Approval Date: December 29, 1992

FREEDOM OF INFORMATION SUMMARY

I. GENERAL INFORMATION

A. File Number

NADA 140-915

B. Sponsor

CIBA-GEIGY Animal Health
CIBA-GEIGY Corporation
Post Office 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	Tablet per Month	Milbemycin oximeper Tablet	Color
Up to 10 lbs	1	2.3 mg	Brown
11 to 25 lbs	1	5.75 mg	Green
26 to 50 lbs	1	11.5 mg	Yellow
51 to 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*, the control of adult *Ancylostoma caninum* (hookworm), and the removal and control of adult *Toxocara canis* (roundworm) and *Trichuris vulpis* (whipworm) infections in dogs over eight weeks of age.

G. Effect of Supplement

Approval of the supplemental NADA will change NADA No. 140-915 by adding indications for the removal and control of adult *Toxocara canis* (roundworm) and *Trichuris vulpis* (whipworm) infections in dogs over eight weeks of age. Data

supporting efficacy for the roundworm and whipworm indications is contained in this supplemental NADA. The supplemental application does not propose any changes in the formulation, dosage forms, manufacturing procedures, recommended dosages or treatment regiment for INTERCEPTOR (milbemycin oxime).

II. EFFECTIVENESS

The Supplemental New Animal Drug Application for milbemycin oxime tablets contains adequate and well-controlled studies which demonstrate efficacy in removing and controlling roundworm and whipworm infections in dogs.

A. Dose Establishment

Controlled studies were undertaken to confirm the effectiveness of milbemycin oxime tablets against adult intestinal stages of roundworm (Toxocara canis) and whipworm (Trichuris vulpis). These additional claims are added to the existing indications for heartworm prevention and hookworm control. One confirmation study was completed for each parasite.

At necropsy, the entire gastrointestinal tract was removed from each dog. The contents of the tract were removed, sieved, and parasites were 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.

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 Table 2. These studies confirmed the effectiveness of milbemycin oxime tablets at a minimum dose of 0.5 mg/kg body weight for the removal and control of adult roundworm and whipworm parasites.

1. **Pivotal Roundworm (*T. canis*) Dose Confirmation Study**

Study No. MR-147-01-89

Purpose: Dose confirmation

Investigator: Dr. Dwight Bowman, Ithaca, New York

Type of study: experimental infections

Animals: 28 beagles entered into study (20 completed study), 2-4 months of age, one treatment group of 14 dogs (10 completed the study). See Table 2.

Dosage form: milbemycin oxime tablets

Route of administration: oral

Controls: 14 dogs administered placebo tablets composed of excipients. Ten dogs completed the study (see Table 2)

Doses tested: 0.5 mg/kg body weight minimum dose

Frequency and interval of treatment: one treatment

Study duration: Initial part of study (16 dogs), 44 day study duration (37 days postinfection, 7 days post-treatment). Extended protocol (11 dogs), 73 day study duration (66 days post-infection, 7 days post-treatment.

Results: 99.5% efficacy

2. **Non-Pivotal, Supportive Roundworm (*Toxocara canis*) Dose Confirmation Study**

Purpose: preliminary efficacy determination

Investigator: Drs. D. Bowman and R. Grieve, Madison, Wisconsin

Type of Study: experimental infection

Animals: 15 ascarid-free beagles 10 weeks of age

Dosage form: milbemycin oxime tablets

Route of administration: oral

Controls: group of 5 dogs administered placebo tablets composed of excipients

Doses tested: two groups of 5 dogs received 5.68 mg (0.27-0.39 mg/kg) and 34.08 mg (1.32 - 2.30 mg/kg), respectively

Frequency and interval of treatment: one treatment

Study duration: 75 days (70 days post-infection, 5 days post-treatment)

Results: 100% efficacy in both milbemycin oxime treated groups

3. **Pivotal Whipworm (*T. vulpis*) Dose Confirmation Study**

Study No. MW-147-01-88

Purpose: dose confirmation

Investigator: Drs. B. Blagburn and C. Hendrix, Auburn, Alabama

Type of study: natural infections

Animals: 24 random source mature dogs of various breeds screened for whipworm infection; one treatment group composed of 12 dogs.

