BOEHRINGER INGELHEIM ANIMAL HEALTH CANADA INC.
5180 SOUTH SERVICE ROAD, BURLINGTON, ON, L7L 5H4
Customer Care No.: 1-800-567-1885
Technical Services No.: 1-877-565-5501
Website: www.boehringer-ingelheim.ca

NEXGARD SPECTRA®

Boehringer Ingelheim

Afoxolaner and Milbemycin Oxime Chewable Tablets

VETERINARY USE ONLY

DESCRIPTION: NEXGARD SPECTRA is a soft, beef-flavoured chewable tablet. Each chewable tablet contains the active ingredients, afoxolaner (an ectoparasiticide of the isoxazoline family) and milbemycin oxime (an endoparasiticide belonging to the group of macrocyclic lactones).

INDICATIONS: NEXGARD SPECTRA chewable tablets are indicated in dogs and puppies 8 weeks of age or older for:

- the treatment and control of flea *(Ctenocephalides felis)* infestations,
- the treatment and control of *Dermacentor variabilis* (American Dog Ticks), *Ixodes scapularis* (Blacklegged Ticks), and *Amblyomma americanum* (Lone Star Ticks),
- the treatment of demodicosis caused by *Demodex canis*,
- the prevention of heartworm disease *(Dirofilaria immitis)* (see **CAUTIONS**),
- the treatment and control of intestinal nematode infections caused by adult hookworms *(Ancylostoma caninum)*, adult roundworms *(Toxocara canis* and *Toxascaris leonina)* and adult whipworms *(Trichuris vulpis);*
- the reduction of *Borrelia burgdorferi* infections as a direct result of killing adult *Ixodes scapularis* vector ticks.

DOSAGE AND ADMINISTRATION: NEXGARD SPECTRA is given orally every 30 days, at the recommended dosage of 2.5 - 5 mg/kg of afoxolaner and 0.5 - 1 mg/kg of milbemycin oxime.

Body Weight (kg)	Afoxolaner per chewable tablet (mg)	Milbemycin Oxime per chewable tablet (mg)
2-3.7	9.4	1.9
3.8-7.5	18.8	3.8
7.6-15	37.5	7.5
15.1-30	75	15
30.1-60	150	30

NEXGARD SPECTRA 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 rejected. If it is suspected that any of the dose has been lost, or vomiting occurs within 2 hours of administration, redose with another full dose. If a dose is missed, administer **NEXGARD SPECTRA** and resume an every-30-day dosing regimen. To be effective **NEXGARD SPECTRA** should be administered every 30 days.

Flea Treatment and Prevention:

For prevention of flea infestation, **NEXGARD SPECTRA** should be administered ideally just 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 Prevention:

Administration of **NEXGARD SPECTRA** should coincide with the time of year the ticks are active.

Treatment of Demodicosis:

NEXGARD SPECTRA should be administered monthly for 3 months. Skin scrapings should be done to assess the response to treatment. As demodicosis is a multi-factorial disease, where possible, it is advisable to also treat any underlying disease appropriately. Severe cases of generalized demodicosis may be difficult to cure.

Heartworm Prevention:

NEXGARD SPECTRA should be administered at monthly intervals beginning within 1 month of the dog's first exposure to mosquitoes and continuing for 6 months after the dog's last exposure to mosquitoes (see **EFFICACY**). To establish a treatment routine, it is recommended that the same day or date be used each month.

If treatment is delayed, whether by a few days or many, immediate treatment with **NEXGARD SPECTRA** and resumption of the recommended dosing regimen will minimize the opportunity for the development of adult heartworms.

Intestinal Nematodes Treatment and Prevention:

Dogs may be exposed to and can become infected with hookworms, roundworms and whipworms throughout the year.

CAUTIONS:

The safety of **NEXGARD SPECTRA** Chewable Tablets has not been evaluated in breeding, pregnant or lactating dogs. The safety of **NEXGARD SPECTRA** in puppies less than 8 weeks of age has not been evaluated.

Afoxolaner is a member of the isoxazoline class. This class has been associated with neurological 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 neurological disorders.

NEXGARD SPECTRA is not 100% effective for the prevention of all strains of heartworm. (see **EFFICACY**).

It is recommended, in accordance with the American Heartworm Society that:

- Infected dogs should be treated with labeled adulticides and microfilaricides (if microfilaria are present) as soon after diagnosis as medically practical.
- Uninfected dogs should be maintained on preventives year-round to protect them from heartworm disease.
- All dogs > 6 months of age should be tested for existing heartworm infection prior to starting treatment for the first time.
- Annual testing of all dogs for heartworm should be done.

