I. GENERAL INFORMATION

A. File Number

NADA 140-915

B. Sponsor

Ciba-Geigy Animal Health
Ciba-Geigy Corporation
P.O. Box 18300
Greensboro, NC 27419

C. Proprietary Name

INTERCEPTOR®

D. Established Name

milbemycin oxime tablets

E. Dosage Form, Route of Administration and Recommended Dosage

The ingredients of INTERCEPTOR are formulated into various sized tablets to be administered orally (swallow) as appropriate for the weight of the dog (see below) at monthly dosing intervals. The tablets supply the recommended minimum dose level of 0.5 mg milbemycin oxime per kilogram (0.23 mg/lb.) of body weight.

Dog Weight	Tablets per Month	Milbemycin Oxime per Tablet	Tablet Color
Up to 10 lbs.	1	2.30 mg	Brown
11-25 lbs.	1	5.75 mg	Green
26-50 lbs.	1	11.50 mg	Yellow
51-100 lbs.	1	23.0 mg	White

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

F. Indication

INTERCEPTOR tablets are indicated for use in the prevention of heartworm disease caused by Dirofilaria immitis and control of adult hookworm infections caused by Ancylostoma caninum in dogs.

II. EFFECTIVENESS

The New Animal Drug Application for milbemycin oxime tablets contains adequate and well-controlled studies which demonstrate efficacy in preventing heartworm disease and controlling hookworm infections in dogs.

A. Dose Establishment

Thirteen controlled studies were undertaken to establish and confirm the optimal effective dose of milbemycin oxime against the tissue migratory phases of

Dirofilaria immitis (canine heartworm) and adult intestinal phases of *Ancylostoma* sp., principally *A. caninum* (canine hookworm disease). These studies included 264 milbemycin oxime treated dogs and 107 placebo control dogs. The milbemycin oxime 1% powder formulation used in the first 5 studies was determined to be bioequivalent to the final formulated tablet used in the remaining eight studies (refer to Table 1 for additional information).

The pleural cavity, cranial vena cava, right atrium, right ventricle, and pulmonary arteries and branches in the lungs from each dog were examined for worms at necropsy in each heartworm study. The worms (*D. immitis*) form each infected dog were counted, and sexed, and preserved in fixative.

At necropsy in each hookworm study, the entire gastrointestinal tract was removed form each dog. The contents of the tract were removed, sieved, and parasites recovered and identified. The opened tracts were examined carefully for remaining parasites which were recovered and identified. Additionally, the small intestine was incubated in saline for recovery of embedded parasites which also were counted and identified.

Total numbers of heartworms and hookworms found at necropsy were analyzed in each study. Percent efficacy was calculated using the formula:

> Mean Number of Parasites in Control Animals - Mean Number of Parasites in Treated Animals / Mean Number of Parasites in Control Animals X 100 = % Efficacy

The studies are identified in Table 1 and the results are summarized in Tables 2 and 3. These studies established the minimal effective dose for heartworm prevention at 0.1 mg/kg, and for hookworm control at 0.5 mg/kg. To support a dual claim for heartworm prevention and hookworm control, the finished pharmaceutical dosage forms (tablets) were formulated to provide a target dose of 0.5 mg/kg body weight. In target animal safety studies, the selected dose (0.5 mg/kg) was determined to have a wide margin of safety.

The heartworm and hookworm dose establishment studies summarized in the following sections are identified in Table 1, and the results are detailed in Tables 2 and 3.

1. **Pivotal Heartworm (*D. immitis*) Prevention Dose Titration Studies**
   Three heartworm prevention studies were conducted to determine the minimum effective prophylactic dose: Refer to Table 2 for additional information.

   Study No. MP-147-0185
   purpose: Dose titration study
   Investigator:
   Dr. R. Bradley
   Alachua, Florida
   type of study: Experimental infections and continuous natural exposure.
   animals: Beagle dogs, approximately 5 months of age, four test groups of 3 males and 3 females each, one control group of 4 males and 4 females.

dosage form: Milbemycin oxime 1% powder in gelatin capsules.
route of administration: Oral
controls: One group of dogs receiving lactose placebo in gelatin capsules.
doses tested:
Milbemycin oxime test groups: 0.1, 0.25, 0.5, 1.0 mg/kg body weight.
Control group: 1 g lactose
frequency and interval of treatment: Five treatments at monthly intervals starting 28 days post infection.
study duration: Six months.
results: All doses of milbemycin oxime tested were 100% effective in preventing heartworm infection.

Study No. MP-147-0285 purpose: Dose titration study.
investigator:
Dr. R. Grieve
Madison, Wisconsin
type of study: Experimental infections.
animals: Beagle dogs, approximately 9 months of age, five test groups and one control group of 3 males and 3 females each.
dosage form: Milbemycin oxime 1% powder in gelatin capsules.
route of administration: Oral
controls: One group of dogs receiving lactose placebo in gelatin capsules.
doses tested:
Milbemycin oxime: 0.05, 0.1, 0.25, 0.5. and 1.0 mg/kg body weight.
Control group: 1 g lactose
frequency and interval of treatment: Five treatments at monthly intervals starting 28 days post infection.
study duration: Six months.
results: ll doses of milbemycin oxime tested were 100% effective in preventing heartworm infection.

Study No. MP-147-0186 **purpose:** Dose titration study.
investigator:
Dr. R. Bradley
Alachua, Florida
type of study: Experimental infections and continuous natural exposure.
animals: Beagle dogs, approximately 9 months of age, three test groups and one control group of 4 males and 4 females each.
dosage form: Milbemycin oxime 1% powder in gelatin capsules.
route of administration: Oral
controls: One group of dogs receiving starch placebo in gelatin capsules.
doses tested:
Milbemycin oxime: 0.005, 0.025, 0.05 mg/kg body weight.
Control group: 75 mg starch.
frequency and interval of treatment: Five treatments at monthly intervals starting 28 days post infection.
study duration: Six months.
results:
Milbemycin oxime doses of 0.005, 0.025 and 0.05 mg/kg body weight were 33%, 55% and 92% effective in preventing heartworm disease respectively. Based upon data from studies MP-147-0185, MP-147-0285, and this study, it

is concluded the minimum effective dose for heartworm prevention lies between 0.05 and 0.1 mg/kg body weight.

2. **Pivotal Heartworm (*D. immitis*) Prevention Dose Confirmation Studies**
Two dose confirmation studies were conducted to confirm the selected dose of 0.5 mg/kg body weight. Refer to Table 2 for additional information.

Study No. MP-147-0487 purpose: Dose confirmation study.
investigators:
Drs. B. Blagburn and C. Hendrix
Auburn, Alabama
type of study: Experimental infections and continuous natural exposure.
animals: Beagle dogs, approximately 5 months of age, one test and one control group of 10 males and 10 females each.
dosage form: Tablets (swallow)
route of administration: Oral
controls: One group of dogs received placebo tablets.
dose tested: Milbemycin oxime: dosed according to label directions for size of dog. Each dog received a minimum of 0.5 mg/kg body weight.
frequency and interval of treatment: Nine treatments at monthly intervals.
study duration: Nine months.
results: The target dose of 0.5 mg/kg body weight was 100% effective in preventing heartworm infection.

Study No. MP-147-0887 purpose: Dose confirmation study.
investigator:
Dr. R. Grieve
Fort Collins, Colorado
type of study: Experimental infections
animals: Beagle dogs, approximately 6 months of age, three test and one control group of 4 males and 4 females each.
dosage form: Tablets (swallow).
route of administration: Oral
controls: One group of dogs received placebo tablets.
dose tested: Milbemycin oxime: dosed according to label directions for size of dog. Each dog received a minimum of 0.5 mg/kg body weight.
frequency and interval of treatment: Each milbemycin oxime test group received one dose either 30, 60, 90 days post infection
study duration: Seven months.
results: Complete (100%) protection was achieved in dogs treated at 30 days post infection, with 95% protection at 60 and 90 days.

