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Virbac

sentinel® flavor tabs®

(milbemycin oxime+lufenuron)

The palatable once-a-month prescription tablet that prevents heartworm disease and flea populations in dogs and puppies. SENTINEL® FLAVOR TABS® (milbemycin oxime/lufenuron) also control flea populations and adult hookworms, and remove and control adult roundworm and whipworm infections in dogs and puppies.

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

Warnings
Not for human use. Keep this and all drugs out of the reach of children.

Description
SENTINEL FLAVOR TABS are available in four tablet sizes in color-coded packages for oral administration to dogs and puppies according to their weight. (See Dosage section). Each tablet is formulated to provide a minimum of 0.23 mg/pound (0.5 mg/kg) of milbemycin oxime and 4.55 mg/pound (10 mg/kg) body weight of lufenuron.

Milbemycin oxime consists of the oxime derivatives of 5-didehydromilbemycins in the ratio of approximately 80% A_4 ($C_{32}H_{46}NO_7$, 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)-phenylaminocarbonyl]-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).

Mode of Action
Milbemycin oxime, one active ingredient in SENTINEL FLAVOR TABS, is a macrocyclic anthelmintic which is believed to act by interfering with invertebrate neurotransmission. Milbemycin oxime eliminates the tissue stage of heartworm larvae and the adult stage of hookworm (*Ancylostoma caninum*), roundworm (*Toxocara canis* and *Toxascaris leonina*) and whipworm (*Trichuris vulpis*) infestations when administered orally according to the recommended dosage schedule.

Lufenuron, the other active ingredient in SENTINEL FLAVOR TABS, is an insect development inhibitor which breaks the flea life cycle by inhibiting egg development. Lufenuron's mode of action is interference with chitin synthesis, polymerization and deposition. Lufenuron has no effect on the adult flea. After biting a lufenuron-treated dog, the female flea ingests a blood meal containing lufenuron which is subsequently deposited in her eggs. Lufenuron prevents most flea eggs from hatching or maturing into adults and thus prevents and controls flea populations by breaking the life cycle. (See Efficacy).

Indications
SENTINEL FLAVOR TABS are indicated for use in dogs and puppies, four weeks of age and older, and two pounds body weight or greater. SENTINEL FLAVOR TABS are also indicated for the prevention of heartworm disease caused by *Dirofilaria immitis,* for the prevention and control of flea populations, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis* and *Toxascaris leonina* (roundworm) and *Trichuris vulpis* (whipworm) infections.

Lufenuron controls flea populations by preventing the development of flea eggs and does not kill adult fleas. Concurrent use of an adulticide product may be necessary for adequate control of adult fleas.

Without concurrent use of an adulticide, adequate flea control may not be achieved in dogs that have repeated exposure to flea infested animals or environments.

Precautions
Do not use in puppies less than four weeks of age and less than two pounds of body weight. Prior to administration of SENTINEL FLAVOR TABS, dogs should be tested for existing heartworm infections. Infected dogs should be treated to remove adult heartworms and microfilariae prior to initiating treatment with SENTINEL FLAVOR TABS. Mild, transient hypersensitivity reactions manifested as labored respiration, vomiting, salivation and lethargy have been noted in some treated dogs carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

SENTINEL FLAVOR TABS immediately break the flea life cycle by inhibiting egg development. However, preexisting flea populations may continue to develop and emerge after treatment with SENTINEL FLAVOR TABS has begun. Based on results of clinical studies, this emergence generally occurs during the first 30-60 days. Therefore, noticeable control may not be observed until several weeks after dosing when a preexisting infestation is present. Cooler geographic areas may have longer lag periods due to a prolonged flea life cycle. The concurrent use of an approved adulticide may be employed depending on the severity of the infestation.

If a SENTINEL FLAVOR TABS-treated dog comes in contact with a flea-infested environment, adult fleas may infest the treated animal. These adult fleas are unable to produce viable offspring. The temporary use of an adulticide product may be necessary to kill these adult fleas.

Efficacy: Milbemycin Oxime
Milbemycin oxime provided complete protection against heartworm infection in both controlled laboratory and clinical trials.

In laboratory studies, a single dose of milbemycin oxime at 0.5 mg/kg was effective in removing roundworms, hookworms and whipworms. In well-controlled clinical trials, milbemycin oxime was also effective in removing roundworms and whipworms and in controlling hookworms.

Efficacy: Lufenuron
Lufenuron provided 99% control of flea egg development for 32 days following a single dose of lufenuron at 10 mg/kg in studies using experimental flea infestations. In well-controlled clinical trials, when treatment with lufenuron tablets was initiated prior to the flea season, mean flea counts were lower on lufenuron-treated dogs versus placebo-treated dogs. After 6 monthly treatments, the mean number of fleas on lufenuron-treated dogs was approximately 4 compared to 230 on placebo-treated dogs.

When treatment was initiated during the flea season, lufenuron tablets were effective in controlling flea infestations on dogs that completed the study. The mean flea count per lufenuron-treated dog was approximately 74 prior to treatment but had decreased to 4 after six monthly doses of lufenuron. A topical adulticide was used in the first eight weeks of the study to kill the pre-existing adult fleas.

Safety: Milbemycin Oxime
Milbemycin oxime has been tested safely in over 75 different breeds of dogs, including collies, pregnant females, breeding males and females, and puppies over two weeks of age. In well-controlled clinical field studies 786 dogs completed treatment with milbemycin oxime. Milbemycin oxime was used safely in animals receiving frequently used veterinary products such as vaccines, anthelmintics, antibiotics, steroids, flea collars, shampoos and dips.

