MERCK ANIMAL HEALTH
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sentinel® spectrum® chews

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Intervet/Merck Animal Health

(milbemycin oxime • lufenuron • praziquantel)

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

Description: SENTINEL® SPECTRUM® Chews are available in four strengths in color-coded packages for oral administration to dogs and puppies according to their weight. Each chewable flavored tablet is formulated to provide a minimum of 0.23 mg/pound (0.5 mg/kg) of milbemycin oxime, 4.55 mg/pound (10 mg/kg) of lufenuron, and 2.28 mg/pound (5 mg/kg) of praziquantel.

Milbemycin oxime consists of the oxime derivatives of 5-didehydromilbemycins in the ratio of approximately 80% A $_4$ ($C_{32}H_{45}NO_7$, MW 555.71) and 20% A $_3$ ($C_{31}H_{43}NO_7$, MW 541.68). Milbemycin oxime is classified as a macrocyclic anthelmintic.

Lufenuron is a benzoylphenylurea derivative with the following chemical composition: N-[2,5-dichloro-4-(1,1,2,3,3,3,-hexafluoropropoxy)-phenyl-aminocarbonyl]-2,6-difluorobenzamide ($C_{17}H_8Cl_2F_8N_2O_3$, MW 511.15). Benzoylphenylurea compounds, including lufenuron, are classified as insect development inhibitors (IDIs).

Praziquantel is an isoquinolone anthelmintic with the chemical name 2-(Cyclohexylcarbonyl)-1,2,3,6,7,-11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one.

Indications: SENTINEL SPECTRUM Chews are indicated for the prevention of heartworm disease caused by *Dirofilaria immitis;* for the prevention and control of flea populations *(Ctenocephalides felis);* and for the treatment and control of adult roundworm *(Toxocara canis, Toxascaris leonina)*, adult hookworm *(Ancylostoma caninum)*, adult whipworm *(Trichuris vulpis)*, and adult tapeworm *(Dipylidium caninum, Taenia pisiformis, Echinococcus multilocularis* and *Echinococcus granulosus)* infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

Dosage and Administration: SENTINEL SPECTRUM Chews should be administered orally, once every month, at the minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime, 4.55 mg/lb (10 mg/kg) lufenuron, and 2.28 mg/lb (5 mg/kg) praziquantel. For heartworm prevention, give once monthly for at least 6 months after exposure to mosquitoes (see **EFFECTIVENESS**).

Dosage Schedule				
Body Weight	**Milbemycin Oxime per chewable**	**Lufenuron per chewable**	**Praziquantel per chewable**	**Number of chewables**
2 to 8 lbs.	2.3 mg	46 mg	22.8 mg	One
8.1 to 25 lbs.	5.75 mg	115 mg	57 mg	One
25.1 to 50 lbs.	11.5 mg	230 mg	114 mg	One
50.1 to 100 lbs.	23.0 mg	460 mg	228 mg	One
Over 100 lbs.	Administer the appropriate combination of chewables			

To ensure adequate absorption, always administer SENTINEL SPECTRUM Chews to dogs immediately after or in conjunction with a normal meal. SENTINEL SPECTRUM Chews may be offered to the dog by hand or added to a small amount of dog food. The chewables 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 a few minutes after administration to ensure that no part of the dose is lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

Heartworm Prevention: SENTINEL SPECTRUM Chews should be administered at monthly intervals beginning within one month of the dog's first seasonal exposure to mosquitoes and continuing until at least 6 months after the dog's last seasonal exposure (see **EFFECTIVENESS**). SENTINEL SPECTRUM Chews may be administered year-round without interruption. When switching from another heartworm preventative product to SENTINEL SPECTRUM Chews, the first dose of SENTINEL SPECTRUM Chews should be given within a month of the last dose of the former product.

Flea Treatment and Prevention: Treatment with SENTINEL SPECTRUM Chews may begin at any time of the year, preferably starting one month before fleas become active and continuing monthly through the end of flea season. In areas where fleas are common year-round, monthly treatment with SENTINEL SPECTRUM Chews 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 protection product, as necessary.

Intestinal Nematode and Cestode Treatment and Control: Dogs may be exposed to and can become infected with roundworms, whipworms, hookworms, and tapeworms throughout the year, regardless of season or climate. Clients should be advised of appropriate measures to prevent reinfection of their dog with intestinal parasites. Because the prepatent period for *E. multilocularis* may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

Contraindications: There are no known contraindications to the use of SENTINEL SPECTRUM Chews.

Warnings: Not for use in humans. Keep this and all drugs out of the reach of children.

Precautions: Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention (see **EFFECTIVENESS**).

Prior to administration of SENTINEL SPECTRUM Chews, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. SENTINEL SPECTRUM Chews are not effective against adult *D. immitis*.