3. **Non-Pivotal, Corroborative Heartworm (*D. immitis*) Prevention Dose Establishment Studies**
   Two non-pivotal, corroborative studies, MP-147-0184 and MP-147-0284 were conducted but are not summarized here. Results can be found in Table 2.

4. **Pivotal Hookworm (*A. caninum*) Dose Titration Study**
   One dose titration study was conducted to determine the minimum effective dose of removal of adult hookworms (*A. caninum*): Refer to Table 2 for additional information.

   Study No. MH-14 7-0286 purpose: Dose titration study
   investigators:
   Drs. B. Blagburn and C. Hendrix
   Auburn, Alabama
   type of study: Natural infections.
   animals: Mature dogs of mixed breed and sex harboring patent, naturally acquired hookworm infections. Three test groups and one control group of 8 animals each.
   dosage forms: Milbemycin oxime 1% powder in gelatin capsules
   route of administration: Oral
   controls: One group of dogs receiving lactose placebo in gelatin capsules.
   doses tested:
   Milbemycin oxime: 0.25, 0.5, 0.75 mg/kg body weight.
   Control group: 0.5 mg/kg lactose placebo.
   frequency of treatment: One treatment with necropsy seven days later.
   results: The minimum effective dose yielding greater than 90% efficacy was 0.5 mg/kg body weight.

5. **Pivotal Hookworm (*A. caninum*) Dose Confirmation Studies**
   Three dose confirmation studies were conducted to demonstrate the effectiveness of the 0.5 mg/kg body weight dose in removing adult hookworms. Refer to Table 2 for additional information.

   Study No. MH-147-0587 purpose: Dose confirmation study
   investigator: Dr. D. Bowman, Ithaca, NY
   type of study: Natural infections
   animals: Mature mixed breed dogs, one test and control group of 6 males and 6 females each
   dosage form: Tablets (swallow)
   route of administration: Oral
   controls: One group of dogs receiving a placebo tablet.
   dose tested: Milbemycin oxime: dosed according to label directions for size of dog. Each dog received a minimum of 0.5 mg/kg of body weight.
   frequency of treatment: One treatment with necropsy seven days later.
   results: The targeted dose of 0.5 mg/kg body weight was confirmed effective (97.6% removal of hookworms).

   Study No. MH-147-0188
   purpose: Dose confirmation study.
   investigator: Dr. D. Bowman, Ithaca, NY
   type of study: Experimental infections.

animals: Beagle dogs, approximately 5 months of age, one test and one control group of 10 females and 10 males each.
dosage form: Tablets (swallow)
route of administration: Oral
control: One group of dogs receiving placebo tablets.
dose tested: Milbemycin oxime: dosed according to label direction for size of dogs. Each dog received a minimum of 0.5 mg/kg body weight.
frequency and interval of treatment: Treated three times at monthly intervals.
duration of study: Three months
results: The targeted dose of 0.5 mg was 100% effective in removing *Ancylostoma* spp. while *Uncinaria* sp. were refractory to treatment.

Study No. MH-147-0386
purpose: Dose confirmation study.
investigators:
Drs. B. Blagburn and C. Hendrix
Auburn, Alabama
type of study: Experimental infections.
animals: Beagle dogs, approximately 6 months of age and of mixed sexes, four test and one control group of 6 dogs each.
dosage form: Tablets (swallow)
route of administration: Oral
control: One group of dogs receiving placebo tablets.
frequency and interval of treatment: The four test groups were dosed once at either 36, 120, 216 or 360 hours post infection.
study duration: Thirty days.
results: The targeted dose of 0.5 mg/kg body weight was confirmed effective (90.6% hookworm removal in the group dose d 360 hours post-infection).

6. **Non-Pivotal, Corroborative Hookworm (*A. caninum*) Dose Establishment Study**
   One non-pivotal, corroborative study, MH-147-0186 was conducted but is not summarized here. Results can be found in Table 2.

7. **Bioequivalence Corroborative Study**

   Study No. MB-147-0187
   Investigators:
   Dr. I. Bekersky and H. Kramer
   Madison, Wisconsin

   A bioequivalence study was conducted in dogs to demonstrate comparable pharmacokinetic values following administration of a 1% powder formulation versus the commercial tablet dosage formulation. This was deemed necessary because several of the early dose establishment studies utilized the powder formulation. The tablet used in this study was formulated to contain 5.68 mg of milbemycin oxime which provides a 0.5 mg/kg dose per animal.

   A classical two-way crossover design (eight dogs per group) was employed with a 30-day washout period between dosing. Serum milbemycin oxime

concentration-time profiles were determined by a high-performance liquid chromatographic assay.

Statistical analysis (ANOVA) of the pharmacokinetic parameters tested indicated no significant difference ($p>0.05$) in bioavailability between the two pharmaceutical dosage forms.

B. Well-Controlled Clinical Field Trial

A multi-location, well-controlled clinical field trial employing essentially identical study protocols was conducted during 1987-88. The overall objective was to evaluate the prevention of heartworm disease and control of hookworm infection when used under typical veterinary practice condition. The study employed a total of 24 individual veterinary hospitals and clinics in the following nine states: Alabama, Florida, Georgia, Indiana, New Jersey, North Carolina, North Dakota, South Carolina, and Texas (Refer to Table 1 for additional information).

Patients were selected for inclusion in the study from animals presented to the hospital or clinic for routine heartworm examination, physical examinations, immunization, etc. The patients were evaluated for their current heartworm status and , if negative, assigned to either treatment group A (milbemycin oxime) or treatment group X (Filaribits Plus, Norden), the reference drug. The treatment assignments were accomplished by following a computer-generated randomization sequence. Each investigator was provided a unique randomization list or lists.

Upon initiation into the study, each patient underwent a complete physical examination including clinical pathology and fecal examination. The study duration for each dogs was 10 months. Patients were returned to the clinic for follow-up evaluation according to the following schedule:

At 7-10 days post treatment, a parasitological (fecal) examination on all dogs previously found to be positive for hookworm.

At the end of the 2nd month, fecal flotation and circulating microfilariae check.

At the end of the 5th month, *D. immitis* adult antigen test, fecal flotation and circulating microfilariae check.

At the conclusion of the study (10 months), repeat *D. immitis* adult antigen test, fecal flotation, circulating microfilariae check; complete physical examination including blood chemistries and CBC.

Critical evaluation end-points were efficacy in preventing heartworm and controlling hookworm, safety of the product as characterized by the professional investigator and overall acceptability as perceived by the pet owner.

Milbemycin oxime was administered monthly in different sizes of tablets (swallow) based on the weight of the dog. The tablets were formulated to provide a minimum monthly dose of 0.5 mg/kg of body weight. Individual dogs received 10 months of treatment. Over 65 different breeds or types of dogs under a wide

variety of circumstances participated in the trials. Puppies as young as 4 weeks old were included in the trials.

As expected during this extended trial period, many dogs were exposed to a variety of veterinary or animal health products including vaccines, anesthetics, analgesics, anthelmintics, ectoparasiticides (including many flea control products), antimicrobials, antibiotics, anti-inflammatories, steroids, hormone, and many ophthalmic and dermatologic preparations. Both milbemycin oxime and the control drug proved completely safe when used concurrently with these medications.

There were no investigator-documented adverse effects reported in either treatment group during the course of the study. Several comments were received from owners, most concerning vomiting, diarrhea, and weight loss. However, upon examination by the investigator none of these responses could be definitely attributed to either the test drug or reference treatment, but rather to changes in diet, housing situations, or some underlying medical problem.

