A. General Information

NADA Number: 140-915

Sponsor: Novartis Animal Health
Post Office Box 18300
Greensboro, NC 27419

Generic Name of Drug: Milbemycin Oxime

Trade Name: INTERCEPTOR® Flavor Tabs® for Cats

Marketing Status: Rx, For use by or on the order of a licensed veterinarian.

Effect of Supplement: Approval of this supplemental NADA will change NADA 140-915 by adding an additional species (cat) to the label. The supplemental application also provides for changes in the dosage and indications for the cat only. No changes are made in the dosage form, dosages or treatment regimen for the dog. The cat will have labeling separate from the dog approval.

B. Indications for Use

Interceptor Flavor Tabs for Cats are indicated for use in the prevention of heartworm disease caused by *Dirofilaria immitis* and for the removal of adult *Toxocara cati* (roundworm) and *Ancylostoma tubaeforme* (hookworm) infections in cats six weeks of age or greater and 1.5 pounds body weight or greater.

C. Dosage Form, Route of Administration, and Recommended Dosage

Interceptor Flavor Tabs for Cats are given orally, once a month, at the recommended minimum dosage of 2.0 mg milbemycin oxime per kilogram (0.91 mg/lb.) of body weight.

Cat Weight	# Tablets per Month	Milbemycin oxime per Tablet
1.5 to 6 lbs.	1	5.75 mg
6.1 to 12 lbs.	1	11.5 mg
12.1 to 25 lbs.	1	23.0 mg

Cats over 25 lbs are provided the appropriate combination of tablets.

D. Effectiveness

1. Dose Establishment

Controlled studies were undertaken to establish and confirm the optimal effective dose of milbemycin oxime tablets against adult intestinal stages of roundworm (*Toxocara cati*) and hookworm (*Ancylostoma tubaeforme*) and against the tissue migratory phases of heartworm (*Dirofilaria immitis*).

At necropsy in the roundworm (*Toxocara cati*) and hookworm (*Ancylostoma tubaeforme*) studies, the entire gastrointestinal tract was removed from each cat. The contents of the tract were removed, sieved, and parasites were recovered, identified, and enumerated. At necropsy in the heartworm (*Dirofilaria immitis*) study, body cavities and the heart and lungs from each cat were examined for the presence of adults or macroscopic larvae. The parasites were enumerated and sexed.

Total numbers of roundworms, hookworms, and heartworms found at necropsy were analyzed in each study. Percent efficacy was calculated as follows, using geometric means:

$$\frac{\text{Mean \# of Worms in Control Cats - Mean \# of Worms in Treated Cats}}{\text{Mean \# of Worms in Control Cats}} \times 100$$

These studies established the minimum effective dose for roundworm removal at 1.0 mg/kg, the minimum effective dose for hookworm removal at 2.0 mg/kg, and confirmed a minimum dose of 2.0 mg/kg as efficacious for heartworm prevention. In order to support a claim for all parasites, the minimum effective dose was set at 2.0 mg/kg.

a. Roundworm (*T. cati*) Dose Titration Study

Purpose: Dose titration

Investigator: Dr. Dwight Bowman
Ithaca, New York

Type of study: Natural infections

Animals: Thirty-two mixed breed cats (14 males, 18 females), ranging in weight from 1.02 to 6.01 kg, were divided into 4 groups of 8 cats each.

Dosage form: Milbemycin oxime tablets (swallow)

Route of administration: Oral

Controls: Untreated

Doses tested: 0.5 mg/kg, 1.0 mg/kg, and 1.5 mg/kg body weight

Frequency and interval of treatment: One treatment

Study duration: The cats were euthanized and adult roundworms were counted 7 days post-treatment.

Results: The following table shows the mean number of roundworms and percent efficacy for each treatment group.

	Mean Number of *T. cati* at Necropsy (range)	**Percent Efficacy**
Untreated Control	9.13 (2-19)	NA
0.5 mg/kg	1.88 (0-9)	79.45%
1.0 mg/kg	0.25 (0-2)	97.26%
1.5 mg/kg	0.00	100%

Conclusions: Milbemycin oxime, at a dose of 1.0 mg/kg, is effective for the removal of *Toxocara cati* in the cat.

