NexGard®
(afoxolaner) Chewables

Designed With Compliance in Mind

Boehringer Ingelheim

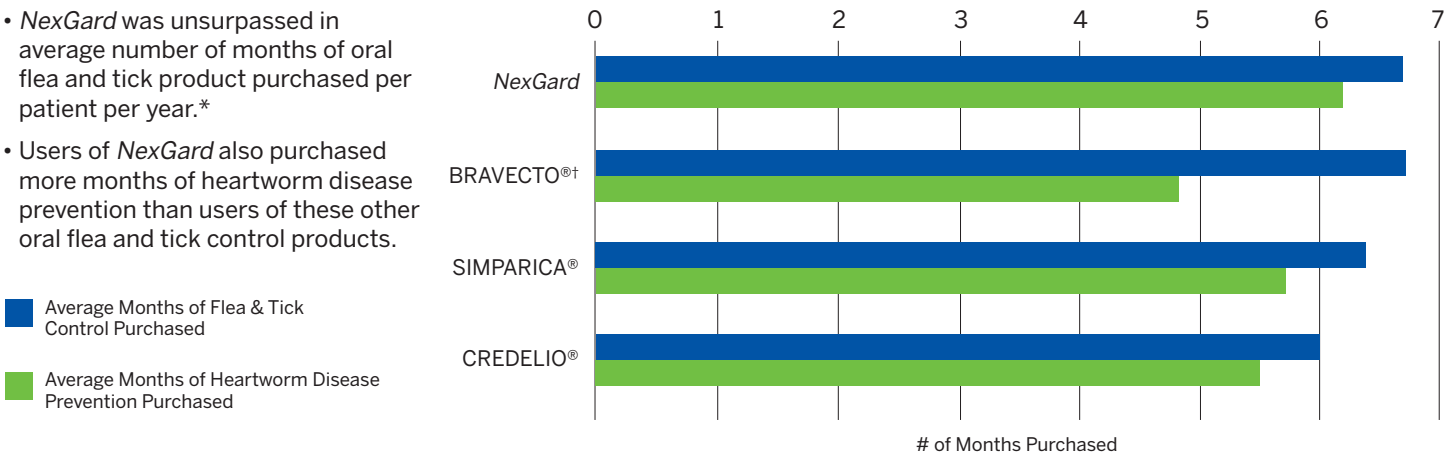
For veterinary preventive healthcare products, compliance is an important, commonly discussed topic. Compliance is dependent on a number of factors, including the need for pet owners to purchase the protection you recommend and administer the product as prescribed.

For the development of *NexGard*® (afoxolaner), the Boehringer Ingelheim team worked tirelessly to create a delicious, beef-flavored chew that dogs would love. Both in-clinic assessments as well as a laboratory study validated the excellent palatability of *NexGard*.[1,2] Studies comparing it against all other oral flea and tick control products showed that *NexGard* is the chew dogs choose over other products.[3] The easy-to-administer *NexGard* chew was designed to provide an ideal experience for both the pet and the pet owner.

Recently, an independent third-party conducted a comprehensive analysis to assess the current purchase patterns for oral flea and tick control products in veterinary clinics in the US. The assessment used PIMS data from >6,500 veterinary clinics for the entirety of 2020 and highlighted the strength of the *NexGard* brand in veterinary clinics.*[4]

Unsurpassed Average Number of Months Purchased per Year*†[4]

- *NexGard* was unsurpassed in average number of months of oral flea and tick product purchased per patient per year.*
- Users of *NexGard* also purchased more months of heartworm disease prevention than users of these other oral flea and tick control products.



Assessment Summary

In the first assessment, the amount of product purchased per dog per year was determined.

- For each of the flea and tick control products evaluated, the average number of months of flea and tick control product purchased per dog per year was determined.
- To evaluate the potential impact that these products may have had on the purchase of heartworm disease prevention, the average number of months of heartworm disease prevention purchased per dog per year was also determined for users of each of the flea and tick control products evaluated.

IMPORTANT SAFETY INFORMATION: *NexGard*® (afoxolaner) is for use in dogs only. The most frequently reported adverse reactions include vomiting, pruritus, lethargy, diarrhea, and lack of appetite. The safe use of *NexGard* in pregnant, breeding, or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures or neurologic disorders. For more information, please see full prescribing information or visit www.NexGardClinic.com.