Seven hundred and sixty-nine (769) milbemycin treated dogs and 743 Filaribits Plus treated dogs were enrolled in the clinical field trial. At the completion of the trial (month 10), 675 milbemycin oxime treated dogs and 658 Filaribits Plus treated dogs were evaluated for efficacy and safety. The remainder of the dogs starting on trial were withdrawn by their owners for a wide variety of reasons, most of which were unrelated to treatment. The most common reasons for declining numbers of patients were the owner moving from the area, change of ownership or death due to unrelated causes.

Interim evaluation points were used to determine the effectiveness of milbemycin oxime for hookworm removal. Dogs with positive hookworm fecal flotations within two weeks of treatment to document removal of adult hookworms.

Only two dogs, which had been identified as heartworm negative prior to the start of the trials, had a heartworm positive indication at completion of the trials. One of the dogs, treated with Filaribits Plus (Norden), was documented as owner non-compliance in giving the medication. The other dog, treated with milbemycin oxime, was documented as an occult infected dog inadvertently admitted to the study. Milbemycin oxime was highly effective in controlling hookworm infections during the clinical studies. Twenty-one percent of the dogs receiving milbemycin in oxime were diagnosed with hookworm infections at some point during the study. By the end of the study period, 97.5% of these dogs were negative on fecal examination. (Refer to Table 3 for additional information.)

Conclusions

Based upon data generated in laboratory studies in over 260 dogs and clinical field trial in well over 600 dogs, it is concluded that milbemycin oxime, administered in a tablet formulation at the recommended dose, is effective at preventing heartworm disease and controlling adult hookworm infections in dogs.

III. TARGET ANIMAL SAFETY

Summary

Five target animal safety studies were conducted in dogs to address the tolerance and safety of milbemycin oxime. Studies were specifically designed to evaluate safety of the drug administered at exaggerated doses in breeding animals, in a long-term (10-month duration) study, in weanling puppies and in dogs with patent heartworm infection. All studies were conducted with the final commercial tablet formulation.

These studies clearly demonstrated that milbemycin oxime tablets provide a wide therapeutic index when administered orally to dogs at the recommended dose of 0.5 mg/kg body weight, monthly. The chronic studies provided evidence that dogs tolerate up to five times the use rate administered on three consecutive days each month while the reproduction study demonstrated no adverse effects in the pregnant bitch or her offspring following daily administration of the drug at three times its monthly use rate throughout pregnancy. A mild, transient shock-like reaction was observed when milbemycin oxime was administered to certain heartworm-infected dogs with high microfilaremic counts.

A. Pivotal Studies

1. **Study 1 - A Reproduction Study in Beagle Dogs with Milbemycin Oxime (CGA-179246), International Research and Development Corporation, Mattawan Michigan, Study No. 382-121.**

   a. Type of Study: This was a reproduction study in which the drug was administered in tablet form at daily doses of 3X the monthly use rate of 0.5 mg/kg body weight.

   b. Investigators Study Director:

      Mr. James Schardein
      International Research and
      Development Corporation
      Mattawan, Michigan

      Co-Study Director:

      Martin Gilman, Ph.D.
      Laboratory Research
      Enterprises
      Kalamazoo, Michigan

c. General Design: The objective of the study was to evaluate the effects of milbemycin oxime on reproduction in the dog. Gonadal function, estrus cycle, mating behavior, conception, length of gestation, parturition, lactation, weaning, viability, growth, and development of the offspring were measured parameters. Additionally, the incidence of any malformations in young puppies was determined by external examinations and examination of skeletal radiographs.

Intended use regiment for milbemycin oxime is once monthly. Preliminary studies indicated that milbemycin oxime accumulates in the mild of lactating bitches following daily dosing. Since nursing pups would then receive an extremely high amout based on their body weight, the study was divided into two phases. In the reproduction phase, studs were dosed daily for a minimum of 90 days through the end of mating and bitches were dosed daily through mating and until one week period to whelping. In the pup safety evaluation phase, untreated pregnant bitches were dosed once either before, on the day of, or shortly after whelping in order to simulate the real-life monthly dosing situation. In both phases, milbemycin oxime was administered at three times the intended use rate.

animals: Purebred beagle dogs.

Twenty adult males and 20 adult females, reproduction phase; 25 pregnant females, pup safety evaluation phase.

All animals were a minimum of two years of age and bitches had whelped at least two litters.

test materials: Placebo tablets were formulated identically to the test tablets but without the inclusion of active ingredient.

Milbemycin oxime tablets were formulated to deliver orally 5.68 mg per tablet.

dosage: 0 (placebo), 1.5 mg/kg body weight/day.

route of administration: Orally by tablet

test duration: From three months prior to breeding of the parental generation to weaning of the F1 generation; the total time of the study was approximately nine months.

pertinent parameters measured: General observations were survival, appearance and behavior, body weight, food consumption, sperm evaluation (P0).

Reproduction and litter observations were stud and bitch fertility indices, mean gestation length, pup viability, pup growth , pup survivability, pup malformations.

d. Results:

clinical observations: No clinical signs of toxicity were observed in the P0 and F1 generation animals. Survival was 100% for all parental animals. No treatment-related body weight effects were observed; no consistent food consumption variances occurred to indicated compound-related effects.

sperm evaluation: The values of the treated group for semen volume, sperm count, percent progressive motility, speed of progression, pH, and sperm morphology and color were not different from the control group values.

reproduction parameters: Treatment with milbemycin oxime had no deleterious effects on reproduction parameters. Stud and bitch fertility indices and mean gestation length for the treated group were not different form the control values.

pup viability: Mean numbers of live and dead pups at birth in the treated group were comparable to the control group values. Pup survival indices throughout lactation did not indicate any adverse treatment effects on offspring viability. Gestation and weaning indices and sex distribution of pups during lactation for the treated group were not different form the control values.

pup growth: Treatment of parental animals with milbemycin oxime did not adversely affect growth of their offspring. Mean pup body weight values for female pups form the treated group were less than the control values on several occasions during lactation (days 4, 7, and 42). However, the mean pup body weight values for the treated group were comparable to or greater than historical control values for that colony.

pup malformations: External evaluation, necropsy of dead animals, and radiographs of live pups from control and treated groups revealed no evidence of treatment-related malformations.

e. Conclusions: Beagle studs and bitches were treated daily with milbemycin oxime at 3X the monthly use level or a placebo throughout a premating and mating period and in bitches until one week prior to whelping in the reproduction phase of this study. Untreated pregnant beagle bitches were treated once with 3X the monthly use level of milbemycin oxime on or about day 4 prior to whelping, day 1 prior to whelping, whelping day, and days 1 and 2 post-whelping in the pup safety evaluation phase. Bitches in both phases were allowed to deliver and nurse their pups through day 42 of lactation. Body weight, food intake, semen quality, reproduction parameters,and pup viability and growth were evaluated.

Milbemycin oxime had no effect on any of the reproduction or litter parameters measured. Data were similar in all groups to concurrent controls, to historical control data, and to data collected during this study period from the production colony.

2. **Study 2- Ten-Month Oral Toxicity Study in Beagle Dogs With Milbemycin Oxime (CGA-179246), International Research and Development Corporation, Mattawan, Michigan, Study No. 382-122**.

   a. Type of study: This was a chronic study (10 months) during which the drug was administered in tablet form at 0, 1X, 3X, or 5X the monthly use rate of 0.5 mg/kg body weight daily for three consecutive days each month.

   b. Investigator: Study Director:

      Edwin Goldenthal, Ph.D.
      International Research and
      Development Corporation
      Mattawan, Michigan

   c. General Design: The objective of the study was to evaluate any chronic toxicity effects of milbemycin oxime in the dog. Observations were made for signs of overt toxicity, morbidity or mortality; body weight changes; food consumption; ophthalmologic examination; hematological, biochemical, and urinalysis determination; and macroscopic and microscopic examination of tissues.

