Date of Approval: June 16, 2012

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-338

INTERCEPTOR SPECTRUM

milbemycin oxime/praziquantel

Chewable Tablets

Dogs

INTERCEPTOR SPECTRUM is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of adult roundworm *(Toxocara canis, Toxascaris leonina)*, adult hookworm *(Ancylostoma caninum)*, adult whipworm *(Trichuris vulpis),* and adult tapeworm *(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.

Sponsored by:

Novartis Animal Health US, Inc.

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I. GENERAL INFORMATION:

A. File Number: NADA 141-338

B. Sponsor: Novartis Animal Health US, Inc.
3200 Northline Ave., suite 300
Greensboro, NC 27408

Drug Labeler Code: 058198

C. Proprietary Name: INTERCEPTOR SPECTRUM

D. Established Name: Milbemycin oxime/praziquantel

E. Pharmacological Category: Antiparasitic

F. Dosage Form: Chewable Tablets

G. Amount of Active Ingredients: Each chewable tablet contains:

2.3 mg milbemycin oxime/22.8 mg praziquantel
5.75 mg milbemycin oxime/57 mg praziquantel
11.5 mg milbemycin oxime/114 mg praziquantel
23 mg milbemycin oxime/228 mg praziquantel

H. How Supplied: INTERCEPTOR SPECTRUM is available in four strengths, in packages of one, six, or twelve chewable tablets each, according to the weight of the dog, as listed below:

2.3 mg milbemycin oxime/22.8 mg praziquantel
5.75 mg milbemycin oxime/57 mg praziquantel
11.5 mg milbemycin oxime/114 mg praziquantel
23 mg milbemycin oxime/228 mg praziquantel

I. How Dispensed: Rx

J. Dosage(s): INTERCEPTOR SPECTRUM is given orally, once a month, at the minimum dosage of 0.23 mg/pound (0.5 mg/kg) body weight of milbemycin oxime and 2.28 mg/pound (5 mg/kg) of praziquantel. For heartworm prevention, give once monthly beginning within 1 month of the dog's first seasonal exposure to mosquitoes and continue until at least 6 months after the dog's last seasonal exposure.

Dosage Schedule

Body Weight	Milbemycin Oxime Per chewable	Praziquantel Per chewable	Number of chewables
2 to 8 lbs.	2.3 mg	22.8 mg	One
8.1 to 25 lbs.	5.75 mg	57 mg	One
25.1 to 50 lbs.	11.5 mg	114 mg	One
50.1 to 100 lbs.	23 mg	228 mg	One
Over 100 lbs.	Administer the appropriate combination of chewables		

K. Route of Administration Oral

L. Species: Dogs

M. Indications: INTERCEPTOR SPECTRUM is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of adult roundworm *(Toxocara canis, Toxascaris leonina)*, adult hookworm *(Ancylostoma caninum)*, adult whipworm *(Trichuris vulpis),* and adult tapeworm *(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.

II. EFFECTIVENESS:

A. Dosage Characterization:

The dose of milbemycin oxime necessary for the prevention of heartworm (*Dirofilaria immitis*) disease and adult hookworm (*Ancylostoma caninum*), roundworm (*Toxocara canis*, *Toxascaris leonina*), and whipworm (*Trichuris vulpis*) infections in dogs was determined to be 0.5 mg/kg body weight under *INTERCEPTOR Flavor Tabs (NADA 140-915; milbemycin oxime; Novartis Animal Health US, Inc.) and SENTINEL Flavor Tabs (NADA 141-084; milbemycin oxime/lufenuron; Novartis Animal Health US, Inc.).*

The dose of praziquantel necessary for the treatment of adult tapeworm (*Taenia pisiformis, Echinococcus multilocularis, Echinococcus granulosus*) in dogs has been well-documented in published literature.[1,2]

A 6-consecutive monthly dosing regime was selected for effectiveness studies against *D. immitis* infections. In well-controlled laboratory studies, neither one dose nor two consecutive monthly doses of INTERCEPTOR SPECTRUM provided 100% effectiveness against induced heartworm infections.

B. Substantial Evidence:

For the prevention of Heartworm Disease:

1. Laboratory Dose Confirmation Study NAH-10-0008

a. Title: Pivotal Efficacy Study of an INTERCEPTOR SPECTRUM Chewable Formulation Administered for Six Consecutive Months for the Prevention of Adult Heartworm Disease Following a Laboratory Infection with *Dirofilaria immitis* (*D. immitis*) in Dogs

b. Investigator: John McCall, PhD
Athens, Georgia

[1] Thomas H, Gönnert R. 1978. The Efficacy of Praziquantel Against Cestodes in Cats, Dogs and Sheep. Res Vet Sci 24(1): 20-5.
[2] Anderson FL, Crellin JR, and Cox DD. 1981. Efficacy of Praziquantel Against Immature *Echinococcus multilocularis* in Dogs and Cats. Am J Vet Res 42(11): 1978-9.

c. Study Design: This study was conducted using principles of Good Clinical Practice (GCP).

1. Objective: Confirm the dose of INTERCEPTOR SPECTRUM Chewables and evaluate the prevention of adult heartworm (*Dirofilaria immitis*) in dogs experimentally infected with larval heartworms.

2. Study Animals: Eighteen purpose-bred Beagles from 20 to 23 weeks of age at the start of acclimation and weighing between 6.4 and 8.8 kilograms (kgs) were included in the study.

3. Treatment Groups: One control (multi-vitamin tablet) group of 9 dogs (5 females and 4 males) and one INTERCEPTOR SPECTRUM-treated group of 9 dogs (4 females and 5 males) were treated on Study Days 0, 30, 60, 90, 120, and 150.

