Looking for Prescribing Information?

Click a logo below to see the prescribing information for *NexGard*® PLUS (afoxolaner, moxidectin, and pyrantel chewable tablets), *NexGard*® (afoxolaner), or *NexGard*® COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution).

NexGard® PLUS (afoxolaner, moxidectin, and pyrantel chewable tablets)

NexGard® (afoxolaner) Chewables

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

For Dogs

For Cats

NexGard® PLUS (afoxolaner, moxidectin, and pyrantel chewable tablets)

For oral use in dogs only

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

Description:
NexGard® PLUS (afoxolaner, moxidectin, and pyrantel chewable tablets) is available in five sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide minimum doses of 1.14 mg/lb (2.5 mg/kg) afoxolaner, 5.45 mcg/lb (12 mcg/kg) moxidectin, and 2.27 mg/lb (5.0 mg/kg) pyrantel (as pamoate salt).

Afoxolaner is a member of the isoxazoline family of compounds. Its chemical name is 1-Naphthalene-carboxamide,4-[5-[3-chloro-5-(trifluoromethyl)-phenyl]-4,5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl.

Moxidectin is a semisynthetic macrocyclic lactone derived from the actinomycete *Streptomycetes cyaneogriseus noncyanogenus.* The chemical name for moxidectin is [6R,23E,25S(E)]-5-O-Demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B.

Pyrantel is a member of the tetrahydropyrimidine family of compounds. Its chemical name is (E)- 1,4,5,6-Tetrahydro-1-methyl-2-[2-(2-thienyl) vinyl] pyrimidine 4, 4' methylenebis [3-hydroxy-2-naphthoate](1:1).

Indications:
NexGard® PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of adult hookworm (*Ancylostoma caninum, Ancylostoma braziliense,* and *Uncinaria stenocephala*) and roundworm (*Toxocara canis* and *Toxascaris leonina*) infections. NexGard® PLUS kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) and the treatment and control of *Ixodes scapularis* (black-legged tick), *Rhipicephalus sanguineus* (brown dog tick), *Dermacentor variabilis* (American dog tick), and *Amblyomma americanum* (lone star tick) infestations for one month in dogs and puppies eight weeks of age and older, weighing four pounds of body weight or greater.

Dosage and Administration:
NexGard® PLUS is given orally once a month at the minimum dosage of 1.14 mg/lb (2.5 mg/kg) afoxolaner, 5.45 mcg/lb (12 mcg/kg) moxidectin, and 2.27 mg/lb (5.0 mg/kg) pyrantel (as pamoate salt).

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

Dosing Schedule:

Body Weight (lbs.)	Afoxolaner Per Chewable (mg)	Moxidectin Per Chewable (mcg)	Pyrantel* Per Chewable (mg)	Chewables Administered
4 to 8	9.375	45	18.75	One
8.1 to 17	18.75	90	37.5	One
17.1 to 33	37.5	180	75	One
33.1 to 66	75	360	150	One
66.1 to 132	150	720	300	One
Over 132	Administer the appropriate combination of chewables			

*As pamoate salt.

NexGard® PLUS can be administered with or without food. Care should be taken to ensure that the dog consumes the complete dose and that part of the dose is not lost or refused. If a dose is missed, administer NexGard® PLUS and resume a monthly dosing schedule.

Heartworm Prevention:
NexGard® PLUS should be administered at monthly intervals year-round or, at a minimum, administration should start within one month of the dog's first seasonal exposure to mosquitoes and should continue at monthly intervals until at least six months after the dog's last exposure (see **Effectiveness**). When replacing another monthly heartworm preventive product, the first dose of NexGard® PLUS should be given within a month of the last dose of the former medication.

Flea Treatment and Prevention:
NexGard® PLUS should be administered year-round at monthly intervals or started at least one month before fleas become active. To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Control:
NexGard® PLUS should be administered year-round at monthly intervals or started at least one month before ticks become active.

Intestinal Nematode Treatment and Control:
NexGard® PLUS treats and controls adult hookworms (*Ancylostoma caninum, Ancylostoma braziliense,* and *Uncinaria stenocephala*) and roundworms (*Toxocara canis* and *Toxascaris leonina*). For the treatment of adult hookworm and roundworm infections, NexGard® PLUS should be administered as a single dose. Monthly use of NexGard® PLUS will control any subsequent infections. Dogs may be exposed to and can become infected with hookworms and roundworms throughout the year, regardless of season or climate.

