Date of Approval: September 28, 2017

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-333

SENTINEL® SPECTRUM®

milbemycin oxime, lufenuron, praziquantel

Chewable Tablets

Dog

This supplement provides for the addition of the treatment and control of adult tapeworm (*Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

Sponsored by:

Virbac AH, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-333

B. Sponsor

Virbac AH, Inc.
3200 Meacham Blvd.
Ft. Worth, TX 76137

Drug Labeler Code: 051311

C. Proprietary Name

SENTINEL® SPECTRUM®

D. Product Established Name

Milbemycin oxime, lufenuron, praziquantel

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablets

G. Amount of Active Ingredient

Each chewable tablet contains:

2.3 mg milbemycin oxime/46 mg lufenuron/22.8 mg praziquantel
5.75 mg milbemycin oxime/115 mg lufenuron/57 mg praziquantel
11.5 mg milbemycin oxime/230 mg lufenuron/114 mg praziquantel
23.0 mg milbemycin oxime/460 mg lufenuron/228 mg praziquantel

H. How Supplied

SENTINEL SPECTRUM is available in four strengths, formulated according to the weight of the dog. Each strength is available in color-coded packages of six or twelve chewable tablets each.

I. Dispensing Status

Rx

J. Dosage Regimen

SENTINEL SPECTRUM 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.

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 to dogs immediately after or in conjunction with a normal meal.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indications

SENTINEL SPECTRUM is 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.

N. Effect of Supplement

This supplement provides for the addition of the treatment and control of adult tapeworm (*Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-333 dated December 8, 2011, contains a summary of dosage characterization information for dogs.

B. Substantial Evidence

For the Treatment and Control of the Gastrointestinal Cestode *Dipylidium caninum*:

1. Laboratory Dose Confirmation and Non-Interference Study NAH-02-0032

Title: Efficacy Evaluation of Flavored Combination Parasiticide Tablets for the Removal of Natural *Dipylidium caninum* (Tapeworm) Infections in Dogs.

Study Dates: August 15, 2002 – June 19, 2005

Study Location: Bloemfontein, South Africa

Study Design:

Objectives: The objectives of the study were to evaluate the effectiveness of a milbemycin oxime/lufenuron/praziquantel combination tablet (non-final formulation) against naturally-acquired adult tapeworm (*D. caninum*) infections in dogs when administered orally; demonstrate that milbemycin oxime and lufenuron does not interfere with the effectiveness of praziquantel against *D. caninum;* and justify the inclusion of praziquantel into the combination.

The study was conducted using the principles of Good Clinical Practices (GCP).

Study Animals: Twenty-nine adult dogs (11 males and 18 females) weighing between 11.2 and 46.9 pounds (5.1 and 21.3 kg) and harboring naturally acquired *D. caninum* infections were included in the study.

Treatment Groups:

Table 1: Study NAH-02-0032 Treatment Groups

Treatment Group	Milbemycin oxime Dose	Lufenuron Dose	Praziquantel Dose
Milbemycin oxime, lufenuron, praziquantel	0.5 mg/kg	10 mg/kg	5 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg	0 mg/kg
Milbemycin oxime, lufenuron tablets	0.5 mg/kg	10 mg/kg	0 mg/kg

Drug Administration: The test and control articles were administered, according to Table 1, once on Day 0, within 30 minutes following ingestion of a meal after an overnight fast. All dogs received the appropriately-sized tablet for the intended weight range for each tablet strength. The actual praziquantel doses ranged from 5.3 mg/kg to 11.2 mg/kg.

Measurements and Observations: All dogs were determined to be healthy, with the exception of *D. caninum* infections confirmed by fecal examination, prior to initiation of the study. All dogs were determined to be heartworm negative prior to Day 0. On Day 0, all dogs were observed hourly for six hours post-dosing, then at 8, 10, 12, 18, and 24 hours for evidence of adverse events. Daily observations of general health continued throughout the study. On Day 12, the dogs were euthanized and necropsied for *D. caninum* recovery and enumeration.

Statistical Methods:

Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group as compared to the control. Geometric means of tapeworm counts were calculated.

Percent Effectiveness = $100 \times [(c_C - c_t)/c_C)]$

Where: c_C = Geometric mean number of worms in the control group
c_t = Geometric mean number of worms in the treatment group

Statistical significance was assessed using Analysis of Variance (ANOVA; SAS PROC MIXED) of logarithmically transformed worm counts at necropsy. Treatment, sex and the treatment-by-sex interaction were included as classification variables in the ANOVA. Study phase was included as a random effect.

Results:

Adequate infection was demonstrated in the control group with six of the nine control dogs, on necropsy, harboring greater than 2 tapeworms. Treatment with milbemycin oxime, lufenuron, praziquantel tablets was 100% effective against naturally-acquired adult *D. caninum* tapeworm infections in dogs (Table 2). The difference in the number of *D. caninum*

recovered between the treated and control groups was statistically significant (p = 0.0018).

Table 2: Study NAH-02-0032 Results

Treatment Group	Number of Dogs	Geometric Mean of *D. caninum* Recovered (range)	Percent Effectiveness
Milbemycin oxime, lufenuron, praziquantel tablets	10	0.0 (NA)	100%
Control	9	13.6 (0-315)	NA
Milbemycin oxime, lufenuron tablets	10	10.0 (1-102)	26.7%

NA=Not applicable

Adverse Reactions:

Diarrhea was reported during the study. Diarrhea was observed in two dogs in the control group and four dogs in the milbemycin oxime, lufenuron, praziquantel tablet group, including one dog with bloody stool noted on Day 6. None of the dogs required treatment.

