Approval Date: June 17, 1998

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 141-084

B. Sponsor

Novartis Animal Health US, Inc.
Post Office Box 26402
Greensboro, NC 27404

C. Proprietary Name

Sentinel™ Flavor Tablets®

D. Established Name

milbemycin oxime/lufenuron tablets

E. Dosage Form

Tablet

F. Dispensing Status

Rx

G. Route of Administration

Oral

H. Recommended 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 and 4.55 mg/lb (10 mg/kg) lufenuron.

Recommended Dosage Schedule

Body Weight	Milbemycin Oxime per Tablet	Lufenuron per Tablet	Product
2 - 10 lbs.	2.3 mg	46 mg	SENTINEL
11 – 25 lbs.	5.75 mg	115 mg	SENTINEL Flavor Tabs
26 - 50 lbs.	11.5 mg	230 mg	SENTINEL Flavor Tabs
51 – 100 lbs.	23.0 mg	460 mg	SENTINEL Flavor Tabs

Dogs over 100 lbs. are provided the appropriate combination of tablets.

I. Species/Class

Dogs

J. Indication

SENTINEL Flavor Tabs are indicated for use in dogs and puppies four weeks of age and older and eleven pounds body weight or greater, 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*, *Toxascaris leonina* (roundworm) and *Trichuris vulpis* (whipworm) infections.

K. Effect of Supplement

Approval of this supplemental NADA will change NADA 141-084 by adding a flavored tablet formulation with the same indications. The flavored tablets (in three tablet sizes) will replace the swallow tablets for dogs $\geq$ 11 pounds. The swallow tablet will remain for dogs between 2-10 lbs.

II. EFFECTIVENESS

The effectiveness of SENTINEL Flavor Tabs is based upon existing Novartis product approvals for milbemycin oxime (INTERCEPTOR® Tablets, NADA 140-915) and lufenuron (PROGRAM® Tablets, NADA 141-035), the combination product (SENTINEL tablets NADA 141-084), and the following study comparing SENTINEL tablets and SENTINEL Flavor Tabs.

A. Hookworm Efficacy Study with Flavored Tablet

Purpose: SENTINEL tablets and SENTINEL Flavor Tabs were compared for efficacy against hookworms (*Ancylostoma caninum*).

Investigator:

Dwight Bowman, Ph.D.
Study Location:
CHK - R&D
Stanwood, Michigan

Type of Study: Natural infections of hookworms Ancylostoma caninum.

Animals: Thirty adult dogs (15 males, 15 females) were divided into three groups of ten dogs each.

Dosage Forms:

- Group 1: Placebo Tablets
- Group 2: SENTINEL (milbemycin oxime/lufenuron) tablets
- Group 3: SENTINEL Flavor Tabs (milbemycin oxime/lufenuron)

Route of Administration: Oral

Dose Tested:

Milbemycin Oxime 0.5 mg/kg
Lufenuron 10 mg/kg

Frequency of Treatment: One treatment.

Controls: Placebo control (group 1)

Duration of Study: The dogs were euthanized 9 days after treatment and worms were recovered, identified and counted.

Results: Efficacy was calculated by comparing the number of worms recovered from each of the two treatment groups versus control animals. The following table shows the mean (geometric) number of worms recovered and the percent efficacy for each group.

Treatment	**Mean # of Worms**	**% Efficacy**
Placebo	14.4	---
SENTINEL	0.0	100
SENTINEL Flavor Tabs	0.07	99.5

Using Wilcoxon Rank Sum Tests, the comparisons of Placebo versus SENTINEL FLAVOR TABS ($p < .0001$), Placebo versus SENTINEL ($p < .0001$), and SENTINEL FLAVOR TABS versus SENTINEL ($p = .3681$) indicated that both SENTINEL FLAVOR TABS and SENTINEL tablets were significantly different from Placebo tablets and were not different from one another. Both SENTINEL FLAVOR TABS and SENTINEL tablets were ³ 99.5% effective in eliminating hookworms from infected dogs when compared to Placebo tablets. There was no difference in effectiveness between SENTINEL FLAVOR TABS- and SENTINEL-treated dogs.

Conclusions: The flavored tablet formulation was equally efficacious as the non-flavored tablet formulation against Ancylostoma caninum infections.

Adverse Reactions: None reported.