Adverse Reactions: None reported

b. Roundworm (*T. cati*) Dose Confirmation Studies

Study No. S147-DC-92-01 and Study No. MCR-147-04-91

Purpose: Dose confirmation

Investigators: Study No. S147-DC-92-01 David Spaulding
Sugar Land, Texas

Study No. MCR-147-04-91 Dr. Dwight Bowman
Ithaca, New York

Type of study: Natural infections

Animals: Study No. S147-DC-92-01--Twenty adult mixed breed cats (9 males, 11 females), ranging in weight from 1.3 to 5.0 kg, were divided into two groups of 10 cats each. Study No. MCR-147-04-91--Twenty mixed breed cats (7 males, 13 females), ranging in weight from 1.48 to 4.09 kg, were divided into two groups of 10 cats each.

Dosage form: Milbemycin oxime tablets (swallow)

Route of administration: Oral

Controls: Untreated

Dose tested: Minimum dose of 1.0 mg/kg body weight

Frequency and interval of treatment: One treatment

Study duration: The cats were euthanized and adult roundworms were counted 7 days post-treatment.

Results: The following tables show the mean number of roundworms and percent efficacy for both studies.

Study No. S147-DC-92-01

	Mean Number of *T. cati* at Necropsy (range)	**Percent Efficacy**
Untreated Control	23.9 (1-49)	NA
≥ 1.0 mg/kg	0.1 (0-1)	99.6%

Study No. MCR-147-04-91

	Mean Number of *T. cati* at Necropsy (range)	**Percent Efficacy**
Untreated Control	27.7 (1-89)	NA
≥ 1.0 mg/kg	0.3 (0-1)	99.0 %

Conclusions: Milbemycin oxime, at a minimum dose of 1.0 mg/kg, is effective for the removal of *Toxocara cati* in the cat.

Adverse Reactions: None reported

c. Hookworm (*A. tubaeforme*) Dose Titration Study

Purpose: Dose titration

Investigator: Dr. Brian Johnson
Waverly, New York

Type of study: Experimental infection with approximately 300 infective L3 stage *A. tubaeforme* orally.

Animals: Forty mixed breed cats (20 males, 20 females), four months old and ranging in weight from 1.69 to 3.63 kg were divided into 4 groups of 10 cats each.

Dosage form: Milbemycin oxime tablets (Flavor Tabs®)

Route of administration: Oral

Controls: Untreated

Doses tested: 1.0 mg/kg, 2.0 mg/kg, and 4.0 mg/kg body weight

Frequency and interval of treatment: One treatment, 29 days after inoculation

Study duration: The cats were euthanized and adult hookworms were counted 7 days post-treatment.

Results: The following table shows the mean number of hookworms and percent efficacy for each treatment group

	Mean Number of *A. tubaeforme* at Necropsy (range)	**Percent Efficacy**
Untreated Control	31.8 (16-62)	NA
1.0 mg/kg	15.1 (0-34)	52.2%
2.0 mg/kg	5.0 (0-16)	84.3%
4.0 mg/kg	1.5 (0-8)	95.3%

Conclusions: Milbemycin oxime, at a dose of 2.0 mg/kg, was 84.3% effective for the removal of *A. tubaeforme* in the cat.

Adverse Reactions: None reported

d. Hookworm (*A. tubaeforme*) Dose Confirmation Studies

Study No. MH-147-01-91 and Study No. MH-147-02-91

Purpose: Dose confirmation

Investigators: Study No. MH-147-01-91 Dr. Dwight Bowman, Ithaca, New York

Study No. MH-147-02-91 Dr. Larry Cruthers, Corapeake, North Carolina

Type of study: Natural infections

Animals: Study No. MH-147-01-91--Twenty mixed breed cats (5 males, 15 females), ranging in weight from 1.14 to 3.86 kg, were divided into two groups of 10 cats each. Study No. MH-147-02-91--Twenty mixed breed cats (15 males, 5 females) were divided into two groups of 10 cats each.

Dosage form: Milbemycin oxime tablets (swallow)

Route of administration: Oral

Controls: Untreated

Dose tested: Minimum dose of 2.0 mg/kg body weight

Frequency and interval of treatment: One treatment

Study duration: The cats were euthanized and adult hookworms were counted 7 days post-treatment.

Results: The following tables show the mean number of hookworms and percent efficacy for both studies.