Dosage form: milbemycin oxime tablets

Route of administration: oral

Controls: group of 12 dogs administered placebo tablets

Doses tested: 0.5 mg/kg body weight minimum dose

Frequency and interval of treatment: one treatment

Study duration: 7 days

Results: 97.1% efficacy

B. Well-Controlled Clinical Field Trial

Study No. MT-147-00-89

A multi-location, well-controlled clinical field trial employing essentially identical study protocols was conducted during 1989-90.

The overall objective was to evaluate the safety and efficacy of milbemycin oxime for the removal and control of roundworms and whipworms when used under typical veterinary practice conditions. The study employed six individual veterinary hospitals or clinics in the following states: Alabama, California, Florida, and Texas.

The specific trial objectives were achieved by comparing the relative effectiveness of milbemycin oxime formulated tablets, administered monthly, to Filaribits Plus chewable tablets (Norden Laboratories) administered daily.

Patients were selected for inclusion in the study from animals presented to the hospital or clinic for routine immunizations, physical examinations, heartworm examinations, etc. Dogs of various breeds, ages, weights and of either sex, were entered into the study. Animals were evaluated for nematode infections by standard fecal egg flotation procedures. When appropriate infections (roundworm, whipworm) were discovered, animals were assigned to treatment group A (milbemycin oxime) or treatment group X (Filaribits Plus, Norden Laboratories) according to a computer-generated randomization table. Each investigator was provided with his own unique randomization table. Fecal egg flotation counts were scored on the case report form according to the following format:

Eggs FoundM	**Score**
0 epg	0
1-5 epg	+ 1
6-20 epg	+ 2
>20 epg	+ 3

Dogs also received the clinic's standard physical examination. Supplies of milbemycin oxime (treatment A) were supplied to the investigator by the sponsor in three tablet sizes. Treatment was administered three times at thirty day intervals. The practical dosing regimen was as follows:

Body Weight Milbemycin oxime 0-10 lbs. 1 Brown tablet 11-25 lbs. 1 Green tablet 26-50 lbs. 1 Yellow tablet 51-100 lbs. 2 Yellow tablets > 100 lbs. Appropriate tablet mix

The reference drug, Filaribits Plus® chewable tablets (Norden Laboratories), was provided by each investigator and administered according to label directions. Test

subjects receiving either treatment A or treatment X were returned to the clinic for follow-up examinations according to the following schedule:

At 7-10 days following the initial treatment, a fecal sample was returned for evaluation of adult worm removal by each treatment, TA and TX.

Thirty days after initial treatment, each TA dog returned to the clinic for fecal examination and the second TA treatment. TX dogs received daily treatments, and also returned on day 30 for follow-up fecal examination.

If the fecal examination at day 30 for a TA dog was positive, another fecal examination was required on day 37-40. For TX dogs, this fecal was not required.

Sixty days after initial treatment, each TA dog returned to the clinic for fecal examination and the final TA treatment. TX dogs received their final fecal and physical examination on day 60.

If the day 60 fecal examination was negative for TA dogs, they received a final physical examination on day 60. If the day 60 fecal was positive, the TA dog returned at day 67-70 for final fecal and physical examinations.

Results:

A total of 231 patients were enrolled in the field trial, 115 in treatment group A (milbemycin oxime) and 116 in treatment group X (Filaribits Plus, Norden Laboratories). Of the 231 patients initially enrolled, 220 (95.28%) successfully completed the study regime. Approximately 77 (33.3%) of the study patients were puppies (6 months or less) and 16 (6.92%) were 10 years old or greater. The study population breakdown by weight was as follows:
•0-10 lbs. - 23.5%
•11-25 lbs. - 24.3%
•26-50 lbs. - 18.3%
•> 50 lbs. - 33.9%

Thirty-four different breeds of dogs were represented as well as a large selection of mixed breeds. See Table 3.