Mild, transient hypersensitivity reactions, such as labored breathing, vomiting, hypersalivation, and lethargy have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Do not use in puppies less than six weeks of age.

Do not use in dogs or puppies less than two pounds of body weight.

The safety of SENTINEL® SPECTRUM® Chews has not been evaluated in dogs used for breeding or in lactating females. Studies have been performed with milbemycin oxime and lufenuron alone (see **ANIMAL SAFETY**).

Adverse Reactions: The following adverse reactions have been reported in dogs after administration of milbemycin oxime, lufenuron, or praziquantel: vomiting, depression/lethargy, pruritus, urticaria, diarrhea, anorexia, skin congestion, ataxia, convulsions, salivation, and weakness.

To report suspected adverse drug events, contact Merck Animal Health at 1-800-224-5381. For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

For technical assistance, call Merck Animal Health at 1-800-224-5318.

Information for Owner or Person Treating Animal: *Echinococcus multilocularis* and *Echinococcus granulosus* are tapeworms found in wild canids and domestic dogs. *E. multilocularis* and *E. granulosus* can infect humans and cause serious disease (alveolar hydatid disease and hydatid disease, respectively). Owners of dogs living in areas where *E. multilocularis* or *E. granulosus* are endemic should be instructed on how to minimize their risk of exposure to these parasites, as well as their dog's risk of exposure. Although SENTINEL SPECTRUM Chews were 100% effective in laboratory studies in dogs against *E. multilocularis* and *E. granulosus*, no studies have been conducted to show that the use of this product will decrease the incidence of alveolar hydatid disease or hydatid disease in humans. Because the prepatent period for *E. multilocularis* may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

Effectiveness

Heartworm Prevention: In a well-controlled laboratory study, SENTINEL SPECTRUM Chews *(milbemycin oxime, lufenuron, praziquantel)* were 100% effective against induced heartworm infections when administered once monthly for 6 consecutive months. In well-controlled laboratory studies, neither one dose nor two consecutive doses of SENTINEL SPECTRUM Chews provided 100% effectiveness against induced heartworm infections.

Intestinal Nematodes and Cestodes Treatment and Control: Elimination of the adult stage of hookworm *(Ancylostoma caninum)*, roundworm *(Toxocara canis, Toxascaris leonina)*, whipworm *(Trichuris vulpis)* and tapeworm *(Dipylidium caninum, Echinococcus multilocularis, Echinococcus granulosus, Taenia pisiformis)* infections in dogs was demonstrated in well-controlled laboratory studies.

Flea Prevention and Control: In well-controlled studies, SENTINEL SPECTRUM Chews were effective in preventing flea eggs from hatching, thus providing control of the development of flea populations *(Ctenocephalides felis).*

Palatability: In a field study of 117 dogs offered SENTINEL SPECTRUM Chews, 113 dogs (96.6%) accepted the product when offered from the hand as if a treat, 2 dogs (1.7%) accepted it from the bowl with food, 1 dog (0.9%) accepted it when it was placed in the dog's mouth, and 1 dog (0.9%) refused it.

Animal Safety: In a margin of safety study, 40 ten-week-old puppies (10 per group) were administered either a sham dose (0X) or doses of 1, 3, or 5X the maximum exposure dose of SENTINEL SPECTRUM Chews once every two weeks for a total of seven treatments. Transient ataxia, lethargy, tremors, and salivation were seen in the 3X and 5X groups following each of the seven doses. Lethargy and ataxia were occasionally reported in sham-dosed (0X) and 1X dogs. Tremors were observed twice post-treatment in the 1X treatment group. Vomiting was seen in all treatment groups but at a higher incidence in the 3X and 5X groups. At the 5X dose, shallow breathing was noted in two dogs and one dog was unable to stand following two different doses. All clinical signs resolved within 24 hours.

In a second margin of safety study, 64 six-week-old puppies (16 per group) were dosed with either a sham (0X) or 1, 3, or 5X the maximum exposure dose of SENTINEL SPECTRUM Chews on days 1, 15, 29, and 43. A dose dependent increase in ataxia, decreased activity, tremors, and salivation was seen within 24 hours of treatment. Splayed hind limbs were observed once in one dog in the 5X treatment group. Vomiting was observed in the 5X treatment group.

For SENTINEL SPECTRUM Chews, the maximum exposure based on product dosing is 2.5 mg/kg for milbemycin oxime, 50.7 mg/kg for lufenuron and 25.1 mg/kg for praziquantel, which is higher than the minimum effective dose used in the safety studies for milbemycin oxime and lufenuron (see below).

Milbemycin Oxime: Two studies were conducted in heartworm-infected dogs treated with milbemycin oxime. Mild, transient hypersensitivity reactions were observed in dogs with high microfilariae counts (see **PRECAUTIONS**).

