Heartworm Infection	• All cats tested negative for heartworm (antibody, antigen, and microfilariae) prior to infection. • Cats were infected with *D. immitis* through transplantation of 6 live adult worms (3 male, 3 female) into the jugular vein. • Day –6: All cats had a positive antigen test and demonstrated the presence of microfilariae.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Treatment

Days 0, 28, and 56: Cats were dosed with either mineral oil or the eprinomectin-containing solution (Table 1).

Table 1
Dose per treatment for each group

Group	Eprinomectin-containing solution dose	Dose volume (mL/kg)
1	0X	1.125
2	1X	0.375
3	3X	1.125

Assessment of Safety

- Physical examinations were performed directly after dosing, 24 and 48 hours after treatment, and on Day 83 (end of study).
- Days 0 to 83: Cats were observed twice daily for any adverse clinical signs.
- Days 0, 28, and 56: Cats were observed 1, 2, 4, 6, 8, and 24 hours after treatment.
- Day 83: All cats were weighed.

Results

- The product was well-tolerated in cats previously infected with adult heartworms, with only 1 cat in the 1X group exhibiting cyanotic mucous membranes and tachypnea for 24 hours following the first treatment; the cat recovered and exhibited no abnormal signs following 2 subsequent treatments.
- 2 control cats died before the end of the study due to hypertrophic cardiomyopathy complicated by severe heartworm-associated systemic vasculitis.
- The product was well-tolerated in cats with induced *D. immitis* infections.

KEY POINT

NexGard COMBO Topical Solution is safe for use in heartworm-positive cats.

Safety When Used Under Field Conditions on Client-Owned Cats[2]

The safety of *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) was also confirmed through several multicenter field studies globally. The safety component of the field study conducted in the United States evaluating the effectiveness of *NexGard*® COMBO Topical Solution against flea infestations is highlighted below. The efficacy portion of this study, including experimental design, is detailed on pages 22 to 25.

Objective	Determine the safety of *NexGard* COMBO Topical Solution in client-owned cats when administered topically 3 times at 1-month intervals
Study	A positive-controlled, blinded, multicenter field study using a randomized block design based on order of enrollment of 201 households with a total of 380 cats (208 females, 172 males) ranging in age from 8 weeks to 17 years and weighing between 1.8 and 23.9 lb Client-owned cats came from 11 veterinary clinics in 3 regions of the United States: • Midwest (3) • Southeast (7) • West (1)
Treatment Groups	**Group 1** Treated with ***NexGard* COMBO Topical Solution** at the intended label dose **Group 2** Treated with **selamectin (active control)** at the intended label dose
Treatment	244 cats were topically treated with *NexGard* COMBO Topical Solution, and 136 were treated with an active control (selamectin).
Assessment of Safety	The safety of *NexGard* COMBO Topical Solution was evaluated over a 90-day period through in-clinic physical examinations and owners reporting abnormalities.

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Results

- There were no serious health abnormalities attributed to treatment.
- Use of *NexGard* COMBO Topical Solution in conjunction with other treatments (e.g., vaccines, antibiotics, analgesics) had no effect on safety.
- Adverse side effects that may have been related to treatment included vomiting, application site change, anorexia, lethargy, and diarrhea.
- The most frequently reported reactions in the *NexGard* COMBO Topical Solution and active control group are presented in Table 1.

Table 1
Summary of the most frequently reported adverse reactions

Event	*NexGard* COMBO Topical Solution		Active control (selamectin)	
	No. of cats	% (n=244)	No. of cats	% (n=136)
Vomiting	16	6.56	8	5.88
Application site hair change	9	3.69	0	0
Anorexia	7	2.87	4	2.94
Lethargy	6	2.46	5	3.68
Bacterial skin infection	4	1.64	1	0.74
Itching	4	1.64	0	0
Sneezing	4	1.64	5	3.68
Skin peeling	3	1.23	2	1.47
Diarrhea	3	1.23	3	2.21
Epiphora	3	1.23	1	0.74
Hypersalivation	3	1.23	0	0
Hyperthermia	3	1.23	0	0

KEY POINTS

- Under field conditions, *NexGard* COMBO Topical Solution was shown to be safe and well-tolerated when used at the recommended dose for treatment of adult flea infestations.
- Concurrent use with other medications did not have an impact on the safety of *NexGard* COMBO Topical Solution.