      The intended use regimen of milbemycin oxime is once monthly. Animals were dosed monthly at 1X, 3X,and 5X the recommended use rate (0.5 mg/kg body weight). However, doses were given daily over three consecutive days each month for a total of ten months.

      animals: Purebred beagle dogs.

      Thirty-two males and 32 females.

      All animals were approximately eight weeks of age at initiation.

      control: A placebo tablet identical to the active tablet but without the inclusion of active ingredient.

      dosage form: Milbemycin oxime tablets formulated to deliver orally 5.68 mg per tablet.

      dosage: By protocol design, technicians dosed the animals without knowledge of which groups were treated. Because of the blinding requirement, all animals received the same number of tablets on each dosing day.

      route of administration: Orally by tablet

      test duration: Ten months on study, starting with eight week-old puppies.

      pertinent parameters measured: Clinical observations, hematologic and serum chemistry measurements, body weight changes, organ weights, and

macroscopic and microscopic tissue evaluations were used to assess any potential effects in the dogs.

d. Results:

clinical observations: All criteria observed at the 1x rate were similar to the control animals. At the 3X rate (dosed daily for three consecutive days) a few dogs exhibited slight to mild transient trembling and/or ataxia during the first three days of the study; no signs were observed during the remainder of the study. At the 5X rate (dosed daily for three consecutive days), transient trembling and/or ataxia was observed in most of the dogs during the first three days of the study; no signs were observed during the remainder of the study.

These ataxia and/or trembling findings were considered a consequence of over-dosage for these young puppies. The dosage had been calculated for adult dogs weighing 11 to 25 lbs., whereas these dogs at study initiation weighed an average of 4 lbs. Therefore, these dogs received a 2.5-5X increase in dosage over the targeted doses of 1X, 3X and 5X the recommended use rate. Side-effects were not seen at any subsequent dosing period. A further study, summarized in this document, more clearly defines the effect of milbemycin oxime in dogs aged eight to twelve weeks.

One control male and one female dosed at the 5X use rate died on day 3 and one male receiving the 1X use rate died on day 38. These deaths were considered unrelated to administration of the test article because of the absence of clinical findings or any dose-response relationship.

laboratory findings: No treatment-related effects were observed in any of the parameters for hematology, clinical chemistry, body weight, organ weight or pathology.

e. Conclusions: No serious drug-related effects were detected following monthly use rate, given daily for three consecutive days. A mild transient ataxia and/or trembling reaction was observed in eight-week-old puppies at rates in excess of 3X and 5X the normal dose. At all subsequent monthly dosings in 12-week and older dogs, neither these nor any other overt signs developed. All parameters including gross and microscopic tissue changes confirmed the absence of compound-related signs of toxicity.

3. **Study 3 - Acute Study in Young Beagle Dogs With Milbemycin Oxime, International Research and Development Corporation, Mattawan, Michigan, Study No. 382-124.**

a. Type of Study: This was an acute study in beagle puppies 8, 10, and 12 weeks of age in which milbemycin oxime was dosed orally (as tablets) at dosage levels of 1X, 5X, 15X, or 25X the recommended use rate, given daily for three consecutive days.

b. Investigator: Study Director:

Edwin Goldenthal, Ph.D.
International Research and
Development Corporation
Mattawan, Michigan

c. General Design:

The objective of this study was to further evaluate the clinical side-effects noted in the previously summarized chronic study in puppies aged 8, 10, and 12 weeks. The drug was administered daily for three consecutive days.

animals: Purebred beagle dogs.

Thirty male and 30 female dogs: ten males and ten females at eight weeks of age; ten males and ten females at ten weeks of age; and ten males and ten females at 12 weeks of age.

control: Animals in the control group were left untreated. No placebo was given.

dosage form: Three sizes of finished dosage form (tablets) containing 2.3 mg, 5.68 mg and 11.36 mg milbemycin oxime, respectively.

dosage: - 0 (no treatment)

- 1X - based on actual body weight, given 0.5 mg/kg on three consecutive days.
- 5X - based on actual body weight, given 2.5 mg/kg on three consecutive days.
- 15X - based on actual body weight, given 7.5 mg/kg on three consecutive days.

- 25X - based on actual body weight, given 12.5 mg/kg on three consecutive days.

route of administration: Orally by tablet, finished dosage form.

test duration: Animals were dosed daily for three consecutive days and observed for 11 days.

pertinent parameters measured: Clinical observations, mortality, and body weight.

d. Results:

clinical observations: Treated animals exhibited transient clinical signs including ataxia, trembling, prostration, and ptyalism. None of these signs were seen after day 6. These effects, especially ataxia and trembling, were dose-related at all ages. Prostration was seen in five of 12 animals at 25X and only one of 12 animals at 15X. Ptyalism was seen in four of 12 animals at 25X and only one of 12 animals at 15X. The severity of the ataxia and trembling was greatest at 25X, especially in eight-week- and ten-week-old animals. Onset of trembling and/or ataxia was noted on the second day of dosing and was generally observed for one or two additional days longer in ten-week-old animals at 25X. Animals were notably affected at 15X especially eight-week- and ten-week-old females, though less severely than at 25X. The effects were slight and sporadic at 5X; six of the 12 5X animals exhibited no ataxia or trembling. There were no effects seen at 1X.

These effects showed a slight age-related occurrence. Twelve-week-old males and females were less affected than eight-week or ten-week-old males and females at 25X. At 15X, 12-week-old females were less affected than eight-week or ten-week-old females; 12 week-old males were similar to eight-week-or ten-week-old males.

mortality and body weights: No effects were noted in these parameters.

e. Statistical analysis: Descriptive statistics were calculated where appropriate.

f. Conclusions: Treatment-related clinical signs, especially ataxia and trembling, were the only effects noted for the parameters measured. These effects were dose-related at all ages. The incidence, severity, and length of occurrence were greatest at 25X, less at 15X, and very slight at 5X. Six of 12 animals at 5X showed no trembling or ataxia. The effects were also slightly age-related; 12-week-old males and females were less affected than eight-week- or ten-week-old animals at 25X and 12-week-old females were less affected than eight-week or ten-week-old females at 15X. There were no effects seen at 1X.

The recommended dosage regime requires administration of milbemycin oxime at the rate of 0.5 mg/kg once every 30 days (or calendar month).

Since no effects were noted at 1X and only minor effects noted at 5X in puppies dosed at these rates for three consecutive days, a wide margin of safety exists for use of this product in young dogs.

4. **Study 4 - A 70-Day Subchronic Toxicity Study in Heartworm (*Dirofilaria immitis*)- Infected Mongrel Dogs with Milbemycin Oxime, Stillmeadow, Inc., Houston, Texas, Study No. 5218-88.**

   a. Type of study: This was a subchronic toxicity study in mixed breed dogs where milbemycin oxime was dosed at 1X and 3X the monthly use rate for three monthly intervals to patently heartworm-infected dogs.

   b. Investigator Study Director:

      Robert Faith, DVM, Ph.D.
      Stillmeadow, Inc.
      Houston, Texas

   c. General Design: The objective of this study was to determine the potential toxicity of milbemycin oxime in heartworm-infected dogs during monthly administration for three months.

      animals: Dogs of unknown breeding or age.

      Forty-seven animals, 27 males and 20 females.