4. Drug Administration: INTERCEPTOR SPECTRUM was administered within 40 minutes of ingestion of food after an overnight fast to provide a milbemycin oxime dose of 0.23 – 0.34 mg/lb (0.50 – 0.74 mg/kg) based on body weights obtained 1 to 3 days prior to each dosing.

5. Measurements and Observations: On Study Day -30, all dogs were inoculated with 50 third stage *D. immitis* larvae. Adult heartworm counts were obtained at necropsy on Study Day 180. The general health of each dog was observed at least twice daily. Dogs were observed for vomiting at 10 minutes post-dosing. Clinical observations made by a trained veterinarian were performed on each dog at 1, 2, 8, and 24 hours post-treatment. Body weights were obtained pre-treatment, and on Study Days -3, 28, 59, 89, 119, 147, and 179.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in heartworm counts in the treated group compared to the control group.

   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

   Worm counts were logarithmically transformed and an analysis of variance (ANOVA) was performed for the treatment comparisons of interest.

d. Results: The geometric means and calculated effectiveness for each group are presented in Table 1 below:

Table 1. Study NAH-10-0008 Results

Treatment	Geometric Mean *D. immitis* Worm Count (Range)	% Effectiveness	p-value
INTERCEPTOR SPECTRUM	0.0 (NA)	100.0	p<0.0001
Control (6 doses)	40.9 (36-46)	NA	p<0.0001

NA = not applicable.

Statistically significant differences in the log (count+1) existed between the treated group and the control group in favor of the treated group (p<0.0001). A minimum of five adult worms was considered to be adequate infection and a minimum of six adequately infected control dogs was required for the study to be considered valid.

e. Adverse Reactions: No adverse reactions related to the administration of INTERCEPTOR SPECTRUM were reported.

f. Body Weight: The mean body weight on Study Days 147 and 179 was significantly higher in the INTERCEPTOR SPECTRUM group than the control group. As the control group was untreated after the induced infection with L_3 *D. immitis* larvae, the difference in weight was likely due to the progression of heartworm disease.

g. Conclusions: INTERCEPTOR SPECTRUM is 100% effective against experimental infection with *Dirofilaria immitis* when administered once per month for 6 consecutive months after laboratory infection.

For the Treatment and Control of Gastrointestinal Nematodes and Cestodes:

1. Laboratory Dose Confirmation and Non-Interference Study NAH-02-0042

a. Study Title: Pivotal Study to Evaluate INTERCEPTOR PLUS[3] (milbemycin oxime and praziquantel) Chewables for the Removal of Naturally Acquired *Ancylostoma caninum* Infections in Dogs

b. Investigator: David R. Young, DVM, PhD
Turlock, California

c. Study Design: This study was conducted using principles of Good Laboratory Practice (GLP).

1. Objective: Confirm the established minimum recommended dose of 0.5 mg/kg milbemycin oxime and evaluate the effectiveness of a milbemycin oxime and praziquantel combination against naturally-acquired adult hookworm (*A. caninum)* infections in dogs when administered monthly.

2. Study Animals: Twenty-four dogs between 5.6 and 49.6 months of age, weighing between 11.2 and 36.7 kg (24.6 and 80.8 lbs), and

[3] INTERCEPTOR PLUS contains the same active ingredients in the same concentrations as INTERCEPTOR SPECTRUM. The proprietary name was changed during product development.

harboring naturally-acquired *A. caninum* infections, were included in the study.

3. Treatment Groups:

Table 2. Study NAH-02-0042 Treatment Groups (8 dogs per group)

Treatment	Milbemycin oxime Dose	Praziquantel Dose
INTERCEPTOR SPECTRUM	0.5 mg/kg	5 mg/kg
Control (untreated)	0 mg/kg	0 mg/kg
Praziquantel tablets	0 mg/kg	5 mg/kg

4. Drug Administration: Treatments were administered once on Study Day 0 according to Table 2, within 30 minutes of ingestion of a meal after an overnight fast, based on body weights obtained on Study Day -1.

5. Measurements and Observations**:** During acclimation, the presence of *A. caninum* eggs in the dogs was documented. On Study Day 0, all dogs were observed hourly for six hours post-dosing, then at 8, 10, 12, 18, and 24 hours for evidence of vomiting or other adverse events. Daily observation of general health status continued throughout the study. On Study Day 7, all dogs were euthanized and necropsied for *A. caninum* recovery and enumeration.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in hookworm counts in the treatment groups compared to the control group.

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

   Where: c_c = geometric mean number of parasites in the control group
   c_t = geometric mean number of parasites in the treatment group

   Worm counts were logarithmically transformed and an analysis of variance (ANOVA) was performed for the treatment comparisons of interest.

d. Results:
Tables 3 and 4 below summarize the study results:

Table 3. Study NAH-02-0042 Results

Treatment	Geometric Mean *A. caninum* worm Count	Percent Effectiveness
INTERCEPTOR SPECTRUM	0.4	99.6
Control	100.6	NA
Praziquantel tablets	86.3	14.3

Table 4. Study NAH-02-0042 Results

Treatment	vs. Treatment Group	p-value
INTERCEPTOR SPECTRUM	Control	<0.0001
INTERCEPTOR SPECTRUM	Praziquantel	<0.0001

e. Adverse Reactions: There were no reports of adverse reactions in dogs treated with INTERCEPTOR SPECTRUM.

f. Conclusions: INTERCEPTOR SPECTRUM is effective against naturally acquired adult hookworm (*A. caninum)* in dogs. Praziquantel alone is not effective against *A. caninum*. The addition of praziquantel to milbemycin oxime did not interfere with milbemycin oxime's effectiveness against *A. caninum.*

Note: Studies to confirm the milbemycin oxime dose necessary for the prevention of roundworm (Toxocara canis, Toxascaris leonina), and whipworm (Trichuris vulpis) infections in dogs were conducted for INTERCEPTOR Flavor Tabs (NADA 140-915; milbemycin oxime; Novartis Animal Health US, Inc.) and SENTINEL Flavor Tabs (NADA 141-084; milbemycin oxime/lufenuron; Novartis Animal Health US, Inc.). Therefore, only one study using the dose-limiting parasite (A. caninum) was necessary to demonstrate effectiveness against the gastrointestinal nematodes.