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

Warnings:
Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician for treatment advice.

Keep NexGard® PLUS in a secure location out of the reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Precautions:
Afoxolaner, one of the ingredients in NexGard® PLUS, 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 dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders.

Treatment with fewer than six monthly doses after the last exposure to mosquitoes has not been evaluated and may not provide complete heartworm prevention.

Prior to administration of NexGard® PLUS, dogs should be tested for existing heartworm infection. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. NexGard® PLUS is not effective against adult *D. immitis.*

The safe use of NexGard® PLUS in breeding, pregnant, or lactating dogs has not been evaluated.

Adverse Reactions:
In a field safety and effectiveness study, NexGard® PLUS was administered to dogs for the prevention of heartworm disease. The study included a total of 272 dogs (134 administered NexGard® PLUS and 138 administered active control) treated once monthly for 11 treatments. Over the 330-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported in the NexGard® PLUS group are presented in the following table.

Table 1. Dogs With Adverse Reactions

Clinical Sign	NexGard® PLUS n = 134 Number (Percentage)	Active Control n = 138 Number (Percentage)
Diarrhea	9 (6.7%)	7 (5.1%)
Vomiting	6 (4.5%)	7 (5.1%)
Lethargy	3 (2.2%)	5 (3.6%)
Itching	3 (2.2%)	3 (2.2%)
Dermatitis	2 (1.5%)	1 (0.7%)
Anorexia	1 (0.7%)	4 (2.9%)
Muscle tremor	1 (0.7%)	1 (0.7%)

One dog in the NexGard® PLUS group was reported to exhibit muscle tremors along with nausea and depression for one day after the Day 0 treatment. The dog remained in the study and muscle tremors were not reported after any subsequent treatments.

Contact Information:
For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, 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 www.fda.gov/reportanimalae.

Clinical Pharmacology:
Mode of Action:
NexGard® PLUS (afoxolaner, moxidectin, and pyrantel chewable tablets) contains the three active pharmaceutical ingredients afoxolaner, moxidectin, and pyrantel (as pamoate salt).

Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and postsynaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Moxidectin is an endectocide in the macrocyclic lactone class. Moxidectin acts by interfering with chloride channel-mediated neurotransmission in susceptible parasites, which results in paralysis and death of the parasite.

Pyrantel is a nematocide belonging to the tetrahydropyrimidine class. Pyrantel acts as a depolarizing, neuromuscular-blocking agent in susceptible parasites, causing paralysis and death or expulsion of the parasite.

Pharmacokinetics:
Following a single oral administration of a near-final formulation of NexGard® PLUS (at mean doses of 3.9 mg/kg afoxolaner, 18.8 mcg/kg moxidectin, and 7.8 mg/kg pyrantel pamoate) in fed and fasted Beagle dogs (10 to 21 months of age), afoxolaner and moxidectin were more rapidly absorbed in the fasted state with a time to maximum concentration (Tmax) of 2 to 3 hours.

The afoxolaner mean maximum plasma concentrations (Cmax) in the fed and fasted states were 1610 and 2200 ng/mL (CV=33 and 16%) and the moxidectin mean Cmax values were 11.1 and 15.5 ng/mL (CV=39 and 24%), respectively. The area under the curve (AUC) for afoxolaner and moxidectin were similar between fed and fasted states. Post-dose pyrantel plasma concentrations were quantifiable out to 24 hours.

Following six oral administrations of NexGard® PLUS at 1, 3, and 5X the maximum exposure dose of 5 mg/kg, 24 mcg/kg, and 10 mg/kg afoxolaner, moxidectin, and pyrantel pamoate, respectively, every 28 days in 8-week-old Beagle dogs, afoxolaner and moxidectin Tmax ranged from 2 to 6 hours. The observed mean Cmax and AUC at steady state in the 1X dose group were 2230 ng/mL and 19000 days*ng/mL for afoxolaner and 14.8 ng/mL and 55.2 days*ng/mL for moxidectin, respectively. Based on mean Cmin, afoxolaner and moxidectin accumulated by less than 4-fold at steady state. Afoxolaner and moxidectin exposure increased in a dose proportional manner between the 1X and 3X dose groups but was less than dose proportional in the 5X dose group.

Pyrantel pamoate is poorly absorbed into systemic circulation. Pyrantel pamoate is intended to remain in the gastrointestinal tract to allow effective concentrations to be delivered to gastrointestinal nematodes.