*Assessment was conducted by IDEXX® and leveraged veterinary clinic PIMS transaction level data for 2020. This analysis included veterinary practices with consistent data from 2018 to 2020. To be included, patients needed to have at least one parasiticide transaction in 2019 and 2020. The analysis was limited to loyal patients, where loyalty was defined as having one flea/tick control brand during the full three-year period.

†This analysis overestimates the duration of efficacy for BRAVECTO. For comparison purposes, each BRAVECTO chew was assessed as providing three months of flea and tick protection versus the labeled 12-week coverage for fleas and three species of ticks, and 8-week coverage for Lone Star ticks.

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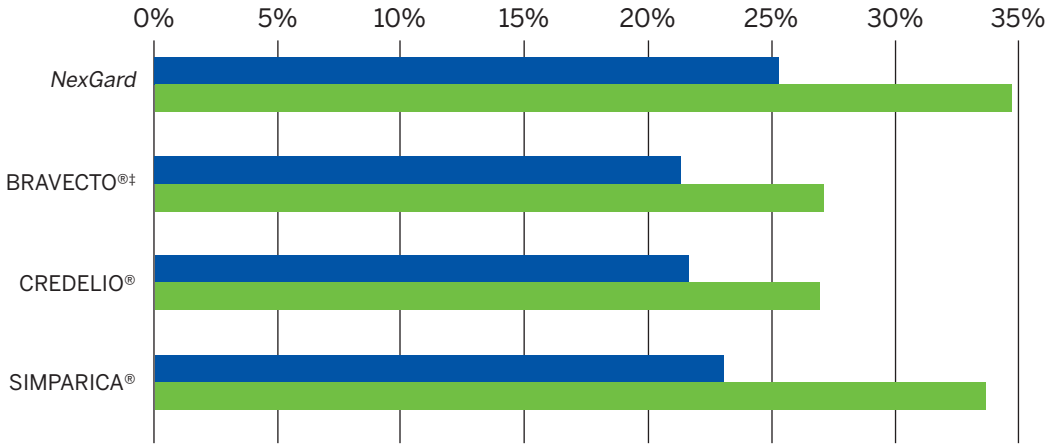
Percent of Dogs Receiving Year-Round Protection*‡[4]

- **More *NexGard*® (afoxolaner) users purchased a full 12 months of flea and tick protection** than users of these other flea and tick control products.
- Users of *NexGard* were also **more likely to purchase a full 12 months of heartworm disease prevention.**



Assessment Summary

In this assessment, for each of the flea and tick control products, the percentage of users who purchased enough product to protect their dogs for a full 12 months was determined.

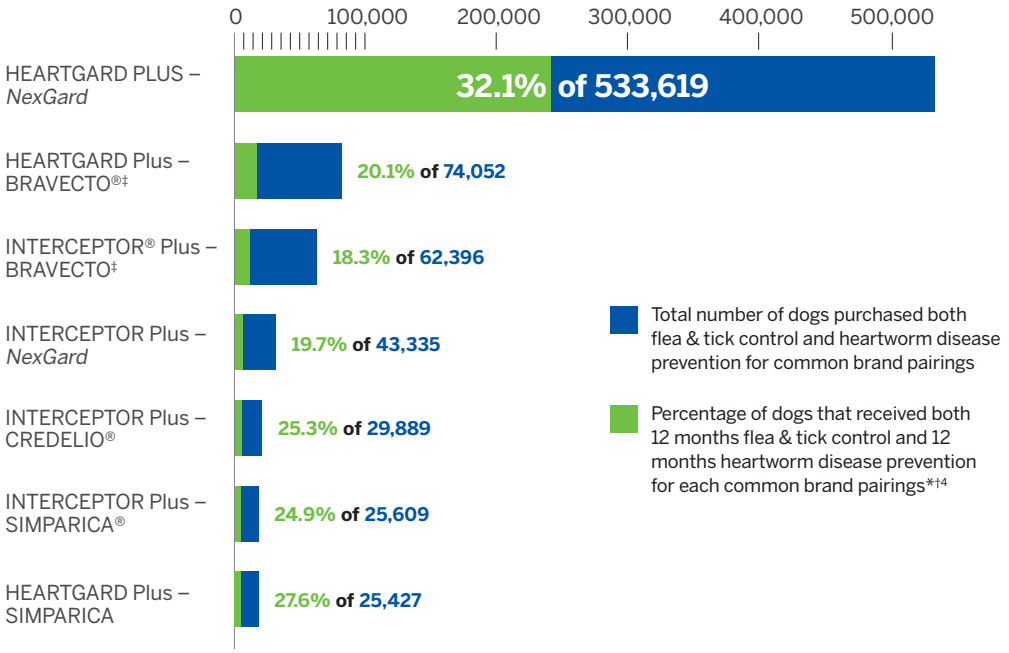
- For each of the flea and tick control products evaluated, the percentage of users of a product who purchased a full 12 months of the product was calculated.
- For each of the flea and tick control products purchased (regardless of the amount purchased), the percentage of users who purchased a full 12 months of heartworm disease prevention was determined.