Safety studies in pregnant dogs demonstrated that doses of 0.6X the maximum exposure dose of SENTINEL SPECTRUM Chews, (1.5 mg/kg of milbemycin oxime), administered daily from mating through weaning, resulted in measurable concentrations of milbemycin oxime in milk. Puppies nursing these females demonstrated milbemycin oxime-related effects (depression, decreased activity, diarrhea, dehydration, nasal discharge). A subsequent study, which evaluated the daily administration of 0.6X the maximum exposure dose of SENTINEL SPECTRUM Chews, from mating until one week before weaning, demonstrated no effects on the pregnant females or their litters. A study, in which pregnant females were dosed once, at 0.6X maximum exposure dose of SENTINEL SPECTRUM Chews before, on the day of, or shortly after whelping, resulted in no effects on the puppies.

Some nursing puppies, at 2, 4, and 6 weeks of age, administered oral doses of 9.6 mg/kg milbemycin oxime (3.8X the maximum exposure dose of SENTINEL SPECTRUM Chews) exhibited tremors, vocalization, and ataxia. These effects were all transient and puppies returned to normal within 24 to 48 hours. No effects were observed in puppies administered 0.5 mg/kg milbemycin oxime (minimum label dose).

A rising-dose safety study conducted in rough-coated Collies resulted in ataxia, pyrexia, and periodic recumbency in one of fourteen dogs administered milbemycin oxime at 12.5 mg/kg (5X the maximum exposure dose of SENTINEL SPECTRUM Chews). Prior to receiving the 12.5 mg/kg dose on day 56 of the study, all animals had undergone a dosing regimen consisting of 2.5 mg/kg milbemycin oxime on day 0, followed by 5.0 mg/kg on day 14, and 10.0 mg/kg on day 32. No adverse reactions were observed in any of the Collies treated with doses less than 12.5 mg/kg.

Lufenuron: In a ten-month study, doses of lufenuron up to 2X the maximum exposure dose of SENTINEL SPECTRUM Chews (10 mg/kg) caused no overt toxicity. A single dose of 200 mg/kg had no marked effect on adult dogs, but caused decreased activity and reduced appetite in eight-week-old puppies. Lufenuron tablets were evaluated with concurrent administration of flea adulticides containing carbaryl, permethrin, chlorpyriphos, and cythioate. No toxicity resulted from these combinations. Lufenuron tablets did not cause cholinesterase inhibition nor did they enhance cholinesterase inhibition caused by exposure to organophosphates.

Two laboratory and two well-controlled field studies were conducted to evaluate reproductive safety of lufenuron tablets in breeding dogs. In one of the laboratory studies, in which lufenuron was administered to Beagle dogs as three divided doses, equivalent to 17.8X the maximum exposure dose of SENTINEL SPECTRUM Chews (10 mg/kg), the ratio of gravid females to females mated was 8/8 or 100% in the control group and 6/9 or 67% in the lufenuron-treated group. The mean number of pups per litter was two animals higher in the lufenuron versus control groups and mean birth weights of pups from treated females in this study was lower than control groups. These pups grew at a similar rate to the control pups. The incidence of nasal discharge, pulmonary congestion, diarrhea/dehydration, and sluggishness was higher in the lufenuron-treated pup group than in the control pup group. The incidence of these signs was transient and decreasing by the end of lactation.

Results from three additional reproductive safety studies, one laboratory and two field studies, evaluating eleven breeds of dogs, did not demonstrate any adverse findings for the reproductive parameters measured, including fertility, pup birth weights, and pup clinical signs, after administration of lufenuron up to 1X the maximum exposure dose of SENTINEL SPECTRUM Chews. The average milk: blood concentration ratio was approximately 60 (i.e. 60X higher drug concentrations in the milk compared to drug levels in the blood of treated females). Nursing puppies averaged 8-9 times higher blood concentrations of lufenuron compared to their dams.

Storage Information: Store in a dry place at controlled room temperature, between 59° and 77°F (15-25°C).

How Supplied: SENTINEL SPECTRUM Chews are available in four strengths, formulated according to the weight of the dog. Each strength is available in color-coded packages of six chewable tablets each.

Manufactured for: Intervet Inc (d/b/a Merck Animal Health), 2 Giralda Farms, Madison, NJ 07940

Approved by FDA under NADA # 141-333

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FOR DOGS AND PUPPIES SIX WEEKS OF AGE AND OLDER		
2-8 lbs	6 chewables 2.3 mg milbemycin oxime • 46 mg lufenuron • 22.8 mg praziquantel	324631 R4

8.1-25 lbs	6 chewables 5.75 mg milbemycin oxime • 115 mg lufenuron • 57 mg praziquantel	346901 R4
25.1-50 lbs	6 chewables 11.5 mg milbemycin oxime • 230 mg lufenuron • 114 mg praziquantel	392656 R3
50.1-100 lbs	6 chewables 23 mg milbemycin oxime • 460 mg lufenuron • 228 mg praziquantel	349148 R3

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