Effectiveness:
Heartworm Prevention:
In two well-controlled laboratory studies, NexGard® PLUS was 100% effective against induced *D. immitis* infections when administered for six consecutive months.

In a well-controlled US field study consisting of 120 dogs administered NexGard® PLUS and 124 administered an active control, no dogs treated with NexGard® PLUS tested positive for heartworm disease. All dogs treated with NexGard® PLUS were negative for *D. immitis* antigen and blood microfilariae at study completion on Day 330.

Flea Treatment and Prevention:
In a well-controlled laboratory study, NexGard® PLUS demonstrated ≥99.8% effectiveness against adult fleas 24 hours after weekly infestations for one month.

In a separate well-controlled laboratory study, afoxolaner alone began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours.

In an additional well-controlled laboratory study, afoxolaner alone demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days and was ≥93% effective at 12 hours post-infestation through Day 21 and on Day 35. On Day 28, afoxolaner alone was 81.1% effective 12 hours post-infestation. Dogs in both the afoxolaner-treated and control groups that were infested with fleas on Day -1 generated flea eggs at 12 and 24 hours post-treatment (0-11 eggs and 1-17 eggs in the afoxolaner-treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12 and 24 hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the afoxolaner-treated group were essentially unable to produce any eggs (0-1 eggs), while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of afoxolaner alone against fleas on the Day 30, 60, and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively.

Collectively, the data from the four studies (three laboratory and one field) demonstrate that NexGard® PLUS kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

Tick Treatment and Control:
In well-controlled laboratory studies, afoxolaner alone demonstrated >97% effectiveness against *Dermacentor variabilis*, >94% effectiveness against *Ixodes scapularis*, and >93% effectiveness against *Rhipicephalus sanguineus*, 48 hours post-infestation, for one month. At 72 hours post-infestation, NexGard® PLUS demonstrated ≥97% effectiveness against *Amblyomma americanum* for one month.

Intestinal Nematode Treatment and Control:
Elimination of adult roundworms (*Toxocara canis* and *Toxascaris leonina*) and hookworms (*Ancylostoma caninum, Ancylostoma braziliense,* and *Uncinaria stenocephala*) was demonstrated in well-controlled laboratory studies.

Target Animal Safety:
Margin of Safety:
NexGard® PLUS was administered orally at 1, 3, and 5X the maximum exposure doses at approximately 28-day intervals for six treatments to 8-week-old Beagle puppies. Dogs in the control group were sham-dosed. There were no clinically relevant, treatment-related effects on body weights, food consumption, clinical pathology (hematology, coagulation, serum chemistry, and urinalysis), gross pathology, histopathology, organ weights, or ophthalmic examinations. Mild, self-limiting diarrhea (with and without blood) was possibly related to treatment, as there were more incidences in the NexGard® PLUS groups than the control group throughout the study, including within 48 hours after treatment.

Avermectin-Sensitive Collie Safety:
NexGard® PLUS was administered orally at 1, 3, and 5X the maximum label dose to MDR1-deficient Collies once on Day 0, with a second administration to the 1X group on Day 28. Dogs in the control group were sham-dosed on Days 0 and 28. No clinical signs of avermectin toxicity were noted in any dog at any time during the study. Vomiting was observed in some dogs in the 3X and 5X groups and resolved without treatment. Diarrhea, with or without blood, was observed in some dogs in all of the NexGard® PLUS groups and resolved without treatment.

Heartworm-Positive Safety:
NexGard® PLUS was administered orally at 1X and 3X the maximum exposure doses at approximately 28-day intervals for three treatments to Beagle dogs with adult heartworm infections and circulating microfilariae. Dogs in the control group were sham-dosed. Diarrhea was observed in one dog in the 1X group and in three dogs in the 3X group, and vomiting was observed in two dogs in the 3X group. No signs of avermectin toxicity were observed at any time during the study. There were no clinical signs associated with death of the microfilariae observed in any of the dogs.

Field Safety:
In a well-controlled field study, NexGard® PLUS was used concurrently with other medications such as vaccines, antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics, sedatives, analgesics, steroids, anthelmintics, antiemetics, and antipruritics. No adverse reactions were associated with the concurrent use of NexGard® PLUS and other medications.

How Supplied:
NexGard® PLUS is available in five strengths of beef-flavored soft chewables formulated according to the weight of the dog (see **Dosage and Administration**). Each chewable size is available in color-coded packages of 1, 3, or 6 chewables.

Storage Information:
Store in original package at or below 25°C (77°F) with excursions permitted up to 40°C (104°F).