2. Laboratory Dose Confirmation Study NAH-02-0039

a. Title: Efficacy Evaluation of a 3-Way (Milbemycin oxime, Lufenuron, Praziquantel) and a 2-Way (Milbemycin oxime, Praziquantel) Chewable for the Removal of Experimentally Induced Adult *Echinococcus multilocularis* Infections in Dogs

b. Investigator: Zac Lloyd, BS
Mattawan, Michigan

c. Study Design: This study was conducted using principles of Good Laboratory Practice (GLP).

1. Objective: Confirm the dose of INTERCEPTOR SPECTRUM and evaluate the effectiveness in dogs experimentally infected with adult *Echinococcus multilocularis*.

2. Study Animals: Twenty (10 male and 10 female) Beagle dogs varying in age from 6 to 7 months and weighing 6.3 to 8.8 kg (14.0 to 19.4 lb) at randomization were included in the study.

3. Treatment Groups:

Table 5. Study NAH-02-0039 Treatment Groups (10 dogs per group)

Treatment	Milbemycin Dose	Praziquantel Dose
INTERCEPTOR SPECTRUM	0.5 mg/kg	5 mg/kg
Control (untreated)	0 mg/kg	0 mg/kg

4. Drug Administration: Test articles were administered, according to Table 5 above, once on Study Day 20 within 30 minutes following ingestion of a meal after an overnight fast. All dogs received the appropriately sized tablet intended for dogs 5.0 – 11.4 kg.

5. Measurements and Observations: On Study Day 0, all dogs were orally infected with approximately 103,360 *E. multilocularis* protoscolices. All dogs were observed at least twice daily for general observations. A detailed clinical examination was performed once pre-treatment, weekly during the study, and approximately every hour for six hours, and at 8, 10, 12, and 24 hours post-dosing on Study Day 20.

Complete physical examinations were conducted once prior to *E. multilocularis* administration, prior to administration of test or control articles, and prior to euthanasia. On Study Day 25, all dogs were euthanized and necropsied for *E. multilocularis* recovery and enumeration.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated groups compared to the control group.

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

   Where: c_c = geometric mean number of parasites in the control group
   c_t = geometric mean number of parasites in the treatment group

   Worm counts were logarithmically transformed and an analysis of variance (ANOVA) was performed for the treatment comparisons of interest. The model included the fixed effects of treatment, sex, and treatment by sex interaction, along with the random effect of block within sex. If the treatment by sex interaction was significant ($p<0.05$), the percent effectiveness and analysis of variance was performed separately for each gender.

d. Results:
Sex was not a significant factor in the ANOVA and the results were pooled over both sexes. Table 6 below summarizes the study results:

Table 6. Study NAH-02-0039 Results

Treatment	**Geometric Mean *E. multilocularis* Counts**	**Percent Effectiveness**	**p-value**
INTERCEPTOR SPECTRUM	0	100.0	<0.0001
Control	46823.1	NA	<0.0001

e. Adverse Reactions: Vomiting was reported in one dog treated with INTERCEPTOR SPECTRUM. The dog vomited twice between 8 and 12 hours post-dosing. Several dogs in both treatment groups were reported to have soft feces. None of the dogs required treatment.

f. Conclusions: INTERCEPTOR SPECTRUM is 100% effective against induced adult *E. multilocularis* infections in dogs.

3. Bioequivalence Study of Chewable and Tablet Formulations, NAH-10-0015

a. Title: A pivotal two-way cross-over bioequivalence trial comparing praziquantel in INTERCEPTOR SPECTRUM chewable and tablet (non-final) formulations in dogs under fasting conditions

b. Investigator: Larry E. Travis, BS
Fort Collins, Colorado

c. Study Design: This study was conducted using principles of Good Laboratory Practice (GLP).

1. Objective: The objective of the study was to determine if the praziquantel in a milbemycin oxime/praziquantel tablet formulation was bioequivalent to the praziquantel in the INTERCEPTOR SPECTRUM chewable formulation in healthy dogs under fasted conditions.

2. Study Animals: Twenty-four female Beagle dogs, 12 months of age or older at randomization and weighing 8.1 to 10.2 kg, were included in the study.

3. Treatment Groups:

Table 7. Study NAH-10-0015 Treatment Groups (12 dogs per group)

Treatment
INTERCEPTOR SPECTRUM on Day 0 / 7-day washout / milbemycin oxime, praziquantel tablet on Day 7
Milbemycin oxime, praziquantel tablet on Day 0 / 7-day washout / INTERCEPTOR SPECTRUM on Day 7

4. Drug Administration: Test articles were administered as outlined in Table 7 above after an overnight fast. Each dog was administered one milbemycin oxime/praziquantel tablet or one INTERCEPTOR SPECTRUM chewable tablet containing 57 mg praziquantel.

5. Measurements and Observations**:**

Plasma concentrations of Praziquantel

Praziquantel was assayed in the collected dog plasma samples by a liquid chromatography/mass spectrophotometry/mass spectrophotometry (LC/MS/MS) method that was previously validated at PPD Laboratories, Middleton, WI.