The 220 patients successfully completing the study regime generated 329 cases of roundworm and whipworm infections. Many patients had dual infections. Treatment group A (milbemycin oxime) results were as follows: 84 cases of roundworm successfully cured, 98.8%, 7 days after the initial treatment, 100% by study completion (60 days); 85 cases of whipworm successfully cured 96.5%, 7 days after the initial treatment, 100% by study completion (60 days). See Table 4. INTERCEPTOR® was used safely in animals receiving frequently used veterinary products such as vaccines, anthelmintics, antibiotics, steroids, flea collars, shampoos, and dips.

Treatment group X (Filaribits Plus) results were as follows: 90 cases of roundworm successfully cured 76.7% after 7 days of treatment, 95.6% by study conclusion after 60 days of treatment, 70 cases of whipworm clinically controlled, 62.9% after 7 days of treatment, 82.9% by study conclusion, after 60 days of treatment. See Table 4.

C. Non-Pivotal Field Trials Conducted in Canada

Three trials were conducted in Canada during 1988-89 which evaluated and corroborated the efficacy of milbemycin oxime for the treatment of intestinal nematodes in dogs. Dogs diagnosed with intestinal nematode infections were treated with a single dose of milbemycin oxime at > 0.5 mg/kg body weight. The identical four tablet formulations used in U.S. trials were administered to dogs in these trials. All dogs were reexamined by fecal flotation 7-10 days following treatment.

Trial 1

Investigator/locations:

Dr. Barbara Cameron, Ostrander Vet Clinic, Tillsonberg, Ontario

Dr. Tony Braithwaite, Kingsville Animal Clinic, Kingsville, Ontario

Dr. Irene Moore, Southridge Animal Clinic, Morpeth, Ontario

Results: Twenty-four (24) dogs were treated with milbemycin oxime, 9 dogs with roundworms, 11 dogs with hookworms and 4 dogs with whipworm infections. All dogs, except one dog with roundworms had negative fecal examinations 7-10 days after treatment.

Trial 2

Investigators/location:

Drs. Alain Villeneuva and Susie Lemay, University of Montreal, Veterinary Teaching Hospital, St. Hyacinthe, Quebec

Drs. Micheline Marcotte and Danielle Jolly, Varennes, Quebec

Drs. Diane Fraud and N. Plourde, Rosemere, Quebec

Results: Twenty (20) dogs with T. canis , 15 dogs with A. caninum and 4 dogs with T. vulpis infections were treated and reexamined during the trial. Fecal egg counts from these dogs were reduced by more than 98% for all three parasites following treatment with milbemycin oxime.

Trial 3

Principal Investigator:

Dr. Owen Slocombe, University of Guelph, Guelph, Ontario

Locations:

University of Guelph, Guelph, Ontario

Braemar Collie Kennels, Moorefield, Ontario

Kelvingrove Kennels, Guelph, Ontario

Roymark Kennels, Brucedale, Ontario

Taybro Kennels, Orton, Ontario

Toronto-North York Hunt Club, Aurora, Ontario

Walter Klausnitzer Kennels, Kenilworth, Ontario

Results: Fourteen (14) dogs with T. canis , 20 dogs with A. caninum and 15 dogs with T. vulpis infections were treated with milbemycin oxime and re-examined during the trials. Fecal egg counts from these dogs were reduced by more than 96% for T. canis , 98% for A. caninum and 99% for T. vulpis following treatment with milbemycin oxime.

Conclusion - Effectiveness

Based upon data generated in laboratory studies and clinical field trials, it can be concluded that milbemycin oxime tablets, at the labeled rate of 0.5 mg/kg, are safe and effective for the removal and control of adult roundworm (T. canis) and whipworm (T. vulpis) parasites in dogs.