PACKAGING AND DOSING

PACKAGING AND DOSING

Packaging

NexGard® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is packaged as a single dose in 2 convenient sizes (0.3 mL for cats weighing 1.8 to 5.5 lb and 0.9 mL for cats weighing 5.6 to 16.5 lb) and is available in cartons containing 1, 3, or 6 doses (Figure 1). *NexGard*® COMBO Topical Solution is applied with an easy-to use applicator that is designed to help reduce stress and mess for cats and their owners.

Figure 1
NexGard COMBO Topical Solution packages

Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Dosage and Administration

NexGard® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is dosed at a minimum of 0.055 mL/lb (0.12 mL/kg), which delivers a minimum dose of 0.65 mg/lb (1.44 mg/kg) esafoxolaner, 0.22 mg/lb (0.48 mg/kg) eprinomectin, and 4.53 mg/lb (9.98 mg/kg) praziquantel.

For heartworm disease prevention, apply once monthly for at least three months after last exposure to mosquitoes (see **Effectiveness** in the prescribing information on page 75).

Administer the entire contents of a *NexGard*® COMBO Topical Solution unit applicator topically once a month as specified in Table 1.

Table 1
Dosing schedule

Cat Weight (lb)	Volume (mL)	Esafoxolaner (mg)	Eprinomectin (mg)	Praziquantel (mg)
1.8–5.5	0.3	3.6	1.2	24.9
5.6–16.5	0.9	10.8	3.6	74.7
16.6–22	0.3 + 0.9	14.4	4.8	99.6
22.1–33	0.9 + 0.9	21.6	7.2	149.4

A veterinarian or veterinary technician should demonstrate or instruct the pet owner regarding the appropriate technique for applying *NexGard* COMBO Topical Solution topically to cats and kittens prior to first use (Figures 2 and 3).

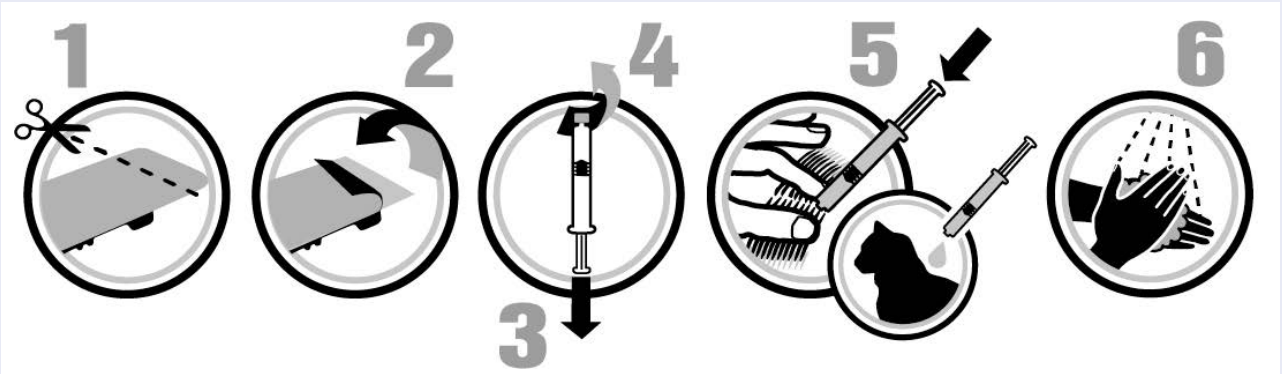
Keep product in original packaging until ready to use.

Figure 2
Plunger applicator: (A) 0.3 mL for cats weighing 1.8 to 5.5 lb and (B) 0.9 mL for cats weighing 5.6 to 16.5 lb

Figure 3
How to apply *NexGard* COMBO Topical Solution

1. Use scissors to cut the blister along the dotted line.
2. Then pull the lid away.
3. Remove the applicator from the package and hold it upright. Pull back the plunger slightly.
4. Twist and pull off the cap.
5. Part the hair on the midline of the neck, between the base of the skull and the shoulder blades until the skin is visible. Place the tip of the applicator on the skin and apply the entire contents directly onto the skin in one spot. The product should be applied to dry skin on an area where the cat cannot lick it off. If the weight of the cat requires a second application, apply the contents in the same manner as described above in the same location.
6. Wash hands after use with soap and water.