Safety

General health observations were conducted once daily for all dogs. On Study Days 0 and 7, clinical observations were conducted prior to dosing and at 10, 20, and 30 minutes, then 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dosing for evidence of vomiting or rejection of the tablet or chewable.

d. Results:

Table 8. Study NAH-10-0015 Results

Variable	INTERCEPTOR SPECTRUM	Milbemycin oxime and praziquantel tablet	Bioavailability[§] (%)		Comparison p-value
			Ratio	90% CI	
$AUC_{(0-t)}$ (ng/mL·h)[†]	887	719	123	116.2-131.3	<0.0001
C_{max} (ng/mL)[†]	602	326	185	160.1-213.0	<0.0001
T_{max} (h)^	1	1	NA	NA	0.9938

[†]Geometric Mean, [§]Ratio test over reference, ^Median, NA=not applicable

e. Adverse Reactions: There were no adverse reactions reported during the study.

f. Conclusions: The results of this study demonstrate that the praziquantel in INTERCEPTOR SPECTRUM is more bioavailable than the praziquantel in the milbemycin oxime and praziquantel tablet formulation. The higher bioavailability of praziquantel in the chewable formulation does not produce a significant safety concern. Additionally, the results of this study allow for a bridge to the results of the tapeworm studies (*E. granulosus*, *E. multilocularis*, and *T. pisiformis*) conducted with the milbemycin oxime/praziquantel tablet formulation (Studies NAH-01-0014 and NAH-01-0022; NAH 01-0015 and NAH-01-0021; NAH-01-0019 and NAH-01-0065; respectively).

4. Laboratory Dose Confirmation and Non-Interference Study NAH-01-0017

a. Title: Efficacy Evaluation of 2 Way and 3 Way Flavored, Combination Parasiticide Tablets for the Removal of Naturally Acquired *A. caninum* (Hookworm) Infections in Dogs.

b. Investigator: Dwight Bowman, PhD
Stanwood, MI

c. Study Design:

1. Purpose: Confirm the established minimum recommended dose of 0.5 mg/kg milbemycin oxime, when administered with praziquantel in a two-way combination tablet, to remove naturally acquired *A. caninum* (hookworms) in dogs.

2. Study Animals: Thirty random source adult dogs (11 males and 19 females), weighing between 23.7 pounds (10.8 kg) and 91.5 pounds (41.6 kg) at the time of treatment, were used in this study.

3. Treatment Groups:

Table 9. Study NAH-01-0017 Treatment Groups (10 dogs per group)

Treatment	Dose of milbemycin	Dose of praziquantel
Milbemycin oxime/ praziquantel tablets	0.5 mg/kg	5 mg/kg
Praziquantel	0 mg/kg	5 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg

4. Drug Administration: Dogs were dosed once on Study Day 0 within 30 minutes of a full meal, according to Table 9 above.

5. Measurements and Observations: All dogs were determined to be healthy with the exception of *A. caninum* infections confirmed by fecal examination prior to initiation of the study. All dogs were determined to be heartworm negative by antigen test prior to administration of test article. Dogs were sacrificed on Study Day 7 and intestines inspected for the presence of adult *A. caninum* worms.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in hookworm counts in the treated group compared to the control group.

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

Worm counts were logarithmically transformed and a mixed model analysis of variance was performed for the treatment comparison of interest.

d. Results:

Table 10. Study NAH-01-0017 Results

Treatment Group	Geometric Mean A. caninum counts	% Effectiveness
Milbemycin oxime /praziquantel tablets	0.0[a]	100
Praziquantel	20.2	-8.3
Control	18.7	NA

[a] Significantly less than control and praziquantel means ($p < 0.0001$)

e. Adverse Reactions: No adverse reactions were reported.

f. Conclusions: A single dose of milbemycin oxime/praziquantel tablets is effective for the removal of adult *A. caninum* worms in dogs. The addition of praziquantel to milbemycin oxime did not interfere with the effectiveness of milbemycin oxime to remove *A. caninum.*

5. Laboratory Dose Confirmation Study NAH-01-0014

a. Title: Efficacy Evaluation of Flavored Combination Parasiticide Tablets For the Removal of Experimentally Induced Adult *Echinococcus granulosus* Infections in Dogs

b. Investigator: C. Steven Godin, PhD, DABT
Mattawan, MI

c. Study Design:

1. Objective: Confirm the established minimum recommended dose of 5 mg/kg praziquantel, when administered with milbemycin oxime in the two-way combination tablets, to remove adult *Echinococcus granulosus* in dogs.

2. Study Animals: A total of 20 purpose-bred Beagle dogs (10 males and 10 females), between 8.5 to 14 months old, weighing between 16.5 pounds (7.5 kg) and 27.9 pounds (12.7 kg) at the time of treatment, were used in this study.

3. Treatment Groups:

Table 11. Study NAH-01-0014 Treatment Groups (10 dogs per group)

Treatment	Milbemycin Dose	Praziquantel Dose
Milbemycin oxime and praziquantel Tablets	0.5 mg/kg	5 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg

4. Drug Administration: All dogs were dosed once on Day 30, within 30 minutes of a full meal, according to Table 11 above.

5. Measurements and Observations: All dogs were determined to be healthy and heartworm negative prior to study initiation. Dogs were artificially infected (orally in canned food) with between 20,000 and 100,000 *E. granulosus* protoscolices on Day 0. All dogs were necropsied on Day 35 and the intestines examined for the presence of adult *E. granulosus* worms.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group compared to the control group.

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

Worm counts were logarithmically transformed and a mixed model analysis of variance was performed for the treatment comparison of interest.

d. Results:

Table 12. Study NAH-01-0014 Results

Treatment	Geometric Mean *E. granulosus* counts (range)	Percent Effectiveness
Milbemycin oxime/praziquantel Tablets	0[a]	100%
Control (inert ingredients)	8,130 (1,900–13,200)	NA

[a] Significantly less than control ($p < 0.0001$)

e. Adverse Reactions: Vomiting was noted in three dogs in the milbemycin oxime/praziquantel group within the first 24 hours post-treatment.

f. Conclusions: A single dose of milbemycin oxime/praziquantel tablets is 100% effective against adult *E. granulosus* worms in dogs. Additionally, based on the results of this study and those of the pharmacokinetics bridging study (NAH-10-0015), the INTERCEPTOR SPECTRUM chewable formulation is determined to be effective against *E. granulosus*.