B. Clinical Palatability/Acceptability Trial

Purpose: To assess the palatability/acceptability of SENTINEL Flavor Tabs in a clinical trial

Investigator/Study Locations:

Dr. Charles Ward
The Animal Hospital
112 W. Main
Carrboro, NC 27510

Dr. Benjamin Jones
Friendly Animal Clinic
712 Guilford College Rd.
Greensboro, NC 27410

Dr. Pat Cryan
Cryan Veterinary Hospital
298 N. West Street
Westerville, OH 43081

Dr. Robert Cape
Greene Meadows Veterinary Hospital
127 Greene Meadows Dr. South
Westerville, OH 43081

Dr. Jodi Black
Best Friends Veterinary Service
1328 Hwy. 65
Eckert, CO 81418

Dr. Mark Leavell
Radford Hills Animal Clinic
1109 N. Judge Ely
Abilene, TX 79601

Dr. Jerry Greene
Academe Animal Hospital
912 East Fletcher Avenue
Tampa, FL 33612

Dr. Todd Henderson
San Angelo Veterinary Hospital
108 N. Milton
San Angelo, TX 76901

Dr. Leonard Sigdestad
Loma Linda Animal Hosp.
2605 S. Waterman Ave.
San Bernardino, CA 92408

Type of Study: Palatability/Acceptability

Animals: Two hundred twenty-five client-owned dogs were enrolled in the study, though only 223 were dosed. One dog was found to be heartworm positive and one dog was hit by a car and killed prior to dosing. Fifteen dogs were dosed with the drug and completed the study but were excluded from analysis for the following reasons: owner non-compliance (4) or use of concomitant drugs that could potentially affect appetite (11). A total of 208 dogs (109 F, 99 M) ranging in age from 2 months to 13 years and in weight from 2 to 100 pounds were included in the analysis of palatability/acceptability.

Dosage Forms:

SENTINEL Flavor Tabs (Milbemycin Oxime/Lufenuron)

Route of Administration: Oral

Dose Tested:

Milbemycin Oxime 0.5 mg/kg
Lufenuron 10 mg/kg

Frequency of Treatment: One dose

Controls: None

Duration of Study: Dogs were offered the tablets by hand and palatability/ acceptability was assessed within 3 minutes. If the dogs did not consume the tablets within this period, the owners were instructed to place the tablets in the food bowl and wait an additional 3 minutes. If this was unsuccessful, the tablets were placed in the dogs' mouths followed by direct manually dosing, if necessary.

Results: Results are displayed in the following table.

Absolute and Cumulative responses provided by Owners.

Question	#Yes	%	Cum. N	Cum %
1 Consumed the tablet when offered from the hand	173	83.0%	--	--
2 Consumed the tablet when offered from food bowl	7	3.4%	180	86.5%
3 Consumed the tablet when placed in dogs mouth	13	6.3%	193	92.8%
Accepted the tablet when attempted to "pill" the dog	12	5.8%	5.8%	98.6%
Refused the tablet	3	1.4%	208	100%

Conclusions: SENTINEL Flavor Tabs are palatable to dogs.

Adverse Reactions: None reported.

III. TARGET ANIMAL SAFETY

The safety of SENTINEL Flavor Tabs is based upon existing Novartis product approvals for milbemycin oxime (INTERCEPTOR® Tablets, NADA 140-915), lufenuron (PROGRAM® Tablets, NADA 141-035), and the combination product (SENTINEL tablets NADA 141-084).

IV. HUMAN FOOD SAFETY

Data on human safety, pertaining to consumption of drug residues in food, were not required for approval of this NADA. This drug is to be labeled for use in dogs which are non-food animals.

V. AGENCY CONCLUSIONS

The data in support of this NADA comply with the requirements of Section 512 of the Act and Section 514 of the Implementing regulations. The data demonstrate that SENTINEL Flavor Tabs (milbemycin oxime/lufenuron), when used under labeled conditions of use are safe and effective.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is judged to be critical for the diagnosis of heartworms, whipworms and hookworms and for the safe use of the product.

Under section 512(c)(2)(F)(iii) of the Federal Food,Drug and Cosmetic Act, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains substantial evidence of the effectiveness of the drug involved, or any studies of animal safety, required for the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to the new flavored formulation in three tablet sizes for which the supplemental application was approved.

Patent # 4,547,520 expires on June 14, 2004

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.