*Assessment was conducted by IDEXX® and leveraged veterinary clinic PIMS transaction level data for 2020. This analysis included veterinary practices with consistent data from 2018 to 2020. To be included, patients needed to have at least one parasiticide transaction in 2019 and 2020. The analysis was limited to loyal patients, where loyalty was defined as having one flea/tick control brand during the full three-year period.

‡This assessment includes BRAVECTO Chew for Dogs and BRAVECTO Topical for Dogs. In this assessment, the duration of efficacy of 4 doses of BRAVECTO® (fluralaner) is overestimated to provide year-round protection. Four doses of BRAVECTO protects against fleas and three species of ticks for 48 weeks. An additional dose would be required to provide year-round protection. Four doses of BRAVECTO would provide coverage against Lone Star ticks for only 32 weeks.

Number of Dogs Receiving Common Brand Pairings and Percentage of Those Dogs Receiving 12 Months of Both Products*‡[4]

- **HEARTGARD® Plus (ivermectin/pyrantel) and *NexGard*® (afoxolaner) were the most common pairing among oral products.** More pet owners paired *NexGard* for flea and tick control with HEARTGARD Plus for heartworm disease prevention than any other possible pairing.
- The users who paired *NexGard* with HEARTGARD Plus were **the most likely to purchase a full year of protection of both** versus other common brand pairings.



Assessment Summary

In this assessment of common brand pairings, the percent of users purchasing 12 months of flea and tick control AND 12 months of heartworm disease prevention was determined.

- This assessment includes brand pairings used on more than 25,000 dogs.
- Unlike the previous assessments where evaluations were made for the groups of users of an individual flea and tick control product, this assessment evaluates the impact of pairing an individual flea and tick control product with a specific heartworm disease preventive.
- For example, the *NexGard* and HEARTGARD Plus® (ivermectin/pyrantel) brand pairing group included dogs that received *NexGard* for flea and tick control and HEARTGARD Plus for heartworm disease prevention.
- The above graph shows the percentage of dogs in each brand pairing group whose owners purchased 12 months of BOTH products.

IMPORTANT SAFETY INFORMATION: *NexGard* is for use in dogs only. The most frequently reported adverse reactions include vomiting, pruritus, lethargy, diarrhea, and lack of appetite. The safe use of *NexGard* in pregnant, breeding, or lactating dogs has not been evaluated. Use with caution in dogs with a history of seizures or neurologic disorders. For more information, see full prescribing information or visit NexGardClinic.com.

IMPORTANT SAFETY INFORMATION: HEARTGARD Plus is well tolerated. All dogs should be tested for heartworm infection before starting a preventive program. Following the use of HEARTGARD Plus, digestive and neurological side effects have rarely been reported. For more information, please see full prescribing information or visit HeartgardClinic.com.

*Assessment was conducted by IDEXX® and leveraged veterinary clinic PIMS transaction level data for 2020. This analysis included veterinary practices with consistent data from 2018 to 2020. To be included, patients needed to have at least one parasiticide transaction in 2019 and 2020. The analysis was limited to loyal patients, where loyalty was defined as having one flea/tick control brand during the full three-year period.

‡This assessment includes BRAVECTO Chew for Dogs and BRAVECTO Topical for Dogs. In this assessment, the duration of efficacy of 4 doses of BRAVECTO® (fluralaner) is overestimated to provide year-round protection. Four doses of BRAVECTO protects against fleas and three species of ticks for 48 weeks. An additional dose would be required to provide year-round protection. Four doses of BRAVECTO would provide coverage against Lone Star ticks for only 32 weeks.