Applicator instructions



Important Safety Information: *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is for topical use only in cats. Use with caution in cats with a history of seizures or neurologic disorders. The most frequently reported adverse reactions include vomiting, application site reactions, and anorexia. If ingested, hypersalivation may occur. Avoid direct contact with application site until visibly dry. For more information, see full prescribing information or visit NexGardCOMBOClinic.com.

Important Safety Information

- Esafoxolaner, one of the ingredients in *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution), is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in cats receiving isoxazoline class drugs, even in cats without a history of seizures. Use with caution in cats with a history of seizures or neurologic disorders.
- The most frequently reported adverse reactions include vomiting, application site reactions, anorexia, and lethargy.
- *NexGard*® COMBO Topical Solution is for topical use only in cats. Do not administer orally. Cats may salivate excessively if *NexGard* COMBO Topical Solution is accidentally administered orally or is ingested through licking/grooming the application site.
- The safety of *NexGard* COMBO has not been tested in breeding, pregnant, or lactating cats, as well as in kittens less than 8 weeks of age or weighing less than 1.8 lbs.

NexGard® COMBO
(esafoxolaner, eprinomectin, and praziquantel topical solution)

For topical use in cats only

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

Description:
NexGard® COMBO is a topical solution containing esafoxolaner, eprinomectin and praziquantel available in 0.3 mL and 0.9 mL unit applicators to treat cats from 1.8 lbs to 33 lbs. Each mL of NexGard® COMBO contains 12 mg of esafoxolaner, 4 mg of eprinomectin, and 83 mg of praziquantel. Inactive ingredients: dimethyl isosorbide, unstabilized glycerol formal, and butylated hydroxytoluene.

Esafoxolaner is a member of the aryl isoxazoline class of compounds. Its chemical name is 4-[(5S)-5-[3-chloro-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-4, 5-dihydro-1,2-oxazol-3-yl]-N-{2-oxo-2-[(2,2,2-trifluoromethyl) amino]ethyl}-1-naphthamide.

Eprinomectin belongs to the avermectin class of anthelmintics and is a mixture of homologous components referred to as eprinomectin B1a and B1b. The chemical name for eprinomectin B1a is (4″R)-acetylamino-5-O-demethyl-4″-deoxyavermectin A_{1a}. The chemical name for eprinomectin B1b is (4″R)-acetylamino-5-O-demethyl-25-de(1-methylpropyl)-4″-deoxy-25-(1-methylethyl) avermectin A_{1a}.

Praziquantel is a pyrazinoisoquinoline anthelmintic. Its chemical name is 2-(Cyclohexylcarbonyl)- 1,2,3,6,7,11b-hexahydro-4H-pyrazino[2,1-a]-isochinolin-4-one.

Indications:
NexGard® COMBO is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of roundworm (fourth stage larval and adult *Toxocara cati*), hookworm (fourth stage larval and adult *Ancylostoma tubaeforme*; adult *Ancylostoma braziliense*), and tapeworm (*Dipylidium caninum*) infections. NexGard® COMBO kills adult fleas (*Ctenocephalides felis*) and is indicated for the treatment and prevention of flea infestations and the treatment and control of *Ixodes scapularis* (black-legged tick) and *Amblyomma americanum* (lone star tick) infestations for one month in cats and kittens 8 weeks of age and older, and weighing 1.8 lbs or greater.

Dosage and Administration:
NexGard® COMBO is dosed at a minimum of 0.055 mL/lb (0.12 mL/kg), which delivers a minimum dose of 0.65 mg/lb (1.44 mg/kg) esafoxolaner, 0.22 mg/lb (0.48 mg/kg) eprinomectin, and 4.53 mg/lb (9.98 mg/kg) praziquantel.

For heartworm disease prevention, apply once monthly for at least three months after last exposure to mosquitoes (see **Effectiveness**).

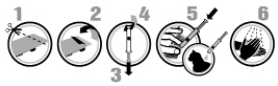
Administer the entire contents of a NexGard® COMBO unit applicator topically once a month as specified in the following table:

Dosing Schedule:

Cat Weight (lb)	Volume (mL)	Esafoxolaner (mg)	Eprinomectin (mg)	Praziquantel (mg)
1.8-5.5	0.3	3.6	1.2	24.9
5.6-16.5	0.9	10.8	3.6	74.7
16.6-22	0.3 + 0.9	14.4	4.8	99.6
22.1-33	0.9 + 0.9	21.6	7.2	149.4

A veterinarian or veterinary technician should demonstrate or instruct the pet owner regarding the appropriate technique for applying NexGard® COMBO topically to cats and kittens prior to first use.