Conclusion:

This study demonstrates that a single dose of milbemycin oxime, lufenuron, praziquantel tablets is effective against naturally-acquired adult *D. caninum* infections in dogs. The addition of milbemycin oxime and lufenuron does not interfere with the effectiveness of praziquantel against *D. caninum* and justifies the inclusion of praziquantel into the combination.

The results of a pharmacokinetics (PK) bridging study (NAH-09-0015) (refer to the Freedom of Information (FOI) Summary for the original approval of NADA 141-333, dated December 8, 2011) allow for a bridge from the milbemycin oxime, lufenuron, praziquantel tablet formulation used in this study to the final chewable formulation.

Therefore, based on the results of this study and those of the PK bridging study (NAH-09-0015), SENTINEL® SPECTRUM® is effective against *D. caninum* infections in dogs. Diarrhea should be considered a potential adverse reaction.

2. Laboratory Dose Confirmation Study NAH-14-093

Title: Experimental Study to Evaluate the Efficacy of SENTINEL® SPECTRUM® for Treatment and Control of *Dipylidium caninum* in Dogs.

Study Dates: September 9, 2015- May 27, 2016

Study Location: Bloemfontein, South Africa

Study Design:

Objective: The objective of the study was to evaluate the effectiveness of SENTINEL® SPECTRUM® against experimentally-induced adult *D. caninum* infections in dogs when administered orally.

This study was conducted using principles of OECD Good Laboratory Principles (GLP).

Study Animals:

Sixteen dogs (11 male and 5 female) between 11 and 23 months of age and weighing between 26.5 and 47.7 pounds (11.5 and 21.7 kg) were included in the study.

The dogs were confirmed to be negative for intestinal parasites during acclimation. The dogs were experimentally infested with topical application of fleas infected with United States (US)-derived *D. caninum* on Days 0, 7, 13, 21, 26, 35, 42, 48 and 55. Dogs were also dosed orally with *D. caninum* infected fleas on Days 0, 14, 27, and 56.

Treatment Groups:

Table 3: Study NAH-14-093 Treatment Groups

Treatment Group	Milbemycin oxime Dose	Lufenuron Dose	Praziquantel Dose
SENTINEL® SPECTRUM®	0.5 mg/kg	10 mg/kg	5 mg/kg
Control (untreated)	0 mg/kg	0 mg/kg	0 mg/kg

Drug Administration: The test article was administered, according to Table 3, once on Day 82, within 30 minutes following ingestion of a meal after an overnight fast. Using a combination of tablet strengths, the dogs were dosed at a minimum target praziquantel dose of 5 mg/kg (2.28 mg/lb). The actual praziquantel doses ranged from 5.0 to 5.4 mg/kg.

Measurements and Observations: All dogs were determined to be healthy with negative fecal examination prior to initiation of the study. All dogs were determined to be heartworm negative prior to Day 82. On Day 82, all dogs were observed hourly for four hours after dose administration for evidence of adverse events. Daily observations of general health occurred throughout the study. On Day 92, the dogs were euthanized and necropsied for *D. caninum* recovery and enumeration.

Statistical Methods:

Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group as compared to the control group. Geometric means of tapeworm counts were calculated.

Percent Effectiveness = $100 \times [(c_C - c_t)/c_C)]$

Where: c_C = Geometric mean number of worms in the control group
c_t = Geometric mean number of worms in the treatment group

Statistical significance was assessed using Analysis of Variance (ANOVA; SAS PROC MIXED) of logarithmically transformed worm counts at necropsy with treatment group as a fixed effect.

Results:

Adequate infection was demonstrated in the control group with all eight control dogs, on necropsy, harboring greater than 5 tapeworms. Treatment with SENTINEL® SPECTRUM® was 100% effective against adult *D. caninum* tapeworms in experimentally-infected dogs (Table 4). The difference in the number of *D. caninum* recovered between the treated and control groups were statistically significant ($p < 0.0001$).

Table 4: Study NAH-14-093 Results

Treatment Group	Number of Dogs	Geometric mean of *D. caninum* recovered	Percent Effectiveness
SENTINEL® SPECTRUM®	8	0.0 (NA)	100%
Control (untreated)	8	30.7 (8-124)	NA

NA=Not applicable

Adverse Reactions:

Vomiting was observed in one dog, several hours after receiving SENTINEL® SPECTRUM®. No treatment was needed.

Conclusion:

SENTINEL® SPECTRUM®, when used at a minimum praziquantel dose of 5 mg/kg (2.28 mg/lb), is effective against *D. caninum* infections in dogs. Vomiting should be considered a potential adverse reaction.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-333 dated December 8, 2011, contains a summary of target animal safety studies for use in dogs.

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to SENTINEL® SPECTRUM®:

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

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that SENTINEL® SPECTRUM®, when used according to the label, is safe and effective for the treatment and control of adult tapeworm (*Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because the product is indicated for the prevention of heartworm infections (*Dirofilaria immitis*) in dogs, which requires veterinary examination and testing to ensure dogs are negative for adult heartworm disease prior to administration of the product.

B. Exclusivity

This supplemental approval for SENTINEL® SPECTRUM® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the treatment and control of adult tapeworm (*Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.