6. Laboratory Dose Confirmation Study NAH-01-0022

a. Title: Efficacy Evaluation of Flavored Combination Parasiticide Tablets for the Removal of Experimentally Induced Adult *Echinococcus granulosus* Infections in Dogs.

b. Investigator: C. Steven Godin, PhD, DABT
Mattawan, MI

c. Study Design:

1. Objective: Confirm the established minimum recommended dose of 5 mg/kg praziquantel, when administered with milbemycin oxime in the two-way combination tablets, to remove adult *Echinococcus granulosus* in dogs.

2. Study Animals: Twenty purpose-bred, 6-month old Beagle dogs (10 males and 10 females), weighing between 15.3 pounds (6.9 kg) and 22.7 pounds (10.3 kg) at the time of treatment, were used in this study.

3. Treatment Groups:

Table 13. Study NAH-01-0022 Treatment Groups (10 dogs per group)

Treatment	Milbemycin Dose	Praziquantel Dose
Milbemycin oxime/praziquantel tablets	0.5 mg/kg	5 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg

4. Drug Administration: All dogs were dosed once on Day 30, within 30 minutes of a full meal, according to Table 13 above.

5. Measurements and Observations: All dogs were determined to be healthy and heartworm negative prior to study initiation. Dogs were artificially infected (orally in canned food) with between 20,000 and

100,000 *E. granulosus* protoscolices on Day 0. All dogs were necropsied on Day 35 and the intestines examined for the presence of adult *E. granulosus* worms.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group compared to the control group.

Percent Effectiveness = 100 x $[(c_c - c_t)/c_c)]$

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

Worm counts were logarithmically transformed and a mixed model analysis of variance was performed for the treatment comparison of interest.

d. Results:

Table 14. Study NAH-01-0022 Results

Test Article	**Geometric Mean *E. granulosus* Counts (range)**	**Percent Effectiveness**
Milbemycin oxime/praziquantel tablets	0[a]	100%
Control	1,091 (300 – 8,300)	NA

[a] Significantly less than control ($p < 0.0001$)

e. Adverse Reactions: Three dogs administered milbemycin oxime/praziquantel experienced salivation within 24 hours post-treatment.

f. Conclusions: A single dose of milbemycin oxime/praziquantel tablets is 100% effective against adult *E. granulosus* worms in dogs. Additionally, based on the results of this study and those of the pharmacokinetics bridging study (NAH-10-0015), the INTERCEPTOR SPECTRUM chewable formulation is determined to be effective against *E. granulosus*.

7. Laboratory Dose Confirmation Study NAH-01-0019

a. Title: Efficacy Evaluation of Flavored Combination Parasiticide Tablets For The Removal of Natural Adult *Taenia pisiformis* (Tapeworm) Infections in Dogs

b. Clinical Investigator: Dwight Bowman, PhD
Stanwood, MI

c. Study Design:

1. Objective: Confirm the established minimum recommended dose of 5 mg/kg praziquantel, when administered with milbemycin oxime in the two-way combination tablets, to remove adult *Taenia pisiformis* in dogs.

2. Study Animals: Sixteen adult random source dogs (8 males and 8 females) weighing between 33.5 pounds (15.2 kg) and 94.5 pounds (42.9 kg) at the time of treatment were used in this study.

3. Treatment Groups:

Table 15. Study NAH-01-0019 Treatment Groups (8 dogs per group)

Treatment	Milbemycin Dose	Praziquantel Dose
Milbemycin oxime/praziquantel tablets	0.5 mg/kg	5 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg

4. Drug Administration: Dogs were dosed once on Study Day 0 within 30 minutes of a full meal, according to Table 15 above.

5. Measurements and Observations: All dogs were determined to be healthy with the exception of *T. pisiformis* infections, confirmed by fecal examination, prior to initiation of the study. All dogs were determined to be heartworm negative by antigen test prior to administration of test article. Dogs were sacrificed on Study Day 12 and the intestines inspected for the presence of adult *T. pisiformis* worms.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group compared to the control group.

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

Worm counts were logarithmically transformed and a mixed model analysis of variance was performed for the treatment comparison of interest.

d. Results:

Table 16. Study NAH-01-0019 Results

Treatment	Geometric Mean *T. pisiformis* Counts	Percent Effectiveness
Milbemycin oxime/praziquantel tablets	0[a]	100%
Control	9.5	N/A

[a] Significantly less than control ($p < .0018$)

e. Adverse Reactions: There were no adverse reactions reported.

f. Conclusions: A single dose of milbemycin oxime/praziquantel tablets is 100% effective for the removal of adult *T. pisiformis* infections in dogs. Additionally, based on the results of this study and those of the pharmacokinetics bridging study (NAH-10-0015), the INTERCEPTOR SPECTRUM chewable formulation is determined to be effective against *T. pisiformis*.

8. Laboratory Dose Confirmation Study NAH-01-0065

a. Title: Efficacy Evaluation of Flavored Combination Parasiticide Tablets

For The Removal of Natural Adult *Taenia pisiformis* (Tapeworm) Infections in Dogs

b. Investigator: David Young, DVM, PhD
Turlock, CA

c. Study Design:

1. Objective: Confirm the established minimum recommended dose of 5 mg/kg praziquantel, when administered with milbemycin oxime in the two-way combination tablets, to remove adult *Taenia pisiformis* in dogs.