Study No. MH-147-01-91

	Mean Number of *A. tubaeforme* at Necropsy (range)	**Percent Efficacy**
Untreated Control	8.6 (3-25)	NA
≥ 2.0 mg/kg	0.4 (0-4)	95.35 %

Study No. MH-147-02-91

	Mean Number of *A.*	**Percent**

	***tubaeforme* at Necropsy (range)**	**Efficacy**
Untreated Control	25.8 (0-86)	NA
≥ 2.0 mg/kg	0.6 (0-4)	97.7%

Conclusions: Milbemycin oxime, at a minimum dose of 2.0 mg/kg, is effective for the removal of *Ancylostoma tubaeforme* in the cat.

Adverse Reactions: None reported

e. Heartworm (*D. immitis*) Dose Confirmation Study

Purpose: Dose confirmation

Investigator: Dr. Brian Johnson
Waverly, New York

Type of study: Experimental infections

Animals: Twenty-four cats (12 males, 12 females), 4 to 6 months of age and weighing between 2.03 and 3.23 kg, were divided into two groups of 12 cats each.

Dosage form: Milbemycin oxime tablets (Flavor Tabs®)

Route of administration: Oral

Controls: Untreated

Dose tested: Minimum dose of 2.0 mg/kg body weight

Frequency and interval of treatment: One treatment administered one month post-inoculation with *D. immitis* L3 larvae.

Study duration: The cats were euthanized and adult heartworms counted 180 days post-inoculation.

Results: No adult or larval heartworms were recovered from any of the cats treated with milbemycin oxime compared with a total of 55 heartworms recovered from the control group, as shown in the following table.

Group	**# of Heartworms**

	Recovered (range)
Untreated Control	55 (0-26)
Milbemycin oxime	0 (0)

Conclusions: Milbemycin oxime, at a minimum dose of 2.0 mg/kg, is 100% effective in preventing the development of *Dirofilaria immitis* in cats.

Adverse Reactions: None reported

2. Well-Controlled Clinical Field Trials

a. Roundworm (*T. cati*) Clinical Field Trial

Type of Study: Natural roundworm infections in pet cats.

Investigators:

Dr. William Campaigne
Seguin Animal Hospital
Seguin, TX

Dr. Jan Strother
N. Alabama Cat and Bird Veterinary Clinic
Hartsell, AL

Dr. Rex Riggs
Best Friends Veterinary Hospital
Columbus, OH

Dr. Herbert Utgard
Dade Animal Hospital
N. Miami Beach, FL

Dr. Ken Schoolmeester
Guilford-Jamestown Veterinary Hospital
Greensboro, NC

Animals: A total of 114 cats completed the study and were included in the analysis, with 76 cats receiving milbemycin oxime and 38 receiving placebo.

Dosage Form: Milbemycin oxime tablets (swallow)

Route of Administration: Oral

Dose Tested: Minimum dose of 1.0 mg/kg

Frequency of Treatment: Once

Controls: Placebo

Duration of Study: Each cat had roundworms at the start of the trial, and was given the test drug or placebo. A fecal examination was performed 7-10 days later.

Results: Of the 76 cats treated with milbemycin oxime, 74 were negative for roundworms at the 7-10 day evaluation for an efficacy of 97.1%. Of the 38 cases enrolled in the placebo group, 4 were negative for roundworms at the 7-10 day evaluation.

Conclusions: Milbemycin oxime is safe and effective for use in cats at a minimum dose of 1.0 mg/kg for the removal of roundworms (*Toxocara cati*).

Adverse Reactions: One cat who was being treated for leg wounds died 1 day post-treatment with milbemycin oxime. No necropsy was conducted. The relationship between the death and treatment with milbemycin oxime could not be determined.

b. Hookworm (*A. tubaeforme*) Clinical Field Trial

Type of Study: Natural hookworms infections in pet cats.

Investigators:

Dr. William Campaigne
Seguin Animal Hospital
Seguin, TX

Dr. Jan Strother
N. Alabama Cat and Bird Veterinary Clinic
Hartsell, AL

Dr. Herbert Utgard
Dade Animal Hospital
N. Miami Beach, FL

Animals: A total of 97 cats completed the study and were included in the analysis, with 65 cats receiving milbemycin oxime and 32 receiving placebo.