Keep product in original packaging until ready to use.



1. Use scissors to cut the blister along the dotted line.
2. Then pull the lid away.
3. Remove the applicator from the package and hold it upright. Pull back the plunger slightly.
4. Twist and pull off the cap.
5. Part the hair on the midline of the neck, betwen the base of the skull and the shoulder blades until the skin is visible. Place the tip of the applicator on the skin and apply the entire contents directly onto the skin in one spot. The product should be applied to dry skin on an area where the cat cannot lick it off. If the weight of the cat requires a second application, apply the contents in the same manner as described above in the same location.
6. Wash hands after use with soap and water.

Heartworm Prevention:
For the prevention of heartworm disease, NexGard® COMBO should be administered once a month year-round. At a minimum, administration of NexGard® COMBO should start at least 1 month before the cat's first expected exposure to mosquitoes and monthly thereafter until at least 3 months after the cat's last seasonal exposure to mosquitoes (see **Effectiveness**). If a dose is missed and a 30-day interval between doses is exceeded, administer NexGard® COMBO immediately and resume the monthly dosing schedule. Treatment with fewer than 3 monthly doses may not provide complete heartworm prevention. When replacing another monthly heartworm preventive product in a heartworm prevention program, the first treatment with NexGard® COMBO should be given within one month of the last dose of the former medication. At the discretion of the veterinarian, cats older than 6 months of age may be tested to determine the presence of existing heartworm infection before treatment with NexGard® COMBO. Cats already infected with adult heartworms can be given NexGard® COMBO monthly to prevent further infections.

Flea Treatment and Prevention:
For the treatment and prevention of flea infestations, the use of NexGard® COMBO may begin at any time of year. NexGard® COMBO should be administered year-round at monthly intervals or begin at least one month before fleas become active. However, an environmental infestation may persist for a short time after beginning treatment with NexGard® COMBO because of the development of adult fleas from eggs that were laid prior to the initiation of treatment.

Tick Treatment and Control:
For the treatment and control of infestations with *Ixodes scapularis* and *Amblyomma americanum*, the use of NexGard® COMBO may begin at any time of year. NexGard® COMBO should be administered year-round at monthly intervals or begin at least one month before the ticks become active.

Treatment and Control of Roundworms, Hookworms, and Tapeworms:
NexGard® COMBO provides treatment and control of roundworms (adult and fourth stage larval *Toxocara cati*), hookworms (adult and fourth stage larval *Ancylostoma tubaeforme*; adult *Ancylostoma braziliense*), and tapeworms (*Dipylidium caninum*). For the treatment of hookworm, roundworm and tapeworm infections, NexGard® COMBO should be administered once as a single dose. Monthly use of NexGard® COMBO will control any subsequent infections. Cats may be exposed to and can become infected with roundworms, hookworms, and tapeworms throughout the year, regardless of season or climate.

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

Human Warnings:
Not for human use. Keep this and all drugs out of sight and reach of children.

Avoid direct contact with application site for 4 hours or until visibly dry.

This product may act as a mild to moderate eye irritant.

Keep product in the original packaging until use. Wash hands after product administration. If the product accidentally gets into the eyes, rinse thoroughly with water. If wearing contact lenses, flush the eyes first with water and then remove the lenses and continue to flush thoroughly with water. In case of accidental ingestion, or if skin or eye irritation occurs, contact a poison control center or physician for treatment advice.

Precautions:
Esafoxolaner, one of the ingredients in NexGard® COMBO, is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in cats receiving isoxazoline class drugs, even in cats without a history of seizures. Use with caution in cats with a history of seizures or neurologic disorders.

Do not administer orally. Cats may salivate excessively if NexGard® COMBO is accidentally administered orally or is ingested through licking/grooming the application site (see **Target Animal Safety**).

The safety of NexGard® COMBO has not been tested in breeding, pregnant, or lactating cats.

The safety of NexGard® COMBO has not been tested in kittens less than 8 weeks of age or weighing less than 1.8 lbs (0.8 kg).