      Source of dogs was the Harris County Rabies/Animal Control, Houston, Texas.

      control: Animals in the control group were left untreated.

      dosage form: Four sizes of finished dosage form (tablets) containing 2.3 mg, 5.68 mg, 11.36 mg and 22.72 mg milbemycin oxime, respectively.

      dosage: - 0 (no treatment)

      - 1X - based on body weight, given 0.5 mg/kg body weight.
      - 3X - based on body weight, given 1.5 mg/kg body weight.

      route of administration: Orally by tablet, finished dosage form.

      test duration: Animals were dosed once a month for three consecutive months. The animals were observed for approximately a two-week period following the last monthly administration.

      pertinent parameters measured: Clinical signs, body weights, food consumption, hematology (at 3 and 24 hours after each dosing), clinical chemistry, urinalysis, gross pathology, microfilarial counts, and estimation of adult heartworms (at necropsy).

d. Results:

clinical observations: Within hours following the initial dosing, several treated animals exhibited varying degrees of reaction including labored respiration, abdominal breathing, pale mucous membranes, vomiting, and lethargy. However, these signs had disappeared in all animals by the end of the second day after dosing.

Following the second and third monthly dosing, fewer animals exhibited side effects which were also less severe and equally transient.

body weights, food consumption, hematology, clinical chemistry, ophthalmology, and urinalysis: No treatment related effects were observed for any of these parameters.

microfilaria: Microfilarial counts decreased markedly in both treated groups within 24 hours after Dose 1. After Doses 2 and 3, little further change in microfilarial count scores occurred.

gross necropsy and heartworm count: None of the lesions found during gross necropsy were considered to be related to treatment with milbemycin oxime. Adult heartworms were found in the hearts and associated vessels of all animals in the study in numbers ranging from 3 worms to over 120 worms. Most animals had no gross lesions other than those associated with the infestation of heartworms.

e. Statistical analysis: Because the test animals were of mixed breed, varying ages and sizes and of unknown history and health (heartworm-infested), only descriptive statistics (means, etc.) were calculated where appropriate.

f. Conclusions: Administration of milbemycin oxime to heartworm-infected mixed breed dogs at 1 or 3 times the use rate once each month for 3 consecutive months resulted in minor clinical signs in several dogs after the initial dose. Symptoms were transient and of generally slight to moderate severity including abdominal respiration, pale mucous membranes, and decreased activity. Clinical signs were rare and even less severe after Doses 2 and 3. These clinical signs were thought to be the result of the microfilariacidal effects of milbemycin oxime. There were no other side-effects seen in milbemycin oxime-treated dogs throughout the study.

A decrease in the numbers of circulating mirofilaria was seen in dogs at both dose levels after each administration when compared to baseline values and to control values.

5. **Study 5 - A 70-Day Subchronic Toxicity Study in Heartworm (*Dirofilaria immitis*) - Infected Mongrel Dogs With Milbemycin Oxime, Auburn University, Department of Pathobiology.**

   a. Type of study: This was a subchronic toxicity study in mongrel dogs where milbemycin oxime was dosed at 1X and 5X the monthly use rate for three monthly intervals to patently heartworm-infected dogs.

   b. Investigator Study Directors:

      Bryon L. Blagburn, Ph.D and Charles M. Hendrix, DVM, Ph.D.
      Department of Pathobiology
      College of Veterinary Medicine
      Auburn University, Auburn, AL

   c. General design: The objective of this study was to determine the potential toxicity of milbemycin oxime in heartworm-infected dogs during monthly administration for three months.

      animals: Dogs of unknown breeding or age.

      Thirty-six animals, 19 males and 17 females.

      Source of dogs was the Department of Laboratory Animal Health, College of Veterinary Medicine, Auburn University, Auburn, Alabama.

      control: Animals in the control group were left untreated.

      dosage form: Four sizes of finished dosage form (tablets) containing 2.3 mg, 5.68 mg, 11.36 mg, and 22.72 mg milbemycin oxime, respectively.

      dosage: - 0 (no treatment)

      - 1X - based on body weight, given 0.5 mg/kg body weight.
      - 5X - based on body weight, given 2.5 mg/kg body weight.

      route of administration: Orally by tablet, finished dosage form.

      test duration: Animals were dosed once a month for three consecutive months. The animals were observed for approximately a two-week period following the last monthly administration.

      pertinent parameters measured: Clinical signs, body weights, food consumption, hematology (at 3 and 24 hours after each dosing), clinical chemistry, ophthalmology, urinalysis, gross pathology, microfilarial counts, and estimation of adult heartworms (at necropsy).

   d. Results:

      clinical observations: Transient clinical reactions were observed in the 1X and 5X groups within hours following the initial dosing with milbemycin

oxime. The signs observed included: depression, labored breathing, recumbency, lethargy, coughing, vomiting, and salivation. Similar signs were not observed following the second or third treatments. This clinical reaction was thought to be the result of the microfilarial action of milbemycin oxime.

other parameters: No other parameters (changes in body weights, ophthalmic examination, food consumption, hematologic values, serum chemistry values, urinalysis, presence of adult heartworm, necropsy findings) were affected by the administration of milbemycin oxime at either the 1X or 5X dosage.

pathology: No treatment related pathological findings were observed. Other findings such as vascular thrombosis and endarteritis were consistent with canine heartworm disease.

e. **Statistical analysis:** Because the test animals were of mixed breed, age and size, and of unknown history and health (heartworm-infested), only descriptive statistics (means, etc.) were calculated where appropriate.

f. **Conclusions:** Administration of milbemycin oxime to patently heartworm-infected mixed breed dogs at 1 and 5 times the use rate once each month for 3 consecutive months resulted in minor clinical signs after the initial dose. Symptoms were transient and of generally slight to moderate severity including depression, labored breathing, recumbency, lethargy, coughing, vomiting, and salivation. No effects were observed after the second or third treatments. These clinical signs were thought to be the results of the microfilarial action of milbemycin oxime. A decrease in the numbers of circulating microfilaria was seen in dogs at both dose levels when compared to initial values and to control values.

B. Corroborative Studies

Preliminary, non-pivotal animals safety studies were conducted to evaluate the potential toxicity of milbemycin oxime and to develop range-finding data in support of pivotal animal safety study protocol development.

1. **Pilot Limit Test in Dogs**
   Milbemycin oxime technical in a powdered formulation was administered orally via gelatin capsules to 2 male and 2 female beagle dogs at a dose of 200 mg/kg. All dogs were observed for 14 days following dosing. Clinical signs observed in all animals included apparent compound in the feces, emesis with apparent compound, inappetence, and few or no feces. The onset of these signs occurred by 2 hours post dose and all animals appeared normal by test day 4. All animals exhibited a body weight gain by test day 15. Hematology and clinical chemistry evaluations performed on all animals on test day 15 were unremarkable. Based on these data and standard evaluation criteria, a single oral dose of 200 mg/kg of milbemycin was well-tolerated by beagle dogs and is considered to have, at most, a lower order of acute oral toxicity in the dog.

2. **Pilot Oral Rising-Dose Tolerance Study**
   Milbemycin oxime technical powder was administered orally to one male and one female beagle dog at successively increasing doses of 2, 4, 8, or 16 mg/kg, at 7-day intervals for 4 consecutive weeks. General observations, body weight, food consumption, hematology, clinical chemistry, urinalysis, and physical examinations were performed on both animals. All doses were well-tolerated and no adverse clinical effects observed.

3. **Oral Toxicity Study in Dogs**
   Milbemycin oxime technical in a powder formulation was administered orally by capsule to two beagle dogs each at dosage levels of 1.5 and 2.5 mg/kg/day for 36 consecutive days. Control dogs received empty gelatin capsules.

   The results demonstrated that all animals survived the six-week study, all criteria examined for the treated groups were considered to be comparable to findings in the control group, and no toxicity related to the administration of the test article was observed in dogs at doses tested; approximately 3X and 5X the use rate.

4. **Pregnant Dog Studies**
   In one study three "proven" purebred beagle bitches each received 1.5 mg/kg (three times the recommended use rate) beginning on the day of the first observed "mating tie" and daily thereafter until weaning.