Dosage Form: Milbemycin oxime tablets (swallow)

Route of Administration: Oral

Dose Tested: Minimum dose of 2.0 mg/kg

Frequency of Treatment: Once

Controls: Placebo

Duration of Study: Each cat had hookworms at the start of the trial, and was given the test drug or placebo. A fecal examination was performed 7-10 days later.

Results: Of the 65 cats treated with milbemycin oxime, 64 were negative for hookworms at the 7-10 day evaluation for an efficacy of 98.3%. Of the 32 cases enrolled in the placebo group, 3 were negative for hookworms at the 7-10 day evaluation.

Conclusions: Milbemycin oxime is safe and effective for use in cats at a minimum dose of 2.0 mg/kg for the removal of hookworms (*Ancylostoma tubaeforme*).

Adverse Reactions: None reported

3. Dosage Form Acceptability Study

Purpose: Evaluate tablet palatability and dose acceptability.

Investigators: Drs. Mark Silvers, Cecilia Ho and Terri Kretzschmar
Greensboro Cat Clinic
Greensboro, NC

Type of study: Palatability study

Animals: Seventy-two cats

Dosage form: Milbemycin oxime tablets (Flavor Tabs®)

Route of administration: Oral, by owner

Controls: None

Dose tested: Minimum dose of 2.0 mg/kg

Frequency and interval of treatment: One treatment

Study duration: Seven days

Results: All 72 cats successfully completed the trial. 72% were successfully dosed when the tablet was offered as a treat, placed in the cat's food or placed in the cat's mouth. Manual dosing was successful in 16% of the cats while 13% of the cats were not successfully dosed in this trial.

Conclusions: The majority of the cats took the tablet as a treat or when placed in the mouth or in food which indicates that the tablet has adequate palatability.

Adverse Events: None reported

E. Target Animal Safety

1. A 90-Day Oral Toxicity Study in Juvenile Cats with Milbemycin Oxime (Interceptor®)

Purpose: Target animal safety

Investigators: Dr. David M. Serrone, Ricera, Inc, Painesville, OH
Dr. James Laveglia, Ricera, Inc, Painesville, OH

Type of study: Laboratory safety study

Animals: Twenty-four Domestic Shorthair kittens (12 males, 12 females), two to three weeks of age and weighing between 147 and 273 grams at initiation, were divided into four groups of 6 cats each.

Dosage form: Milbemycin oxime tablets (swallow)

Route of administration: Oral

Controls: Placebo

Doses tested: 2.0 mg/kg, 6.0 mg/kg, and 10.0 mg/kg of body weight

Frequency and interval of treatment: One treatment every 14 days for 90 days

Study duration: 90 days

Results: All cats survived to termination. No clinical observations were seen at the one-hour post dosing observation period in either male or female animals. There were no drug-related oculopathies seen at either of the eye examinations. No significant differences in body weight or body weight gains occurred for any of the study animals when compared to controls. Mean food consumption values for both male and female animals receiving test article were comparable to controls.

No significant differences were observed in clinical pathology (hematology, clinical chemistry and urinalysis) values when groups receiving test article were compared to controls.

At necropsy, no observations were made which were considered to be related to the administration of the test article. There were no treatment-related changes in absolute organ weight data for either males or females when compared to controls. No identifiable histopathologic effects were observed.

Conclusions: Milbemycin oxime is safe for kittens when given at recommended label dose. The kittens in this study were dosed at multiples of the minimum recommended dose (2.0 mg/kg). Once marketed, the drug will be administered to all kittens weighing 6 pounds or less in a 5.75 mg tablet. This represents a dose higher than the minimum recommended dose for the kittens at the low end of the weight range. Based on the weights and ages of the kittens and the doses administered, it was determined that the label should restrict use to kittens six weeks of age or greater and 1.5 pounds body weight or greater.

2. A 90-Day Oral Toxicity Study in Young Adult Cats with Milbemycin Oxime (Interceptor®)

Purpose: Target animal safety

Investigators: Dr. David Serrone, Ricera, Inc, Painesville, OH; Dr. James Laveglia, Ricera, Inc, Painesville, OH

Type of Study: Laboratory safety study

Animals: Twenty-four Domestic Shorthair young adult cats (12 males, 12 females), 3 to 4 months of age and weighing between 1.4 and 1.9 kg at initiation, were divided into four groups of six cats each.