Hypersensitivity reactions manifested by laboured respiration, lethargy, vomiting and salivation have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by the release of protein from dead or dying microfilariae. In some cases, death has been reported as an outcome of the adverse event.

Some Collies and other p-glycoprotein-deficient dogs with MDR or ABCB1-1 delta gene mutation are known to be more sensitive to the macrocyclic lactone class of medications. Such dogs may be susceptible to macrocyclic lactone toxicity with over-dosing or when used in combination with other macrocyclic

lactone drugs. Signs of depression, hypersalivation, tremor and ataxia have been associated with macrocyclic lactone toxicity.

WARNINGS: Keep out of reach of children. In case of accidental ingestion, contact a physician immediately.

ADVERSE REACTIONS: Although all adverse reactions are not reported, the following information is based on voluntary post-approval drug experience reporting. It is generally recognized that this results in significant under-reporting. The adverse events listed here reflect reporting and not necessarily causality. Although very rare, the following adverse events have been reported: Pruritus, diarrhea, vomiting, anorexia, hyperactivity and erythema.

CLINICAL PHARMACOLOGY

MODE OF ACTION:

Afoxolaner binds to flea and tick nerve cell chloride channels activated by the neurotransmitter GABA (gamma-aminobutyric acid), which blocks 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/acarines and mammals may be inferred by the differential sensitivity of the insects/acarines' GABA receptors versus mammalian GABA receptors.

Afoxolaner acts systemically to kill fleas and ticks. The time of exposure needed for the flea or tick to die depends on the time it takes the flea or tick to attach and exchange fluids with the host dog as well as the drug dose needed to kill fleas or a specific species of tick and the dog's drug plasma concentration at the time of attachment. Once feeding begins for fleas *(C. felis)*, the onset of effect is within 8-24 hours. For ticks, *Dermacentor variabilis,* and *Ixodes scapularis* >90% are killed within 48 hours and for *Amblyomma americanum* >90% are killed within 72 hours.

Milbemycin Oxime acts by disrupting the glutamate neuro transmission in invertebrates. Milbemycin Oxime increases glutamate binding with consequent enhanced chloride ion flow into the cell. This leads to hyperpolarisation of the neuromuscular membrane resulting in paralysis and death of the parasites.

EFFICACY:

Fleas: In two well-controlled laboratory studies, **NEXGARD SPECTRA** demonstrated consistent 99.6% to 100% effectiveness against adult fleas 24 hours post-infestation for 35 days. 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 (mean count of 8.5 and 1.6 eggs in **NEXGARD SPECTRA** treated dogs and a mean count of 38.5 and 82.3 in the control dogs at 12 and 24 hours, respectively). At subsequent infestations, every week between 7 and 35 days after treatment, fleas from dogs in the treated group were unable to produce any eggs while fleas from dogs in the control group continued to produce eggs (means 8.9-82.3).

Data from the laboratory studies demonstrate that **NEXGARD SPECTRA** kills fleas before they can lay eggs, thus preventing subsequent flea infestations after the initial treatment of existing flea infestations.

Ticks: In well-controlled laboratory studies, **NEXGARD SPECTRA** demonstrated > 90% effectiveness for 30 days against *Amblyomma americanum* 72 hours post-infestation. Based on data from an E-max model and studies conducted with afoxolaner > 90% efficacy is predicted against *Ixodes scapularis,* and *Dermacentor variabilis,* 48 hours post-infestation.

In two separate, well-controlled laboratory studies, **NEXGARD SPECTRA** was effective at preventing *Borrelia burgdorferi* infections after dogs were infested at room temperature, with adult *Ixodes scapularis* vector ticks 28 days post-treatment.

Demodicosis: In a multi-center European field trial **NEXGARD SPECTRA** or afoxolaner was administered on study day 0, 28 and 56 to 41 client-owned dogs aged 8 weeks and older for the treatment of generalized demodicosis. **NEXGARD SPECTRA** and afoxolaner alone were administered orally, at the recommended treatment dose of **NEXGARD SPECTRA** of 2.5 -5 mg/kg. The results of the study revealed combined efficacy for the **NEXGARD SPECTRA** and afoxolaner treatment groups of 79.8% efficacy on study day 28, 93.5% efficacy on study day 56 and 95.8% on study day 84. Total skin lesion severity, skin lesion extension, and pruritus scores showed significant improvement ($P<0.0001$) at day 84.

Heartworm:

In three well-controlled laboratory studies, **NEXGARD SPECTRA** was 100% effective against induced heartworm infections when administered for 6 consecutive monthly doses after infection. These laboratory studies used US isolates obtained from Georgia (Duke and Pepper strains) and Michigan (Michigan strain).