   In a separate evaluation, five "proven," pregnant, purebred beagle bitches scheduled to whelp in two weeks received 1.5 mg/kg per day for days 1-12 and approximately 0.75 mg/kg through the remaining dosing period. Each bitch was dosed beginning approximately two weeks prior to whelping and continuing through one week post-whelping.

   The bitches from both studies gained weight, remained healthy and did not exhibit any clinical signs of toxicity. Some puppies nursing these bitches exhibited possible compound-related effects. These effects were attributed to the exaggerated dosing regimens used; up to three times the recommended dose administered daily instead of monthly.

5. **Determination of Milbemycin Oxime Residues in the Colostrum of Dogs**
   Analysis of milk samples from the nursing bitches described in the Pregnant Dog Studies determined the presence of milbemycin oxime at levels varying from 0.26 to 0.54 ppm.

6. **Young Puppy Study**
   The purpose of this study was to evaluate the direct effect of exaggerated doses of milbemycin oxime given to newborn (day of birth) puppies.

   A total of 50 one-day-old purebred beagle puppies from 10 different litters were included in this study. Thirty puppies were dosed with milbemycin oxime at 0.5 ppm, 15 received water only.

   Each of the puppies received the allotted test material, suspended in water. All of the animals were dosed on their day of birth (Day 1) by gavage and for a total of six consecutive days. The amount of fluid dispensed was approximately that obtained one nursing period.

   One of 30 puppies receiving 0.5 ppm and four of 15 puppies receiving 1.0 ppm died from possible compound-related effects attributed to exaggerated dosing. One of five control puppies died from placebo dosing-related complications.

7. **Effects of Treatment of Adult Collies with Milbemycin Oxime**
   The objective of this study was to determine if observable adverse reactions occur following treatment of adult collies with milbemycin oxime at dosages of 0.5 (recommended dose) and 2.5 mg/kg body weight (five times the recommended dose).

   Ten adult collies (five males and five females) were assigned to one of two treatment groups: Group I dogs received a dose of 0.5 mg/kg body weight and Group II dogs received a dose of 2.5 mg/kg body weight. Each dog was treated twice, one week apart. The study was repeated in cross-over fashion; in this case, dogs having received milbemycin oxime at 0.5 mg/kg body weight were treated at 2.5 mg/kg body weight and those treated at 2.5 mg/kg were treated at 0.5 mg/kg body weight. Each dog received two treatments, one week apart.

   For a period of 8 hours following treatment, dogs were observed at 30-minute and one-hour intervals for adverse reactions to or side-effects resulting from administration of milbemycin oxime.

   All collies appeared normal after treatment with milbemycin oxime at both dosages. No apparent adverse reactions or side-effects were observed.

8. **Oral Rising-Dose Toxicity Study in Collies**
The purpose of this study was to determine whether observable adverse effects occur following treatment with milbemycin oxime at rising dosages of 2.5 mg/kg (5X the recommended dose), 5.0 mg/kg (10X), 10 mg/kg (20X) and 12.5 mg/kg (25X) in collie dogs.

Fourteen collie dogs (8 males, 6 females) ages one to seven years were treated with milbemycin oxime technical powder according to the following regime:

Day Dose	**No. Treated**	**Dosage**	**X Label Dose**
0	14	2.5 mg/kg	5X
14	14	5.0 mg/kg	10X
28	7	10.0 mg/kg	20X
32	7	10.0 mg/kg	20X
56	14	12.5 mg/kg	25X

Dogs were observed hourly for eight hours post-treatment for any adverse reactions to or side-effects resulting from milbemycin oxime administration. Blood for hematology and serum chemistry evaluation was drawn from all animals three hours post-treatment. Prior to treatment, parasitologic examinations revealed the presence of various nematodes and/or acarines in eleven of fourteen dogs. Treatment of collie dogs with milbemycin oxime at 2.5 mg/kg (5X), 5.0 mg/kg (10X) and 10.0 mg/kg (20X) did not result in demonstrable toxic reactions. Results of hematology and serum chemistries from blood drawn three hours following each treatment revealed no obvious abnormal trends.

Treatment with milbemycin oxime at 12.5 mg/kg (25X) resulted in an adverse reaction in one collie. The animal was markedly ataxic, pyrexic and demonstrated periodic recumbency. Results of hematology and serum chemistry evaluation revealed elevated blood glucose which was attributed to stress from the adverse reaction. The animal was euthanized due to the likelihood of an unacceptably long period of convalescence. On post-mortem examination, this dog was found to be parasitized with adult *Dirofilaria immitis*. Histopathologic examination demonstrated changes consistent with canine heartworm disease. No other adverse reactions were observed in animals following treatment with milbemycin oxime at 12.5 mg/kg (25X).

Summary

In summary, the corroborative safety studies demonstrated safety in adult dogs, including collies. Additional studies in pregnant dogs provided evidence that milbemycin oxime is safe for pregnant dogs. Puppies nursing females which received exaggerated dosing regimens (up to three times the recommended dose given daily instead of monthly), demonstrated compound related effects. These effects were directly attributable to the exaggerated dosing regimen. Subsequent pivotal safety studies using exaggerated, but less severe, dosing regimens demonstrated safety to pregnant females and puppies.

IV. HUMAN SAFETY

Human Safety Relative to Food Consumption:

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.

Human Safety Relative to Possession, Handling and Administration:

Labeling contains adequate caution statement.

Labeling states: "Keep out of reach of children."

V. AGENCY CONCLUSIONS

The data submitted in support of this NADA comply with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. The data demonstrated that Interceptor (milbemycin oxime) Tablets when used under the labeled conditions of use is safe and effective.

Under Section 512 (c)(2)(F)(i) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this New Animal Drug Application qualifies for five years of marketing exclusivity because milbemycin oxime is a new drug that has never been previously approved under Section 512 (b)(1) of the Federal Food, Drug, and Cosmetic Act.

The drug is restricted to use by or on the order of a licensed veterinarian because professional expertise is required to determine the existence of heartworm and/or hookworm infection, and to then properly treat existing heartworm infection prior to starting treatment with Interceptor (milbemycin oxime) Tablets in a prevention program, and for the control of hookworm infection.

Table 1: Identification of Investigators and Locations for Milbemycin Oxime Dose Establishment and Clinical Field Trial Studies