2. Study Animals: Fourteen random source, adult dogs (7 males and 7 females) weighing between 11.6 pounds (5.3 kg) and 61.9 pounds (28.1 kg) at the time of treatment were used in this study.

3. Treatment Groups:

Table 17. Study NAH-01-0065 Treatment Groups (7 dogs per group)

Treatment Article	Milbemycin Dose	Praziquantel Dose
Milbemycin oxime/praziquantel tablets	0.5 mg/kg	5 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg

4. Drug Administration: Dogs were dosed once on Study Day 0 within 30 minutes of a full meal, according to Table 17 above.

5. Measurements and Observations: All dogs were determined to be healthy with the exception of *T. pisiformis* infections, confirmed by fecal examination, prior to initiation of the study. All dogs were determined to be heartworm negative by antigen test prior to administration of test article. Dogs were sacrificed on Day 12 and the intestines inspected for the presence of adult *T. pisiformis* worms.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group compared to the control group.

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

Worm counts were logarithmically transformed and a mixed model analysis of variance was performed for the treatment comparison of interest.

d. Results:

Table 18. Study NAH-01-0065 Results

Treatment	Geometric Mean *T. pisiformis* Counts	Percent Effectiveness
Milbemycin oxime/praziquantel tablets	0 [a]	100%
Control	11.2	NA

[a] Significantly less than control ($p < 0.001$)

e. Adverse Reactions: There were no adverse reactions reported.

f. Conclusions: A single dose of milbemycin oxime/praziquantel tablets is 100% effective against of adult *T. pisiformis* infections in dogs. Additionally, based on the results of this study and those of the pharmacokinetics bridging study (NAH-10-0015), the INTERCEPTOR SPECTRUM chewable formulation is determined to be effective against *T. pisiformis*.

9. Laboratory Dose Confirmation Study NAH-01-0015

a. Title: Efficacy Evaluation of Flavored Combination Parasiticide Tablets for the Removal of Experimentally Induced Adult *Echinococcus multilocularis* Infections in Dogs

b. Investigator: C. Steven Godin, PhD, DABT
Mattawan, MI

c. Study Design:

1. Objective: Confirm the established minimum recommended dose of 5 mg/kg praziquantel, when administered with milbemycin oxime in the two-way combination tablets, to remove adult *Echinococcus multilocularis* in dogs.

2. Study Animals: Twenty purpose-bred Beagle dogs (10 males and 10 females), between 1 and 3 years old, weighing between 14.9 pounds (6.8 kg) and 23.4 pounds (10.6 kg) at the time of treatment, were used in this study.

3. Treatment Groups:

Table 19. Study NAH-01-0015 Treatment Groups (10 dogs per group)

Treatment	Milbemycin Dose	Praziquantel Dose
Milbemycin oxime/praziquantel tablets	0.5 mg/kg	5 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg

4. Drug Administration: All dogs were dosed once on Study Day 20, within 30 minutes to one hour of a full meal, according to Table 19 above.

5. Measurements and Observations: All dogs were determined to be healthy and heartworm negative prior to study initiation. Dogs were artificially infected via oral gavage with between 20,000 and 100,000

E. multilocularis protoscolices on Day 0. All dogs were necropsied on Study Day 25 and the intestines examined for the presence of adult *E. multilocularis* worms.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group compared to the control group.

Percent Effectiveness = 100 x $[(c_c - c_t)/c_c)]$

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

Worm counts were logarithmically transformed and a mixed model analysis of variance was performed for the treatment comparison of interest.

d. Results:

Table 20. Study NAH-01-0015 Results

Test Article	Geometric Mean *E. multilocularis* Counts (range)	Percent Effectiveness
Milbemycin oxime/praziquantel tablets	0[a]	100%
Control	26,349.6 (12,500–54,300)	NA

[a] Significantly less than control ($p < 0.0001$)

e. Adverse Reactions: One dog exhibited abnormal leaning behavior within 24 hours of treatment with milbemycin oxime/praziquantel.

f. Conclusions: A single dose of milbemycin oxime/praziquantel tablets is 100% effective at removing adult *E. multilocularis* worms in dogs. Additionally, based on the results of this study and those of the pharmacokinetics bridging study (NAH-10-0015), the INTERCEPTOR SPECTRUM chewable formulation is determined to be effective against adult *E. multilocularis*.

10. Laboratory Dose Confirmation Study NAH-01-0021

a. Title: Efficacy Evaluation of Flavored Combination Parasiticide Tablets for the Removal of Experimentally Induced Adult *Echinococcus multilocularis* Infections in Dogs.

b. Investigator: C. Steven Godin, PhD, DABT
Mattawan, MI

c. Study Design:

1. Objective: Confirm the established minimum recommended dose of 5 mg/kg praziquantel, when administered with milbemycin oxime in the two-way combination tablets, to remove adult *Echinococcus multilocularis* in dogs.

2. Study Animals: Twenty purpose-bred Beagle dogs (10 males and 10 females), between 1 and 3 years old, weighing between 17.0 pounds (7.7 kg) and 23.4 pounds (10.6 kg) at the time of treatment, were used in this study.

3. Treatment Groups:

Table 21. Study NAH-01-0021 Treatment Groups (10 dogs per group)

Treatment	Milbemycin Dose	Praziquantel Dose
Milbemycin oxime/praziquantel tablets	0.5 mg/kg	5 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg

4. Drug Administration: All dogs were dosed once, within 30 minutes of a full meal, on Study Day 20, according to Table 21 above.

5. Measurements and Observations: All dogs were determined to be healthy and heartworm negative prior to study initiation. Dogs were artificially infected by oral gavage with between 20,000 and 100,000 *E. multilocularis* protoscolices on Study Day 0. All dogs were necropsied on Study Day 25 and the intestines examined for the presence of adult *E. multilocularis* worms.