Dosage form: Milbemycin oxime tablets (swallow)

Route of administration: Oral

Controls: Placebo

Dose tested: 2.0 mg/kg, 6.0 mg/kg, and 10.0 mg/kg of body weight

Frequency and interval of treatment: One treatment every 14 days for 90 days

Study duration: 90 days

Results: All animals survived to termination. All animals were normal at weekly physical examinations and at the one hour post-dosing observation period. No drug-related oculopathies were observed at the terminal examinations. No significant differences in body weight occurred when compared to controls. Mean food consumption values for animals receiving test article were comparable to controls. At necropsy, no observations were made which were considered to be related to the administration of the test article.

Conclusions: Milbemycin oxime is safe for young adult cats (3-4 months) when given at recommended label dose.

3. A Tolerability Study in Kittens with Milbemycin Oxime (Interceptor®)

Purpose: Target animal safety

Investigator: Elizabeth Reagan
Food and Drug Research Laboratories
Waverly, NY

Type of study: Laboratory safety study

Animals: Twelve Domestic Shorthair kittens, (6 males, 6 females), eight weeks of age and weighing between 0.373 and 0.794 kg, were divided into two groups of six cats each.

Dosage form: Milbemycin oxime tablets (swallow)

Route of administration: Oral

Controls: Placebo

Dose tested: 20 mg/kg of body weight

Frequency and interval of treatment: One treatment

Study duration: 15 days

Results: One test group female died on study day twelve. On study day nine, this animal appeared to be losing weight, however, no overt signs of toxicity were noted. On the day of death, this animal was prostrate and exhibited labored breathing. A dark, blood-like mucous substance in the stomach was the only finding noted for this animal during gross necropsy examination. No significant lesions were noted during microscopic examination of tissues. The relationship of this kitten's death to treatment could not be determined.

All other test and control group kittens survived to study termination (day 15), appeared normal throughout the observation period and gained weight from study initiation to termination. Test group food consumption, however, was lower than the control group throughout the study, by a mean value of 53 grams per day.

Conclusions: Milbemycin oxime proved safe for eight week old kittens at dose levels up to 10X the minimum recommended dose.

4. Tolerability Study in Young Adult Cats

Purpose: Target animal safety

Investigator: Elizabeth Reagan
Food and Drug Research Laboratories
Waverly, NY

Type of Study: Laboratory safety study

Animals: Twelve Domestic Shorthair young adult kittens, (6 males, 6 females), 9-11 months of age and weighing between 2.55 and 6.05 kg, were divided into two groups of three cats each.

Dosage form: Milbemycin oxime tablets (swallow)

Route of administration: Oral

Controls: Untreated

Dose tested: 20 mg/kg of body weight

Frequency and interval of treatment: One treatment

Study duration: 15 days

Results: All cats survived to study termination (day 15). All cats gained weight from study initiation to termination. The male test group food consumption was periodically lower (by a mean value of approximately 42 grams per day over the course of the study) than the control group during the study, which was probably because one control group male consumed more food than any other cat on study. The female group food consumption was similar between test and control groups throughout the study.

Conclusions: Milbemycin oxime proved safe for young adults at dose levels up to 10X the minimum recommended dose.

F. Human Safety

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

G. Agency Conclusions

The data in support of this supplement comply with the requirements of Section 512 of the Act and Part 514 of the implementing regulations. The data demonstrate that Interceptor Flavor Tabs for Cats (milbemycin oxime), when used under labeled conditions of use, are safe and effective.

According to the Center's supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for an additional species (cat) at a minimum dose of 2 mg/kg for use in the prevention of heartworm disease caused by *Dirofilaria immitis* and for the removal of adult *Toxocara cati* (roundworm) and *Ancylostoma tubaeforme* (hookworm) infections in cats six weeks of age or greater and 1.5 pounds body weight or greater.

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 hookworms and the assessment of heartworm status in cats.

Under section 512(c)(2)(F)(iii) of the FFDCA, 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 species for which the supplemental application was approved.

Patent information: #4,547,520, expires 6-14-04.

H. Labeling (Attached)

a. Veterinary Insert
b. Client Insert
c. Dispensing Envelope