1. Data on file at Boehringer Ingelheim. 2. Data on file at Boehringer Ingelheim. 3. Data on file at Boehringer Ingelheim. 4. Data on file at IDEXX Laboratories, Inc. Westbrook, Maine USA.

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US-PET-0895-2020.

Boehringer Ingelheim

NexGard®
(afoxolaner) Chewables

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

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

Indications:
NexGard kills adult fleas and is indicated for the treatment and prevention of flea infestations *(Ctenocephalides felis)*, and the treatment and control of Black-legged tick *(Ixodes scapularis)*, American Dog tick *(Dermacentor variabilis)*, Lone Star tick *(Amblyomma americanum)*, and Brown dog tick (*Rhipicephalus sanguineus*) infestations in dogs and puppies 8 weeks of age and older, weighing 4 pounds of body weight or greater, for one month. 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
4.0 to 10.0 lbs.	11.3	One
10.1 to 24.0 lbs.	28.3	One
24.1 to 60.0 lbs.	68	One
60.1 to 121.0 lbs.	136	One
Over 121.0 lbs.	Administer the appropriate combination of chewables	

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

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

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

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

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

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

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.

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.nexgardfordogs.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.

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

In well-controlled laboratory studies, NexGard demonstrated >97% effectiveness against *Dermacentor variabilis,* >94% effectiveness against *Ixodes scapularis,* and >93% effectiveness against *Rhipicephalus sanguineus,* 48 hours post-infestation for 30 days. At 72 hours post-infestation, NexGard demonstrated >97% effectiveness against *Amblyomma americanum* for 30 days. 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 a well-controlled field study, 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: Frontline Vet Labs™, a Division of Boehringer Ingelheim Animal Health USA Inc.
Duluth, GA 30096

Made in Brazil.

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FRONTLINE VET LABS
A DIVISION OF BOEHRINGER INGELHEIM ANIMAL HEALTH USA INC.

Heartgard® Plus
(ivermectin/pyrantel)

CHEWABLES

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS: For use in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for a month (30 days) after infection and for the treatment and control of ascarids (*Toxocara canis, Toxascaris leonina*) and hookworms (*Ancylostoma caninum, Uncinaria stenocephala, Ancylostoma braziliense*).

DOSAGE: HEARTGARD® Plus (ivermectin/pyrantel) should be administered orally at monthly intervals at the recommended minimum dose level of 6 mcg of ivermectin per kilogram (2.72 mcg/lb) and 5 mg of pyrantel (as pamoate salt) per kg (2.27 mg/lb) of body weight. The recommended dosing schedule for prevention of canine heartworm disease and for the treatment and control of ascarids and hookworms is as follows:

Dog Weight	Chewables Per Month	Ivermectin Content	Pyrantel Content	Color Coding On Foil Backing and Carton
Up to 25 lb	1	68 mcg	57 mg	Blue
26 to 50 lb	1	136 mcg	114 mg	Green
51 to 100 lb	1	272 mcg	227 mg	Brown

HEARTGARD Plus is recommended for dogs 6 weeks of age and older.
For dogs over 100 lb use the appropriate combination of these chewables.

ADMINISTRATION: Remove only one chewable at a time from the foil-backed blister card. Return the card with the remaining chewables to its box to protect the product from light. Because most dogs find HEARTGARD Plus palatable, the product can be offered to the dog by hand. Alternatively, it may be added intact to a small amount of dog food.The chewable should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole.

Care should be taken that the dog consumes the complete dose, and treated animals should be observed for a few minutes after administration to ensure that part of the dose is not lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

HEARTGARD Plus should be given at monthly intervals during the period of the year when mosquitoes (vectors), potentially carrying infective heartworm larvae, are active. The initial dose must be given within a month (30 days) after the dog's first exposure to mosquitoes. The final dose must be given within a month (30 days) after the dog's last exposure to mosquitoes.

When replacing another heartworm preventive product in a heartworm disease preventive program, the first dose of HEARTGARD Plus must be given within a month (30 days) of the last dose of the former medication.