Approved by FDA under NADA # 141-554

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

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Boehringer Ingelheim

NexGard® (afoxolaner) Chewables

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

Description:
NexGard® (afoxolaner) is available in four sizes of beef-flavored, soft chewables for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide a minimum afoxolaner dosage of 1.14 mg/lb (2.5 mg/kg). Afoxolaner has the chemical composition 1-Naphthalenecarboxamide, 4-[5- [3-chloro-5-(trifluoromethyl)-phenyl]-4, 5-dihydro-5-(trifluoromethyl)-3-isoxazolyl]-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl.

Indications:
NexGard® kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of *Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick), *Amblyomma americanum* (lone star tick), *Rhipicephalus sanguineus* (brown dog tick), and *Haemaphysalis longicornis* (longhorned tick) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month. NexGard® is indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Dosage and Administration:
NexGard® is given orally once a month, at the minimum dosage of 1.14 mg/lb (2.5 mg/kg).

Dosing Schedule:

Body Weight	Afoxolaner Per Chewable (mg)	Chewables Administered
4 to 10 lbs.	11.3	One
10.1 to 24 lbs.	28.3	One
24.1 to 60 lbs.	68	One
60.1 to 121 lbs.	136	One
Over 121 lbs.	Administer the appropriate combination of chewables	

NexGard® can be administered with or without food. Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes to ensure that part of the dose is not lost or refused. If it is suspected that any of the dose has been lost or if vomiting occurs within two hours of administration, redose with another full dose. If a dose is missed, administer NexGard® and resume a monthly dosing schedule.

Flea Treatment and Prevention:
Treatment with NexGard® may begin at any time of the year. In areas where fleas are common year-round, monthly treatment with NexGard® should continue the entire year without interruption.

To minimize the likelihood of flea reinfestation, it is important to treat all animals within a household with an approved flea control product.

Tick Treatment and Control:
Treatment with NexGard® may begin at any time of the year (see **Effectiveness**).

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

Warnings:
Not for use in humans. Keep this and all drugs out of the reach of children. In case of accidental ingestion, contact a physician immediately. Keep NexGard® in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

Precautions:
Afoxolaner 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 dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders.

The safe use of NexGard® in breeding, pregnant or lactating dogs has not been evaluated.

Adverse Reactions:
In a well-controlled US field study, which included a total of 333 households and 615 treated dogs (415 administered afoxolaner; 200 administered active control), no serious adverse reactions were observed with NexGard®.

Over the 90-day study period, all observations of potential adverse reactions were recorded. The most frequent reactions reported at an incidence of > 1% within any of the three months of observations are presented in the following table. The most frequently reported adverse reaction was vomiting. The occurrence of vomiting was generally self-limiting and of short duration and tended to decrease with subsequent doses in both groups. Five treated dogs experienced anorexia during the study, and two of those dogs experienced anorexia with the first dose but not subsequent doses.

Table 1: Dogs With Adverse Reactions.

	Treatment Group			
	Afoxolaner		Oral active control	
	N[1]	% (n=415)	N[2]	% (n=200)
Vomiting (with and without blood)	17	4.1	25	12.5
Dry/Flaky Skin	13	3.1	2	1.0
Diarrhea (with and without blood)	13	3.1	7	3.5
Lethargy	7	1.7	4	2.0
Anorexia	5	1.2	9	4.5

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

In the US field study, one dog with a history of seizures experienced a seizure on the same day after receiving the first dose and on the same day after receiving the second dose of NexGard®. This dog experienced a third seizure one week after receiving the third dose. The dog remained enrolled and completed the study. Another dog with a history of seizures had a seizure 19 days after the third dose of NexGard®. The dog remained enrolled and completed the study. A third dog with a history of seizures received NexGard® and experienced no seizures throughout the study.

In a second US field safety and effectiveness study, NexGard® was administered to 130 dogs with fleas. Adverse reactions included pruritus, diarrhea (with or without blood), vomiting, anorexia, and lethargy.

Post-Approval Experience (July 2018):
The following adverse events are based on post-approval adverse drug experience reporting. Not all adverse events are reported to FDA/CVM. It is not always possible to reliably estimate the adverse event frequency or establish a causal relationship to product exposure using these data.

The following adverse events reported for dogs are listed in decreasing order of reporting frequency for NexGard®:

Vomiting, pruritus, lethargy, diarrhea (with and without blood), anorexia, seizure, hyperactivity/restlessness, panting, erythema, ataxia, dermatitis (including rash, papules), allergic reactions (including hives, swelling), and tremors.

