

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: butylated hydroxytoluene, un-stabilized glycerol formal, and dimethyl isosorbide.

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-(2,2-trifluoromethylamino)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 A1a. The chemical name for eprinomectin B1b is (4'R)-acetylamino-5-O-demethyl-25-del(1-methylpropyl)-4''-deoxy-25-(1-methylethyl)avermectin A1a.

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

Indications:

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

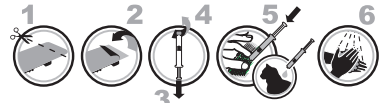
Dosage and Administration:

NexGard® COMBO is dosed at a minimum of 0.055 mL/lb (0.12 mL/kg), which delivers a minimum dose of 0.66mg/lb (1.45mg/kg) esafoxolaner, 0.23 mg/lb (0.51 mg/kg) eprinomectin, and 4.55 mg/lb (10.0 mg/kg) praziquantel.

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

Eprinomectin belongs NexGard® COMBO unit applicator topically once a month as specified in the following table:

Cat Weight (lbs.)	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



Dosing Schedule:

To apply NexGard® COMBO, pull back the plunger of the unit applicator slightly and remove the cap. Part the hair in one spot on the midline of the neck between the base of the skull and the shoulder blades, place the tip of the unit applicator on the skin and apply the contents directly on the skin. If the weight of the cat requires a second application, apply the contents in the same manner as described above in the same location.

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, and 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 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:

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**). 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.

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

¹Number of cats treated with NexGard® COMBO with the identified abnormality.

²Number 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.

Mode of Action:

Esafoxolaner is a member of the isoxazoline family, shown to bind at a novel 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 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 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.

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 90-day multi-center field 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, hyperthermia, 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. The required number of applicators to be dispensed is dependent upon the weight of the cat (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

Origin France.

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

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THE PROTECTION YOUR CAT NEEDS IN ONE EASY, MONTHLY APPLICATION

All cats need parasite protection. *NexGard® COMBO* (esafoxolaner, eprinomectin, and praziquantel topical solution) is the first and only monthly topical treatment specifically formulated for cats that protects against fleas, ticks, heartworm disease, roundworms, hookworms, and tapeworms.



NEVER MISS A DOSE OF ONE-AND-DONE MONTHLY PROTECTION WITH FREE MONTHLY REMINDERS



IMPORTANT SAFETY INFORMATION: *NexGard® COMBO* 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.



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THE ONE YOU WANT FOR ONE-AND-DONE MONTHLY PROTECTION



- Protects Against Fleas and Ticks
- Prevents Heartworm Disease
- Treats & Controls Roundworms and Hookworms
- The First & Only Broad-Spectrum Parasite Protection That Kills Tapeworms



PROTECTS AGAINST FLEAS

Fleas are biting pests that feed on your cat's blood.

Fleas Are Found Indoors and Outdoors

Risks can be found everywhere, both indoors and out. There are several ways fleas can get into your home and find their way on to your cat. They may be carried into your home by other pets, especially if those pets are not already treated with a flea control product. Fleas can also "hitch a ride" into your home on a person's skin or clothing.

Fleas Can Cause a Number of Problems:

- Scratching and Discomfort
- Anemia
- Infestations
- Flea Allergy Dermatitis



FLEA

Preventing Flea Infestations Is Essential

The adult fleas you see on an untreated cat are usually only about 5% of the flea population in the cat's environment.¹ If left untreated, fleas on your cat will multiply and quickly cause an infestation in your home.

- Preventing a flea infestation is easier and less expensive than trying to eliminate an established infestation.
- NexGard[®] COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) kills fleas on your cat before they can lay eggs, all month long, and prevents flea infestations



PROTECTS AGAINST TICKS

Ticks are blood-sucking parasites that feed on cats and other animals. While it may not be possible to keep your cat from encountering ticks, it's important to be proactive and give your cat tick protection.



TICK

All Cats Need Tick Protection

- Ticks can be difficult to spot under your cat's fur.
- Ticks are often the carriers of dangerous diseases.

Ticks Aren't Just Found in the Woods

- Ticks can be found throughout the country year-round.
- Urban wildlife carry ticks into residential areas including yards and gardens.
- Ticks can find their way into your home on your body or clothing.



PREVENTS HEARTWORM DISEASE

Cats can contract heartworm disease, which is spread by mosquitoes. Heartworms can cause illness and even death in cats.

- A single mosquito bite is all it takes to transmit heartworms to your cat.
- One study found that 1 in 4 heartworm-infected cats lived indoors.²
- Year-round heartworm disease prevention can help prevent your cat from developing heartworm disease.



HEARTWORMS



NexGard[®] COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) is safe in kittens as young as 8 weeks, weighing 1.8 lbs or more.

Heartworm Disease Has No Cure in Cats

- The first sign of heartworm disease in some cases is sudden collapse of the cat, or even sudden death.
- A heartworm test administered by your vet is the only way to detect heartworms—not all cats develop noticeable symptoms.
- There is no treatment for heartworm disease in cats.

² Atkins C, et al. Heartworm infection in cats: 50 cases (1985-1997). JAVMA. 2000;217(3):355-358.



TREATS & CONTROLS ROUNDWORMS, HOOKWORMS, AND TAPEWORMS

Roundworms, hookworms, and tapeworms are common intestinal parasites that are risks for your cat. Left untreated, these nasty intestinal parasites can make an animal seriously sick.

The Risks of Roundworms

- Cats can pick up roundworms while grooming themselves after walking or digging through contaminated soil.
- Roundworms can cause vomiting, diarrhea, and malnourishment.



ROUNDWORMS

The Hazards of Hookworms

- Cats can pick up hookworms by walking or digging in contaminated soil, then ingesting hookworm larvae while grooming, or from hunting and ingesting other hosts.

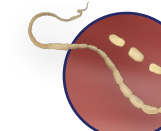


HOOKWORMS

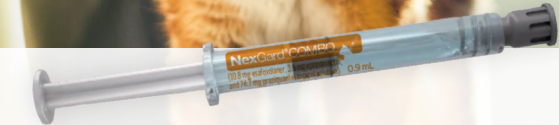
- Hookworms attach to the intestinal wall and feed off the host's blood, causing vomiting, diarrhea, and anemia.

The Trouble With Tapeworms

- Cats often contract tapeworms by ingesting infected fleas while grooming.
- Tapeworms attach to the small intestines, stealing nutrients and can cause vomiting and weight loss.

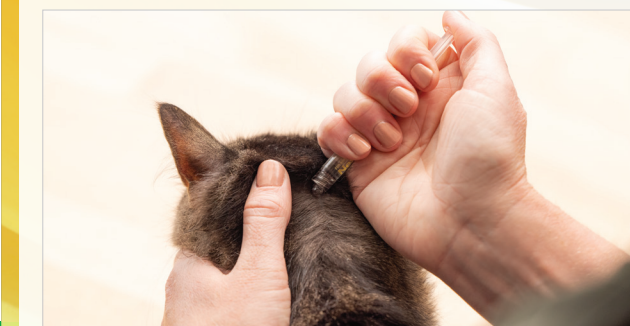


TAPEWORMS



BROAD-SPECTRUM PROTECTION THAT'S EASY TO APPLY

NexGard[®] COMBO (esafoxolaner, eprinomectin, and praziquantel topical solution) comes in a convenient applicator that makes one-and-done monthly parasite protection easy for you and your cat. It's safe for kittens 8 weeks of age and older, weighing 1.8 lbs or more.



¹ Dryden M. Biology of fleas of dogs and cats. *Compend Contin Educ Vet.* 1993(4):569-579.

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