Adverse Reactions:
In a field safety and effectiveness study, which included a total of 201 households and 380 treated cats (244 cats treated with NexGard® COMBO, 136 cats treated with an active control), the safety of NexGard® COMBO was evaluated over a 90-day period through in-clinic physical examinations or through reporting of abnormalities by the owner.The most frequently reported reactions in the NexGard® COMBO and active control groups are presented in the following table.

Adverse Reactions by Treatment Group

EVENT	Treatment Group			
	NexGard COMBO		Active Control	
	n[1]	% (n=244)	n[2]	% (n=136)
Vomiting	16	6.56	8	5.88
Application Site Hair Change	9	3.69	0	0.00
Anorexia	7	2.87	4	2.94
Lethargy	6	2.46	5	3.68
Bacterial Skin Infection	4	1.64	1	0.74
Itching	4	1.64	0	0.00
Sneezing	4	1.64	5	3.68
Skin Peeling	3	1.23	2	1.47
Diarrhea	3	1.23	3	2.21
Epiphora	3	1.23	1	0.74
Hypersalivation	3	1.23	0	0.00
Hyperthermia	3	1.23	0	0.00
Alopecia	2	0.82	0	0.00
Dermal Thickening	2	0.82	0	0.00
Ear Pruritus	2	0.82	1	0.74
Application Site Redness	2	0.82	0	0.00
Conjunctivitis	1	0.41	1	0.74

[1]Number of cats treated with NexGard® COMBO with the identified abnormality.
[2]Number of cats treated with Active Control with the identified abnormality.

Contact Information:
To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251 or www.nexgardforpets.com.

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

The Safety Data Sheet (SDS) provides additional occupational safety information. For customer service or to obtain product information, including the SDS, call 1-888-637-4251.

Clinical Pharmacology:
Mode of Action:
Esafoxolaner is a member of the isoxazoline family, shown to bind at a 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 esafoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of esafoxolaner between insects/acarines and mammals may be inferred by the differential sensitivity of the insects/acarines' GABA receptors versus mammalian GABA receptors.

Eprinomectin is an endectocide in the macrocyclic lactone class that binds to glutamate gated chloride channels that are present in invertebrate nerve and muscle cells and increases the permeability of the cell membrane to chloride ions that triggers hyperpolarization of the nerve or muscle cell in susceptible parasites, resulting in paralysis and death of the parasite.

Praziquantel's mode of action is not precisely known, but treated tapeworms undergo muscular paralysis accompanied by a rapid influx of calcium ions and the disruption of the tegument.

Pharmacokinetics:
After a single topical administration to healthy male and female cats of a combined topical formulation containing esafoxolaner (12 mg/mL), eprinomectin (4 mg/mL), and praziquantel (83 mg/mL), at dose volumes of 0.06, 0.12, or 0.24 mL/kg, there was a dose proportional increase in the exposure of each ingredient based on maximum plasma concentration (Cmax) and area under the plasma concentration time curve (AUC). After repeated monthly doses of the combined topical formulation at the target dose of 1.44 mg/kg esafoxolaner, 0.48 mg/kg eprinomectin, and 9.98 mg/kg praziquantel, steady state was reached by the fourth dose for esafoxolaner and after the second dose for eprinomectin and praziquantel. Additionally, modest accumulation was observed for esafoxolaner (approximately 3-fold) and praziquantel (approximately 1.5- to 2-fold) between the first and fifth dose, whereas no accumulation was observed for eprinomectin.

Effectiveness:
Heartworm Prevention:
In well-controlled laboratory studies, NexGard® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) was 100% effective in preventing the development of heartworms in cats inoculated with infective larvae of *Dirofilaria immitis* 30 days prior to the first of three consecutive monthly treatments.

Flea Treatment and Prevention:
In a well-controlled laboratory study, NexGard® COMBO killed >92% of fleas within 24 hours. During subsequent weekly infestations, NexGard® COMBO killed ≥95.5% of fleas within 24 hours through Day 31 and killed fleas before they could lay eggs. The effectiveness against adult fleas at 24 hours post-infestation in the treated cats virtually eliminated flea egg production (99.8 – 100% control of flea egg production by 24 hours) throughout the remainder of the month.