Trial Number	Formulation[1]	Investigator(s)	Location/ Address	Type of Trial[2]
MH-147-0286	1%	Drs. B. Blagburn and C. Hendrix	Auburn Univ. Auburn, AL	ED
MH-147-0587	M	Dr. D. Bowman	Cornell Univ. Ithaca, NY	ED
MH-147-0188	M	Dr. D. Bowman	Cornell Univ. Ithaca, NY	ED
MH-147-0386	M	Drs. B. Blagburn and C. Hendrix	Auburn Univ. Auburn, AL	ED
MH-147-0186	1%	Drs. B. Blagburn and C. Hendrix	Auburn Univ. Auburn, AL	ED
MH-147-0487	M	Drs. B. Blagburn and C. Hendrix	Auburn Univ. Auburn, AL	ED
MP-147-0185	1%	Dr. R. Bradley	Alachua, FL	ED
MP-147-0285	1%	Dr. R. Grieve	Univ. of Wisconsin Madison, WI	ED
MP-147-0186	1%	Dr. R. Bradley	Alachua, FL	ED
MP-147-0887	M	Dr. R. Grieve	Colorado State Univ. Fort Collins, CO	ED
MB-147-0187	1% & M	Drs. B. Blagburn, C. Hendrix, and H. Kramer	Auburn Univ. Auburn, AL Hazleton Labs Madison, WI	ED
MP-147-0184	1%	Dr. R. Bradley	Alachua, FL	ED
MP-147-0284	1%	Drs. B. Blagburn and C. Hendrix	Auburn Univ. Auburn, AL	ED
ADL-MT-147-00-87	M	Dr. B. Adler	Woodbridge Vet. Group Woodbridge, NJ	ET
AYC-MT-147-00-87	M	Drs. E. Aycock and W. Legg	Lewisville North Animal Lewisville, TX	ET
COB-MT-147-00-87	M	Dr. S. Cobb	Cobb Animal Clinic Greensboro, NC	ET
COL-MT-147-00-87	M	Dr. J. Colley	Opelika Animal Hospital Opelika, AL	ET
DAY-MT-147-00-87	M	Dr. J. Dorney	Summit Dog & Cat Hospital Summit, NJ	ET
FEI-MT-147-00-87	M	Dr. D. Feinberg	Charles Towne Vet. Hospital Charleston, SC	ET
GLO-MT-147-00-87	M	Dr. P. Glouton	Lilburn Animal Hospital Lilburn, GA	ET
GRA-MT-147-00-87	M	Dr. R. Graves	Ocean Breeze Animal Clinic Jensen Beach, FL	ET
HAL-MT-147-00-87	M	Dr. M. Hall	Ocoee Animal Hospital Ocoee, FL	ET
JAC-MT-147-00-87	M	Dr. M. Jacobsen	Michigan Road Animal Hospital Indianapolis, IN	ET
KIN-MT-147-00-87	M	Dr. J. Kinnarney	Reidsville Veterinary Hospital Reidsville, NC	ET
MAR-MT-147-00-87	M	Dr. C. Maret	Crestview Animal Hospital Indianapolis, IN	ET
PAR-MT-147-00-87	M	Dr. W. Paramore	Keystone Square Animal Hospital Indianapolis, IN	ET

Trial Number	Formulation[1]	Investigator(s)	Location/ Address	Type of Trial[2]
PAS-MT-147-00-87	M	Dr. D. Passman	Port St. Lucie Animal Hospital Fort Pierce, FL	ET
RAA-MT-147-00-87	M	Dr. J. Raab	Tri-County Animal Hospital Fort Pierce, FL	ET
SAI-MT-147-00-87	M	Dr. J. Saidla	Auburn Animal Hospital Auburn, AL	ET
MEE-MT-147-00-87	M	Dr. K. Schoolmeester	Guilford-Jamestown Veterinary Hospital Greensboro, NC	ET
SCH-MT-147-00-87	M	Dr. W. Schrader	Central Houston Vet. Hospital Houston, TX	ET
SIM-MT-147-00-87	M	Dr. L. Simmons	Sand Lake Animal Clinic Orlando, FL	ET
SMI-MT-147-00-87	M	Dr. C.P. Smith	Trail Animal Clinic Miami, FL	ET
STR-MT-147-00-87	M	Dr. N. Striegel	Animal Health Clinic Fargo, ND	ET
THO-MT-147-00-87	M	Dr. S. Thompson	The Pet Vet Veterinary Clinic Mt. Pleasant, SC	ET
UTG-MT-147-00-87	M	Dr. H. Utgard	Dade Animal Hospital North Miami Beach, FL	ET
WAD-MT-147-00-87	M	Dr. T. Wade	Jamestown Veterinary Clinic Jamestown, NC	ET

[1]1% = Milbemycin oxime 1% powder formulation; T = Unformulated milbemycin oxime; M = Market formulation, tablets
[2]ED = Efficacy - Dose titration or confirmation; ET = Efficacy - Well-controlled clinical field trial

Table 2: Summary of Milbemycin Oxime Dose Establishment Studies for Prevention of Heartworm Disease and Hookworm Control

Hookworm Control (*Ancylostoma* sp.)

Treatment[1] – Milbemycin Oxime mg/kg	No. of Dogs Treated	No. of Dogs with Adult Worms Found	Range of Worm Counts in Infected Dogs	Total Worms Found	Percent Efficacy
1% MH-147-0286-Naturally Acquired Infections Placebo Control	8	8	14-536	1,155	-
1% MH-147-0286-Naturally Acquired Infections 0.25	8	8	1-161	362	68.7

Treatment[1] – Milbemycin Oxime mg/kg	**No. of Dogs Treated**	**No. of Dogs with Adult Worms Found**	**Range of Worm Counts in Infected Dogs**	**Total Worms Found**	**Percent Efficacy**
1% MH-147-0286-Naturally Acquired Infections 0.50	8	6	0-38	59	94.9
1% MH-147-0286-Naturally Acquired Infections 0.75	8	2	0-8	12	98.9
M MH-147-0587 - Naturally Acquired Infection Placebo Control	12	12	9-136	930	-
M MH-147-0587 - Naturally Acquired Infection 0.5	12	5	0-11	16	97.6
M MH-147-0188-Experimentally Induced Infection Placebo Control	10	10	6-123	561	-
M MH-147-0188-Experimentally Induced Infection 0.5	10	0	0	0	100
M MH-147-0386-Experimentally Induced Infection Placebo Control	6	6	15-185	589	-

Treatment[1] – Milbemycin Oxime mg/kg	**No. of Dogs Treated**	**No. of Dogs with Adult Worms Found**	**Range of Worm Counts in Infected Dogs**	**Total Worms Found**	**Percent Efficacy**
M MH-147-0386-Experimentally Induced Infection 0.5-36 Hour Post-Infection	6	6	26-29	301	48.9
M MH-147-0386-Experimentally Induced Infection 0.5-120 Hour Post-Infection	6	6	10-31	99	83.2
M MH-147-0386-Experimentally Induced Infection 0.5-216 Hour Post-Infection	6	6	7-35	111	81.2
M MH-147-0386-Experimentally Induced Infection 0.5-360 Hour Post-Infection	6	5	0-30	55	90.6
1% MH-147-0186-Naturally Acquired Infections Placebo Control	9	9	14-545	1,559	-
1% MH-147-0186-Naturally Acquired Infections 0.01	4	4	47-299	521	24.8
1% MH-147-0186-Naturally Acquired Infections 0.1	9	9	17-112	614	60.6

Treatment[1] – Milbemycin Oxime mg/kg	**No. of Dogs Treated**	**No. of Dogs with Adult Worms Found**	**Range of Worm Counts in Infected Dogs**	**Total Worms Found**	**Percent Efficacy**
1% MH-147-0186-Naturally Acquired Infections 0.25	9	7	0-217	585	62.5
1% MH-147-0186-Naturally Acquired Infections 0.5	9	6	0-88	121	92.2
M MH-147-0847-Experimentally Acquired Infections Placebo Control	8	8	51-462	1,160	-
M MH-147-0847-Experimentally Acquired Infections 0.5-Single Treatment	9	7	0-41	131	89.9
M MH-147-0847-Experimentally Acquired Infections Placebo Control	10	10	13-83	302	-
M MH-147-0847-Experimentally Acquired Infections 0.5-Multiple Monthly Treatments	10	8	0-5	13	95.7

Heartworm Prevention

Treatment[1] – Milbemycin Oxime mg/kg	**No. of Dogs Treated**	**No. of Dogs with Adult Worms Found**	**Range of Worm Counts in Infected Dogs**	**Total Worms Found**	**Percent Efficacy**
1% MP-147-0185 - Experimentally Induced and Naturally Exposed Infections Placebo Control	8	8	2-14	67	-
1% MP-147-0185 - Experimentally Induced and Naturally Exposed Infections 0.1	6	0	0	0	100
1% MP-147-0185 - Experimentally Induced and Naturally Exposed Infections 0.25	6	0	0	0	100
1% MP-147-0185 - Experimentally Induced and Naturally Exposed Infections 0.50	6	0	0	0	100
1% MP-147-0185 - Experimentally Induced and Naturally Exposed Infections 1.0	6	0	0	0	100