6. Statistical Methods: Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group compared to the control group.

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

Worm counts were logarithmically transformed and a mixed model analysis of variance was performed for the treatment comparison of interest.

d. Results:

Table 22. Study NAH-01-0021 Results

Treatment	Geometric Mean *E. multilocularis* Counts (range)	Percent Effectiveness
Milbemycin oxime/praziquantel tablets	0[a]	100%
Control	41,494.1 (13,000-81,900)	NA

[a] Significantly less than control ($p < 0.0001$)

e. Adverse Reactions: There were no adverse reactions reported.

f. Conclusions: A single dose of milbemycin oxime/praziquantel tablets is 100% effective against adult *E. multilocularis* worms in dogs. Additionally, based on the results of this study and those of the pharmacokinetics

bridging study (NAH-10-0015), the INTERCEPTOR SPECTRUM chewable formulation is determined to be effective against adult *E. multilocularis*.

11. Field Study NAH-02-0054

a. Title: Palatability/Acceptability Trial of 3-Way and 2-Way Chewable Formulation in Dogs

b. Investigators:

Harvey Goho, DVM Greensboro, NC	Richard Hawkins, DVM Durham, NC
Ronald Komich DVM Greensboro, NC	Janet Raczkowski, DVM Greensboro, NC

c. Study Design: This study was conducted using principles of Good Clinical Practice (GCP).

1. Objective: To determine the acceptability and safety of INTERCEPTOR SPECTRUM when administered to client-owned dogs under conditions of use.

2. Study Animals: One hundred-twenty client-owned dogs were enrolled. Five dogs were excluded from the study. The remaining 115 dogs consisted of 52 males and 63 females of various breeds, with ages ranging from less than 1 year to greater than 10 years, and weights ranging from 2 lbs to greater than 100 lbs. All dogs were healthy and free from conditions that could affect their appetite or feeding behavior.

3. Treatment Groups: Dogs received the appropriately-sized test article based on their body weight at the time of study enrollment. In order to mask the owners and clinical investigators to the treatment given, dogs received either INTERCEPTOR SPECTRUM or a control chewable tablet (multi-vitamin) on treatment days.

4. Drug Administration: The test article was offered by hand for approximately 60 seconds. If it was taken from the hand and eaten, the owner recorded that result. If the test article was not taken from the hand, the owner was instructed to place it in the dog's bowl for 60 seconds. If the test article was eaten from the bowl, the owner recorded that result. If it was not eaten from the bowl, the owner was instructed to place it in the dog's mouth for 60 seconds. If the test article was not eaten when placed in the dog's mouth, the owner recorded that result and discarded the tablet.

d. Results:
The results of the study are outlined in Table 23 below:

Table 23. Study NAH-02-0054 Results
Treatment Acceptance (number of dogs) by Presentation

Treatment	Hand	Bowl	Mouth	Refuse
INTERCEPTOR SPECTRUM	108	1	2	4

e. Adverse Reactions: On one occasion, one dog vomited immediately after accepting the chewable from the owner's hand.

f. Conclusions: INTERCEPTOR SPECTRUM, administered orally under field conditions in the United States, is well-accepted in client-owned dogs.

III. TARGET ANIMAL SAFETY:

1. Acute Oral Safety Study

Note: Studies demonstrating the acute tolerability of high doses (10X) of milbemycin oxime were conducted for INTERCEPTOR Flavor Tabs (milbemycin oxime; NADA 140-915; Novartis Animal Health US, Inc.), and SENTINEL Flavor Tabs (milbemycin oxime/lufenuron; NADA 141-084; Novartis Animal Health US, Inc.).

2. Laboratory Repeat Dose Target Animal Safety Study (NAH-03-0004)

a. Title: A 13-week oral safety study of milbemycin oxime and praziquantel in 10-week old beagle puppies.

b. Investigator: Joseph C. Siglin, PhD., DABT
Spencerville, OH

c. Study Design: This study was conducted using principles of Good Laboratory Practice (GLP).

1. Objective: The objective of this study was to evaluate the safety of repeated doses of INTERCEPTOR SPECTRUM when administered to Beagle puppies, ten weeks of age, at 1, 3, and 5X the maximum label exposure.

2. Study Animals: Forty purpose-bred Beagles (20 males and 20 females), approximately ten weeks of age at the time of treatment were used in this study.

3. Treatment Groups:

Table 24. Study NAH-03-0004 Treatment Groups (10 dogs per treatment group)

Treatment	Milbemycin dose	Praziquantel dose
Control (sham-dosed)	0 mg/kg	0 mg/kg
INTERCEPTOR SPECTRUM (1X)	2.5 mg/kg	25.1 mg/kg
INTERCEPTOR SPECTRUM (3X)	7.5 mg/kg	75.3 mg/kg
INTERCEPTOR SPECTRUM (5X)	12.5 mg/kg	125.5 mg/kg

4. Drug Administration: Dogs were dosed every two weeks for seven treatments.

5. Measurements and Observations: Physical examinations were conducted twice prior to treatment and three times during the course of the study. Venous blood samples for hematology and clinical chemistry, and urine samples for urinalysis, were collected once pre-treatment and at weeks 3, 7, and 13. Dogs were observed for clinical signs hourly for the first six hours and at 8, 10, 12, 18, and 24 hours post-dose during the first day after treatment. Dogs were observed twice daily for the other days of the study. Body weights were recorded at least once prior to treatment, at least weekly throughout the study, and immediately prior to necropsy. Food and water consumption were recorded daily throughout the study. Electrocardiogram (ECG), indirect blood pressure, and ophthalmologic evaluations were performed once prior to dosing and within one week of study termination. Dogs were euthanized and necropsied at study termination. All dogs were evaluated for gross pathology and tissues from all dogs were examined histopathologically.