Contact Information:
For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, 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 www.fda.gov/reportanimalae.

Mode of Action:
Afoxolaner is a member of the isoxazoline family, shown to bind at a binding site to inhibit insect and acarine ligand-gated chloride channels, in particular those gated by the neurotransmitter gamma-aminobutyric acid (GABA), thereby blocking pre- and post-synaptic transfer of chloride ions across cell membranes. Prolonged afoxolaner-induced hyperexcitation results in uncontrolled activity of the central nervous system and death of insects and acarines. The selective toxicity of afoxolaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Effectiveness:
In a well-controlled laboratory study, NexGard® began to kill fleas four hours after initial administration and demonstrated >99% effectiveness at eight hours. In a separate well-controlled laboratory study, NexGard® demonstrated 100% effectiveness against adult fleas 24 hours post-infestation for 35 days, and was ≥93% effective at 12 hours post-infestation through Day 21, and on Day 35. On Day 28, NexGard® was 81.1% effective 12 hours post-infestation. Dogs in both the treated and control groups that were infested with fleas on Day -1 generated flea eggs at 12- and 24-hours post-treatment (0-11 eggs and 1-17 eggs in the NexGard® treated dogs, and 4-90 eggs and 0-118 eggs in the control dogs, at 12- and 24-hours, respectively). At subsequent evaluations post-infestation, fleas from dogs in the treated group were essentially unable to produce any eggs (0-1 eggs) while fleas from dogs in the control group continued to produce eggs (1-141 eggs).

In a 90-day US field study conducted in households with existing flea infestations of varying severity, the effectiveness of NexGard® against fleas on the Day 30, 60 and 90 visits compared with baseline was 98.0%, 99.7%, and 99.9%, respectively. In a second 90-day US field study, the effectiveness of NexGard® against fleas on the Day 30, 60 and 90 visits compared with baseline was 97.5%, 99.7%, and 99.9%, respectively. Dogs in the second study with signs of Flea Allergy Dermatitis (FAD) showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation following treatment, as a direct result of eliminating fleas. Collectively, the data from these studies (two laboratory and two field) demonstrate that NexGard® kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the start of treatment of existing flea infestations.

In well-controlled laboratory studies, NexGard® demonstrated >97% effectiveness against *Dermacentor variabilis*, >94% effectiveness against *Ixodes scapularis*, and >93% effectiveness against *Rhipicephalus sanguineus*, 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard® demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days and ≥98.5% effectiveness against *Haemaphysalis longicornis* for 31 days. In two separate, well-controlled laboratory studies, NexGard® was effective at preventing *Borrelia burgdorferi* infections after dogs were infested with *Ixodes scapularis* vector ticks 28 days post-treatment.

Animal Safety:
In a margin of safety study, NexGard® was administered orally to 8 to 9-week-old Beagle puppies at 1, 3, and 5 times the maximum exposure dose (6.3 mg/kg) for three treatments every 28 days, followed by three treatments every 14 days, for a total of six treatments. Dogs in the control group were sham-dosed. There were no clinically-relevant effects related to treatment on physical examination, body weight, food consumption, clinical pathology (hematology, clinical chemistries, or coagulation tests), gross pathology, histopathology or organ weights. Vomiting occurred throughout the study, with a similar incidence in the treated and control groups, including one dog in the 5x group that vomited four hours after treatment.

In two well-controlled field studies, NexGard® was used concomitantly with other medications, such as vaccines, anthelmintics, antibiotics (including topicals), steroids, NSAIDs, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of NexGard® with other medications.

Storage Information:
Store at or below 30°C (86°F) with excursions permitted up to 40°C (104°F).

How Supplied:
NexGard® is available in four sizes of beef-flavored soft chewables: 11.3, 28.3, 68 or 136 mg afoxolaner. Each chewable size is available in color-coded packages of 1, 3 or 6 beef-flavored chewables.

Approved by FDA under NADA # 141-406

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

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-trifluoroethyl) 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]-isoquinolin-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).**

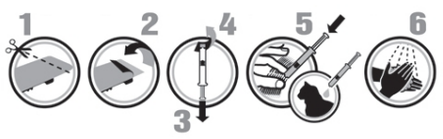
Administer the entire contents of a NexGard® COMBO unit applicator topically once a month as specified in the following table:

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, 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.

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, roundworms 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 fully evaluated 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 reporting adverse drug experiences 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.
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

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