If the interval between doses exceeds a month (30 days), the efficacy of ivermectin can be reduced. Therefore, for optimal performance, the chewable must be given once a month on or about the same day of the month. If treatment is delayed, whether by a few days or many, immediate treatment with HEARTGARD Plus and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Monthly treatment with HEARTGARD Plus also provides effective treatment and control of ascarids (*T. canis, T. leonina*) and hookworms (*A. caninum, U. stenocephala, A. braziliense*). Clients should be advised of measures to be taken to prevent reinfection with intestinal parasites.

EFFICACY: HEARTGARD Plus Chewables, given orally using the recommended dose and regimen, are effective against the tissue larval stage of *D.immitis* for a month (30 days) after infection and, as a result, prevent the development of the adult stage. HEARTGARD Plus Chewables are also effective against canine ascarids (*T. canis, T. leonina*) and hookworms (*A. caninum, U. stenocephala, A. braziliense*).

ACCEPTABILITY: In acceptability and field trials, HEARTGARD Plus was shown to be an acceptable oral dosage form that was consumed at first offering by the majority of dogs.

PRECAUTIONS: All dogs should be tested for existing heartworm infection before starting treatment with HEARTGARD Plus which is not effective against adult *D. immitis*. Infected dogs must be treated to remove adult heartworms and microfilariae before initiating a program with HEARTGARD Plus.

While some microfilariae may be killed by the ivermectin in HEARTGARD Plus at the recommended dose level, HEARTGARD Plus is not effective for microfilariae clearance. A mild hypersensitivity-type reaction, presumably due to dead or dying microfilariae and particularly involving a transient diarrhea, has been observed in clinical trials with ivermectin alone after treatment of some dogs that have circulating microfilariae.

Keep this and all drugs out of the reach of children.
In case of ingestion by humans, clients should be advised to contact a physician immediately. Physicians may contact a Poison Control Center for advice concerning cases of ingestion by humans.

Store between 68°F - 77°F (20°C - 25°C). Excursions between 59°F - 86°F (15°C - 30°C) are permitted. Protect product from light.

ADVERSE REACTIONS: In clinical field trials with HEARTGARD Plus, vomiting or diarrhea within 24 hours of dosing was rarely observed (1.1% of administered doses). The following adverse reactions have been reported following the use of HEARTGARD: Depression/lethargy, vomiting, anorexia, diarrhea, mydriasis, ataxia, staggering, convulsions and hypersalivation.

To report suspected adverse drug events, for technical assistance, or to obtain a copy of the Safety Data Sheet (SDS), contact Boehringer Ingelheim Animal Health USA Inc. at 1-888-637-4251. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS, or online at http://www.fda.gov/AnimalVeterinary/SafetyHealth.

SAFETY: HEARTGARD Plus has been shown to be bioequivalent to HEARTGARD, with respect to the bioavailability of ivermectin. The dose regimens of HEARTGARD Plus and HEARTGARD are the same with regard to ivermectin (6 mcg/kg). Studies with ivermectin indicate that certain dogs of the Collie breed are more sensitive to the effects of ivermectin administered at elevated dose levels (more than 16 times the target use level) than dogs of other breeds. At elevated doses, sensitive dogs showed adverse reactions which included mydriasis, depression, ataxia, tremors, drooling, paresis, recumbency, excitability, stupor, coma and death. HEARTGARD demonstrated no signs of toxicity at 10 times the recommended dose (60 mcg/kg) in sensitive Collies. Results of these trials and bioequivalency studies, support the safety of HEARTGARD products in dogs, including Collies, when used as recommended.

HEARTGARD Plus has shown a wide margin of safety at the recommended dose level in dogs, including pregnant or breeding bitches, stud dogs and puppies aged 6 or more weeks. In clinical trials, many commonly used flea collars, dips, shampoos, anthelmintics, antibiotics, vaccines and steroid preparations have been administered with HEARTGARD Plus in a heartworm disease prevention program.

In one trial, where some pups had parvovirus, there was a marginal reduction in efficacy against intestinal nematodes, possibly due to a change in intestinal transit time.

HOW SUPPLIED: HEARTGARD Plus is available in three dosage strengths (See DOSAGE section) for dogs of different weights. Each strength comes in convenient cartons of 6 and 12 chewables.

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

Made in U.S.A.

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