In a field safety and effectiveness study in the United States, conducted in households with existing flea infestations, the effectiveness of NexGard® COMBO against fleas was 97.8%, 99.6%, and 99.9% when assessed on Days 30, 60, and 90, respectively. Cats with signs of flea allergy dermatitis showed improvement in alopecia, dermatitis/pyodermatitis, pruritus, erythema, papules, and scaling, as a direct result of eliminating fleas.

Tick Treatment and Control:
In well-controlled laboratory studies, NexGard® COMBO demonstrated ≥95.1% effectiveness against *Ixodes scapularis* 48 hours post-infestation for a month and ≥95.6% effectiveness against *Amblyomma americanum* 72 hours post-infestation for a month.

Treatment and Control of Roundworms, Hookworms, and Tapeworms:
In 2 well-controlled laboratory studies, NexGard® COMBO provided 98.9% and 100% effectiveness against natural and/or induced roundworm infections with the dose-limiting gastrointestinal nematode species (adult *Toxocara cati*), respectively. Effectiveness studies against fourth stage larval *Toxocara cati* and hookworms (adult and fourth stage larval *Ancylostoma tubaeforme*; adult *Ancylostoma braziliense*) were conducted with an early formulation. The doses of eprinomectin in this early formulation are equivalent to that of the final formulation of NexGard® COMBO. In well-controlled laboratory studies, NexGard® COMBO provided on average 92.8% effectiveness against natural and/or induced infections with *Dipylidium caninum*.

Target Animal Safety:
Margin of Safety Study:
NexGard® COMBO was applied topically to healthy kittens (8 to 9 weeks of age) at 1X, 3X, or 5X the maximum exposure dose six times at 28-day intervals; kittens in the control group were dosed with mineral oil. One kitten in the 5X group exhibited recumbency, tremors, hypothermia, ataxia, disorientation, and pupil dilation (responsive to light) 9 hours after the third dose. This kitten received supportive care, including washing the application site, and recovered within 48 hours post-dose. During necropsy, a dark red subcutaneous area (≤5 mm diameter) was observed in the treatment site area of three cats in the 5X group, but microscopic examination revealed no histologic abnormalities. No significant changes related to NexGard® COMBO were observed for physical examination, body weight, clinical pathology (hematology, coagulation, and serum chemistry), histopathology, or organ weights.

Study in Heartworm Positive Cats:
Adult cats, 4.7 to 6.6 months of age, were experimentally infected with adult heartworms (*D. immitis*) by venous transplantation. All cats were negative for heartworm antibody, antigen and microfilariae prior to transplantation. Two weeks after transplantation, immunoserology verified positive antigen and the presence of microfilariae in all enrolled cats. A combination of fipronil, eprinomectin, praziquantel, and (S)-methoprene was applied topically to cats at 1X or 3X the maximum exposure dose once every 28 days for three consecutive treatments; cats in the control group were dosed with mineral oil. One cat in the 1X group exhibited cyanotic mucous membranes and tachypnea for 24 hours following the first treatment. The cat recovered and exhibited no abnormal signs following two subsequent treatments. There was no difference between the treatment groups in the number of adult *D. immitis* recovered at the end of the study.

Oral Administration Study:
Oral tolerance was evaluated to assess the effects of accidental oral ingestion. Kittens (male and female) ranging in age from 7.4 to 8.9 weeks were orally administered NexGard® COMBO at 1X the maximum exposure dose; kittens in the control group were dosed with saline. Cats were observed for adverse reactions at 1, 2, 3, 4, and 8 hours following administration, then twice a day until Day 14. All 8 cats administered NexGard® COMBO immediately exhibited excessive hypersalivation after oral administration. However, all cats stopped salivating within 1 hour after exposure. No additional health-related observations were seen for the remainder of the study.

How Supplied:
NexGard® COMBO is packaged as a single dose in 0.3 mL (for cats 1.8-5.5 lb) and 0.9 mL (for cats 5.6-16.5 lb) applicators. (see **Dosage and Administration**). Each size applicator is available in cartons containing 1, 3, or 6 applications.

Storage Information:
Store at 59° – 86°F (15° – 30° C). Brief periods up to 104° F (40° C) are permitted. Protect from light.

Approved by FDA under NADA # 141-570

Marketed by: Boehringer Ingelheim Animal Health USA Inc., Duluth, GA 30096

184238-002 Rev. 02/2023
US-PET-0187-2023

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