Two studies in heartworm-infected dogs were conducted which demonstrated mild, transient hypersensitivity reactions in treated dogs with high microfilaremia counts (see Precautions for reactions observed). Safety studies in pregnant dogs demonstrated that high doses (1.5 mg/kg = 3X) of milbemycin oxime given in an exaggerated dosing regimen (daily from mating through weaning), resulted in measurable concentrations of the drug in milk. Puppies nursing these females which received exaggerated dosing regimens demonstrated milbemycin-related effects. These effects were directly attributable to the exaggerated experimental dosing regimen. The product is normally intended for once-a-month administration only. Subsequent studies included using 3X daily from mating to one week before weaning and demonstrated no effects on the pregnant females or their litters. A second study where pregnant females were dosed once at 3X the monthly use rate either 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, given greatly exaggerated oral doses of milbemycin oxime (9.6 mg/kg = 19X) exhibited signs typified by 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 given the recommended dose of milbemycin oxime (0.5 mg/kg). This product has not been tested in dogs less than 2.2 pounds in body weight.

A rising-dose safety study conducted in rough-coated collies manifested a clinical reaction consisting of ataxia, pyrexia and periodic recumbency in one of fourteen dogs treated with milbemycin oxime at 12.5 mg/kg (25X monthly use rate). Prior to receiving the 12.5 mg/kg dose (25X monthly use rate) on day 56 of the study, all animals had undergone an exaggerated dosing regimen consisting of 2.5 mg/kg milbemycin oxime (5X monthly use rate) on day 0, followed by 5.0 mg/kg (10X monthly use rate) on day 14 and 10.0 mg/kg (20X monthly use rate) on day 32. No adverse reactions were observed in any of the collies treated with this regimen up through the 10.0 mg/kg (20X monthly use rate) dose.

Safety: Lufenuron
Lufenuron tablets have been used and tested safely in over forty breeds of dogs, including pregnant females, breeding males and puppies over six weeks of age. In well-controlled clinical trials, 151 dogs completed treatment with lufenuron tablets. Lufenuron tablets were used safely in animals receiving frequently used veterinary products such as vaccines, anthelmintics, antibiotics and steroids. In a ten-month study, doses up to 10X the recommended dose rate of 10 mg/kg caused no overt toxicity. A single dose of 200 mg/kg (20X the recommended dose rate) had no marked effect on adult dogs, but caused decreased activity and appetite in eight week old puppies. Mean body weights of male and female puppies were higher in treated versus control group at the end of the study. In specifically designed target animal safety studies, lufenuron tablets were tested 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.

Four reproductive safety studies were conducted in breeding dogs with lufenuron tablets: two laboratory and two well-controlled clinical studies. In one of the laboratory studies, where lufenuron was administered to beagle dogs at doses equivalent to 90X (3X daily) the monthly recommended dose of 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 treated versus control groups and the mean birth weights of pups from treated females in this study was lower than control groups.

These pups grew at a similar rate to control pups. There was a higher incidence of four clinical signs in the lufenuron-treated versus control group: nasal discharge, pulmonary congestion, diarrhea/dehydration and sluggishness. 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 clinical 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 5X the recommended monthly use rate.

Data from analysis of milk from lactating animals treated with lufenuron tablets at 2X and 6X the recommended monthly use rate demonstrates that lufenuron concentrates in the milk of these dogs. 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.

Dosage
SENTINEL FLAVOR TABS are given orally, once a month, at the recommended minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime and 4.55 mg/lb (10mg/kg) lufenuron. Dogs over 100 lbs are provided the appropriate combination of tablets.

Administration
TO ENSURE ADEQUATE ABSORPTION,
ALWAYS ADMINISTER **SENTINEL FLAVOR TABS** TO DOGS
IMMEDIATELY AFTER OR IN CONJUNCTION WITH A NORMAL MEAL.

SENTINEL FLAVOR TABS are palatable and most dogs will consume the tablet when offered by the owner. As an alternative to direct dosing, the tablets can be hidden in food. Be certain the dog consumes the entire tablet or tablets. Administer SENTINEL FLAVOR TABS to dogs immediately after or in conjunction with a normal meal. Food is essential for adequate absorption of lufenuron. Watch the dog closely following administration to be sure the entire dose has been consumed. If it is not entirely consumed, redose with the full recommended dose as soon as possible.

Recommended Dosage Schedule

Body Weight	Milbemycin Oxime Per Tablet	Lufenuron Per Tablet
2 to 10 lbs.	2.3 mg	46 mg
11 to 25 lbs.	5.75 mg	115 mg
26 to 50 lbs.	11.5 mg	230 mg
51 to 100 lbs.	23 mg	460 mg

SENTINEL FLAVOR TABS must be administered monthly, preferably on the same date each month. Treatment with SENTINEL FLAVOR TABS may begin at any time of year. In geographic areas where mosquitoes and fleas are seasonal, the treatment schedule should begin one month prior to the expected onset and should continue until the end of "mosquito and flea season." In areas with year-round infestations, treatment should continue through the entire year without interruption.

If a dose is missed and a 30-day interval between dosing is exceeded, administer SENTINEL FLAVOR TABS immediately and resume the monthly dosing schedule. If SENTINEL FLAVOR TABS replace daily diethylcarbamazine (DEC) for heartworm prevention, the first dose must be given within 30 days after the last dose of DEC.

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

To report suspected adverse drug events, contact Virbac at 1-800-338-3659.
For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

How Supplied
SENTINEL FLAVOR TABS are available in four tablet sizes (see Dosage section) formulated according to the weight of the dog. Each tablet size is available in color-coded packages of 6 or 12 tablets each, which are packaged 10 per display carton.

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

Questions? Comments?
Please Call 1-800-338-3659
Visit our website at us.virbac.com

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10/17