Treatment[1] – Milbemycin Oxime mg/kg	**No. of Dogs Treated**	**No. of Dogs with Adult Worms Found**	**Range of Worm Counts in Infected Dogs**	**Total Worms Found**	**Percent Efficacy**
1% MP-147-0285 - Experimentally Acquired Infections Placebo Control	6	6	5-20	75	-
1% MP-147-0285 - Experimentally Acquired Infections 0.05	6	0	0	0	100
1% MP-147-0285 - Experimentally Acquired Infections 0.1	6	0	0	0	100
1% MP-147-0285 - Experimentally Acquired Infections 0.25	6	0	0	0	100
1% MP-147-0285 - Experimentally Acquired Infections 0.5	6	0	0	0	100
1% MP-147-0285 - Experimentally Acquired Infections 1.0	6	0	0	0	100

Treatment[1] – Milbemycin Oxime mg/kg	**No. of Dogs Treated**	**No. of Dogs with Adult Worms Found**	**Range of Worm Counts in Infected Dogs**	**Total Worms Found**	**Percent Efficacy**
1% MP-147-0186 - Experimentally Induced and Naturally Exposed Infections Placebo Control	8	8	2-20	98	-
1% MP-147-0186 - Experimentally Induced and Naturally Exposed Infections 0.005	8	8	2-14	66	32.6
1% MP-147-0186 - Experimentally Induced and Naturally Exposed Infections 0.025	8	6	0-14	44	55.1
1% MP-147-0186 - Experimentally Induced and Naturally Exposed Infections 0.05	8	2	0-7	8	91.8
M MP-147-0887 - Experimentally Induced Infections Placebo Control	8	8	16-25	163	-

Treatment[1] – Milbemycin Oxime mg/kg	**No. of Dogs Treated**	**No. of Dogs with Adult Worms Found**	**Range of Worm Counts in Infected Dogs**	**Total Worms Found**	**Percent Efficacy**
M MP-147-0887 - Experimentally Induced Infections 0.5 – Treated 30 Days Post Infct.	8	0	0	0	100
M MP-147-0887 - Experimentally Induced Infections 0.5 – Treated 60 Days Post Infct.	8	3	0-6	8	95
M MP-147-0887 - Experimentally Induced Infections 0.5 – Treated 90 Days Post Infct.	8	6	0-3	9	94.6
M MP-147-0487 - Experimentally Induced and Naturally Exposed Infections Placebo Control	10	9	0-21	93	-
M MP-147-0487 - Experimentally Induced and Naturally Exposed Infections 0.5	10	0	0	0	100

Treatment[1] – Milbemycin Oxime mg/kg	**No. of Dogs Treated**	**No. of Dogs with Adult Worms Found**	**Range of Worm Counts in Infected Dogs**	**Total Worms Found**	**Percent Efficacy**
1% MP-147-0184 - Experimentally Induced Infections Placebo Control	4	4	3-20	49	-
1% MP-147-0184 - Experimentally Induced Infections 1.0	6	0	0	0	100
1% MP-147-0284 - Experimentally Induced Infections Placebo Control	4	4	3-8	25	-
1% MP-147-0284 - Experimentally Induced Infections 0.5 – Treated 28 Days Post Infct.	5	0	0	0	100
1% MP-147-0284 - Experimentally Induced Infections 0.5 – Treated 59 Days Post Infct.	5	0	0	0	100
1% MP-147-0284 - Experimentally Induced Infections 1.0 – Treated 28 Days Post Infct.	5	0	0	0	100
1% MP-147-0284 - Experimentally Induced Infections 1.0 – Treated 59 Days Post Infct.	5	1	0-6	6	81

[1]1% = Milbemycin oxime 1% powder formulation; M = Market formulation, tablets

Table 3: Effects of Milbemycin Oxime on the Prevention of Heartworm Disease and Hookworm Control in Dogs During Clinical Field Trails

Investigator/Location	Treatment*	Number of Dogs	Age Range (Years)	Milbemycin Oxime Heartworm Prevention %	Milbemycin Oxime Hookworm** Control %	Filaribits Plus Hookworm Prevention %
Adler/New Jersey	A	25	<1-14	100	No Cases	
Adler/New Jersey	X	24	<1-13			100
Aycock and Legg/Texas	A	22	<1-12	100	100 (8/8)	
Aycock and Legg/Texas	X	22	<1-10			100
Cobb/North Carolina	A	25	<1-7	100	100 (1/1)	
Cobb/North Carolina	X	22	<1-10			100
Colley/Alabama	A	49	<1-11	100	100 (25/25)	
Colley/Alabama	X	49	<1-10			100
Dorney/New Jersey	A	23	<1-12	100	No Cases	
Dorney/New Jersey	X	21	<1-12			100
Feinberg/South Carolina	A	24	<1-10	100	100 (1/1)	
Feinberg/South Carolina	X	25	<1-11			100
Glouton/Georgia	A	19	<1-10	100	100 (4/4)	
Glouton/Georgia	X	24	<1-15			100
Graves/Florida	A	11	<1-14	100	100 (2/2)	
Graves/Florida	X	14	<1-6			100
Hall/Florida	A	17	<1-12	100	100 (8/8)	
Hall/Florida	X	18	<1-12			100
Jacobsen/Indiana	A	46	<1-13	100	100 (6/6)	
Jacobsen/Indiana	X	49	<1-12			100
Kinnarney/North Carolina	A	31	<1-10	100	100 (19/19)	
Kinnarney/North Carolina	X	35	<1-10			100
Maret/Indiana	A	24	<1-13	100	60 (3/5)	
Maret/Indiana	X	23	<1-12			100
Paramore/Indiana	A	26	<1-9	100	100 (1/1)	
Paramore/Indiana	X	25	<1-11			100
Passman/Florida	A	31	<1-11	100	100 (7/7)	
Passman/Florida	X	27	<1-7			100

Investigator/Location	**Treatment***	**Number of Dogs**	**Age Range (Years)**	**Milbemycin Oxime Heartworm Prevention %**	**Milbemycin Oxime Hookworm** Control %**	**Filaribits Plus Hookworm Prevention %**
Raab/Florida	A	30	<1-13	100	100 (9/9)	
Raab/Florida	X	28	<1-11			100
Saidla/Alabama	A	45	<1-12	100	100 (7/7)	
Saidla/Alabama	X	48	<1-15			100
Schoolmeester/North Carolina	A	37	<1-13	100	100 (5/5)	
Schoolmeester/North Carolina	X	36	<1-15			100
Schrader/Texas	A	28	<1-12	100	100 (10/10)	
Schrader/Texas	X	28	<1-14			100
Simmons/Florida	A	27	<1-12	100	50 (1/2)	
Simmons/Florida	X	21	<1-10			75
Smith/Florida	A	27	<1-10	100	100 (17/17)	
Smith/Florida	X	20	<1-10			100
Striegel/North Dakota	A	47	<1-12	100	100 (1/1)	
Striegel/North Dakota	X	42	<1-12			100
Thompson/South Carolina	A	24	<1-12	100	93 (13/14)	
Thompson/South Carolina	X	24	<1-12			86
Utgard/Florida	A	30	<1-14	100	100 (7/7)	
Utgard/Florida	X	27	<1-12			100
Wade/North Carolina	A	7	2-13	100	100 (1/1)	
Wade/North Carolina	X	6	<1-5			100
Total	A	675		100	98 (156-160)	
Total	X	658				97

*Treatment Description; A - Milbemycin Oxime, X - Filaribits Plus Chewable Tablets (Norden).
**Number of dogs with zero egg count (fecal flotation examination) at final evaluation/number of dogs with detectable hookworm infections (positive egg counts).

VI. ATTACHMENTS

Copies of applicable labels may be obtained by writing to the:

Freedom of Information Office
Center for Veterinary Medicine, FDA
7500 Standish Place
Rockville, MD 20855

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.