In two well-controlled laboratory studies, **NEXGARD SPECTRA** was 69% effective against heartworm infections induced with the US JYD-34 strain when administered for 6 consecutive monthly doses.

In a well-controlled six-month US field study, no dogs treated with **NEXGARD SPECTRA** were positive for heartworm infection as determined by heartworm antigen testing and microfilariae testing.

Intestinal Nematodes: In well-controlled laboratory studies, **NEXGARD SPECTRA** demonstrated > 90% effectiveness against adult hookworms *(Ancylostoma caninum)*, adult roundworms *(Toxocara canis* and *Toxascaris leonina)* and adult whipworms *(Trichuris vulpis)*.

In a palatability trial, **NEXGARD SPECTRA** was shown to be a palatable oral dosage form which was consumed by 71.4% of the dogs at first offering.

ANIMAL SAFETY:

In a well-controlled US field study in client-owned dogs, which evaluated safety and effectiveness against *Dirofilaria immitis* in a total of 315 treated dogs (160 treated with **NEXGARD SPECTRA**, 155 treated with an oral active control; all dogs were administered one dose at monthly intervals for six consecutive administrations). No serious adverse reactions were attributed to **NEXGARD SPECTRA**. All reactions were regarded as mild in nature and were not necessarily proven to be treatment related. The most frequently reported adverse reaction in the **NEXGARD SPECTRA** and active control groups was vomiting. The occurrence of vomiting was generally self-limiting and of short duration.

The table below presents the most common adverse reactions during the study.

Reported Adverse Reactions during the 6-month study

Adverse Reaction	Treatment Group					
	NEXGARD SPECTRA			Active Control		
	N[1]	Overall %	Average Monthly %	N[1]	Overall %	Average Monthly %
Vomiting	23	14.4	2.4	30	19.4%	3.2
Diarrhea with and without blood	15	9.4	1.6	17	11%	1.8
Pruritus	14	8.8	1.5	7	4.5%	0.8
Dermatitis and eczema	13	8.1	1.4	7	4.5%	0.8
Lethargy	9	5.6	0.9	9	5.8%	1.0
Skin Disorders not specified	9	5.6	0.9	5	3.2%	0.5
Bacterial Skin Infection	8	5.0	0.8	4	2.6%	0.4
Erythema	7	4.4	0.7	5	3.2%	0.5
Anorexia	7	4.4	0.7	3	1.9%	0.3

[1]Number of dogs treated with the identified adverse reaction

In the clinical field-study there were 2 dogs in the **NEXGARD SPECTRA** group and one dog in the active control group that had diarrhea associated with *Clostridium perfringens* infection. One of the dogs in the **NEXGARD SPECTRA** group with a *Clostridium perfringens* infection died suddenly. It is not believed these adverse reactions were treatment related.

In a margin of safety study, **NEXGARD SPECTRA** Chewable Tablets were administered orally to Beagle puppies 8 weeks old at 1, 3, and 5 times the maximum exposure dose (5 mg/kg of Afoxolaner and 1 mg/kg of Milbemycin Oxime) 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. Clinical observations included diarrhea, diarrhea with blood and vomiting which were observed sporadically across all groups, including the controls. One female dog (1x dose group) had sporadic emesis and diarrhea with blood and slightly increased body temperature and decreased white blood cell count. *Clostridium perfringens* infection and gastritis with hypomotility were detected and were not determined to be treatment related. The dog recovered with treatment.

There were no clinically relevant treatment-related effects on physical examination, body weight, food consumption, clinical pathology (hematology, plasma chemistry, coagulation profiles), gross pathology, histopathology or organ weights.

STORAGE: Store at room temperature between 15 - 30°C. Brief exposure (not to exceed 24 hours) up to 40°C is permitted. Keep the blister in the outer carton in order to protect from light.

HOW SUPPLIED: NEXGARD SPECTRA chewable tablets are available in five soft, beef-flavoured chewable tablets strengths packaged in blister packs: 9.4/1.9 mg, 18.8/3.8 mg, 37.5/7.5 mg, 75.0/15.0 mg or 150.0/30.0 mg of Afoxolaner/Milbemycin Oxime per chewable tablet, formulated according to the weight of dogs. Each strength is available in colour-coded packages of 3, 6 or 12 chewable tablets. Not all pack sizes may be marketed.

DIN 02473364 (9.4 mg/1.9 mg), 02473372 (18.8 mg/3.8 mg), 02473380 (37.5 mg/7.5 mg), 02473399 (75 mg/15 mg), 02473402 (150 mg/30 mg)

Boehringer Ingelheim Animal Health Canada Inc., 5180 South Service Road, Burlington, ON L7L 5H4

Version April 16, 2021

CPN: 1182158.2