6. Statistical Methods: For endpoints measured once, analysis of variance (ANOVA) or analysis of covariance (ANCOVA) techniques, as appropriate, were used to analyze the data. For endpoints measured multiple times, repeated measures analysis of variance (RMANOVA) or repeated measures analysis of covariance (RMANCOVA) techniques, as appropriate, were used to analyze the data.

d. Results: All dogs survived to study completion. Clinical signs were noted following each dose and followed a dose-related pattern in onset, overall incidence, and duration.

   Ataxia and decreased activity were noted in the 3X and 5X groups. These signs were first observed three hours after dosing and persisted up to 18 hours before spontaneously resolving. Salivation was observed in the 3X and 5X treated dogs beginning immediately after dosing and up to six hours post-dose. Vomiting was noted in all treatment groups, but there was a higher incidence of vomiting in the 3X and 5X treatment groups. Vomiting was observed at one to 24 hours post-dose. Diarrhea was observed with a similar incidence in all groups. No drug-related clinical signs were noted on non-dosing days.

e. Conclusions: INTERCEPTOR SPECTRUM, administered at multiples of the maximum label exposure, produced clinical signs consistent with avermectin toxicity (ataxia, decreased activity, vomiting, and salivation) that followed a dose-related pattern in onset, overall incidence, and duration.

3. Laboratory Repeat Dose Target Animal Safety Study (NAH-04-0001)

a. Title: An Oral Safety Study of a Milbemycin Oxime and Praziquantel Combination Chewable Formulation in Beagle Puppies Beginning at 6 Weeks of Age.

b. Investigator: Zac Lloyd, BS
   Mattawan, Michigan

c. Study Design: This study was conducted using principles of Good Laboratory Practice (GLP).

   1. Objective: To evaluate the safety of repeated doses of INTERCEPTOR SPECTRUM when administered to Beagle puppies at six weeks of age at approximately 1, 3, and 5X the maximum label exposure.

2. Study Animals: Sixty-four purpose-bred beagles (32 males and 32 females) approximately six weeks of age at the time of treatment.

3. Treatment Groups

Table 25. Study NAH-04-0001 Treatment Groups (16 dogs per treatment group)

Treatment	Milbemycin dose	Praziquantel dose
Control (sham-dosed)	0 mg/kg	0 mg/kg
INTERCEPTOR SPECTRUM (1X)	2.5 mg/kg	25.1 mg/kg
INTERCEPTOR SPECTRUM (3X)	7.5 mg/kg	75.3 mg/kg
INTERCEPTOR SPECTRUM (5X)	12.5 mg/kg	125.5 mg/kg

4. Drug Administration: Dogs were dosed every two weeks for four treatments.

5. Measurements and Observations: Physical examinations were conducted prior to treatment and twice during the course of the study. Venous blood samples for hematology and clinical chemistry, and urine samples for urinalysis, were collected once pretreatment and at study termination. Test animals were observed for clinical signs immediately pre and post-dose, hourly for the first six hours, then at 8, 10, 12, 18, and 24 hours post-dose. Animals were observed twice daily for the other days of the study. Body weights were recorded at least once prior to treatment, at least weekly throughout the study and immediately prior to necropsy. Ophthalmoscopic and electrocardiographic examinations were performed on all animals pretest and prior to study termination. Test animals were euthanized and necropsied at study termination. All animals were evaluated for gross pathology and tissues from all dogs were examined histopathologically.

6. Statistical Methods: For each treatment group there were four litters. Each litter contained two males and two females. Data were analyzed using litter as the experimental unit. Hematology, clinical chemistry and urinalysis parameters were analyzed by analysis of covariance, with pretest value (baseline) as a covariate.

d. Results:
All dogs survived to study completion. Clinical signs were noted following each dose and followed a dose-related pattern in onset, overall incidence, and duration. Decreased activity was observed in all groups and the incidence increased with increased dose. In the 1X treatment group decreased activity was reported in five of the 16 animals following the first treatment and six of the 16 animals following the third treatment. In the 1X treatment group ataxia was reported one time in one animal after the first treatment. For both decreased activity and ataxia, incidence and duration increased in the 3X and 5X groups. These signs were observed during the first 24 hours before resolving. Salivation and tremors were observed in the 3X and 5X treated dogs beginning immediately after dosing and up to six hours post-dose. Vomiting was observed in the 5X treatment group on most, but not all, treatment days. No drug related clinical signs were noted on non-dosing days.

e. Conclusions: INTERCEPTOR SPECTRUM was well-tolerated when administered to puppies 6 weeks of age and older. INTERCEPTOR SPECTRUM, when dosed at multiples of the maximum label exposure, produced clinical signs consistent with avermectin toxicity (ataxia, decreased activity, salivation, tremors and vomiting) that followed a dose-related pattern in onset, overall incidence, and duration.

IV. HUMAN FOOD SAFETY:

This drug is intended for use in dogs, which are non-food animals. 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 INTERCEPTOR SPECTRUM:

"Not for human use. 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 and 21 CFR part 514. The data demonstrate that INTERCEPTOR SPECTRUM, when used according to the label, is safe and effective for the prevention of heartworm disease caused by *Dirofilaria immitis*, and for the treatment and control of adult roundworm *(Toxocara canis, Toxascaris leonina)*, adult hookworm *(Ancylostoma caninum)*, adult whipworm *(Trichuris vulpis),* and adult tapeworm *(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.

A. Marketing Status:

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for 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 to dogs.

B. Exclusivity:

Under Section 512(c)(2)(F)(ii) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for THREE years of marketing exclusivity beginning on the date of the approval.

C. Patent Information:

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