III. ANIMAL SAFETY

No adverse side effects were attributed to milbemycin oxime during the well controlled clinical field trial.

This supplemental NADA does not require re-evaluation of target animal safety data submitted in support of the initial NADA No. 140-915. Please refer to the original Freedom of Information Summary (NADA 140-915) for additional information on target animal safety studies.

IV. HUMAN SAFETY

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

V. AGENCY CONCLUSIONS

The data in support of this supplemental NADA complies with the requirements of Section 512 of the Act and Section 514.111 of the implementing regulations. It demonstrates that INTERCEPTOR® (milbemycin oxime) tablets when used under the labeled conditions of use is safe and effective.

According to the Center's supplemental approval policy (42 FR 6436) this is a Category II change. This supplement provides for the addition of claims to include the removal and control of roundworms (*Toxocara canis*) and whipworms (*Trichuris vulpis*). The approval of the supplemental application has no adverse effect on the safety and effectiveness of the new animal drug. Accordingly, this approval did not require a reevaluation of the safety and effectiveness data in the parent application.

For this supplement, the drug is restricted to use by or on the order of a licensed veterinarian because professional expertise and proper diagnosis are required to determine the existence of roundworm and/or whipworm infection. In addition, 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 (original approval).

Under Section 512(c)(2)(F)(iii) of the Generic Animal Drug and Patent Term Restoration Act of 1988, this supplemental new animal drug application qualifies for three years of marketing exclusivity because new clinical or field investigations conducted by the sponsor were essential to the approval of this supplemental NADA.

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

Trial Number	Investigator	Location / Address	Type of Trial
MW-147-01-88	Drs. B. Blagburn and C. Hendrix	Auburn University, Auburn, AL	Dose confirmation
MR-147-01-89	Dr. D. Bowman	Cornell University, Ithaca, New York	Dose confirmation
COL-MT-147-00-89	Dr. J. Colley	Opelika Animal Hospital, Opelika, AL	Field trial
LEG-MT-147-00-89	Dr. W. Legg	Lewisville North Animal Clinic, Lewisville, TX	Field trial
STO-MT-147-00-89	Dr. K. Stocks	San Joaquin Animal Clinic, Fresno, CA	Field trial
UTG-MT-147-00-89	Dr. H. Utgard	Dade Animal Hospital, North Miami, FL	Field trial

Table 2: Summary of Milbemycin Oxime Dose Confirmation Studies for Removal of Adult Roundworms and Whipworms in Dogs

Roundworm Removal-Pivotal

Treatment	No. of Dogs Treated	No. of Dogs with Worms	Range of Worms Found	Total Worm Counts	Efficacy Percent Efficacy
Control	10*	10	5-60	193	
0.5 mg/kg	10*	1	0-1	1	99.5%

Roundworm Removal-Non-Pivotal

Treatment	No. of Dogs Treated	No. of Dogs with Worms	Range of Worms Found	Total Worm Counts	Efficacy Percent Efficacy
Control	5	5	2-19	52	
0.27-0.39 mg/kg	5	0	0	0	100%
1.32-2.30 mg/kg	5	0	0	0	100%

Whipworm Removal-Pivotal

Treatment	No. of Dogs Treated	No. of Dogs with Worms	Range of Worms Found	Total Worm Counts	Efficacy Percent Efficacy
Control	12	12	3-278	860	
0.5 mg/kg	12	3	0-13	25	97.1%

Table 3: Milbemycin Oxime Case Studies - MT-147-00-89
Number of Animals by Breed

Number of Animals	Breed
1	Akita
1	Alaskan Malamute
6	Australian Cattle Dog
4	Beagle
5	Chihuahua
2	Chow Chow
9	Cocker Spaniel
2	Collie (smooth, rough)
3	Dachshund
1	Dalmatian
10	Doberman Pinscher
2	English Setter
2	English Springer Spaniel
18	German Shepherd Dog
7	Golden Retriever
4	Great Dane
1	Irish Setter
1	Keeshond
19	Labrador Retriever
3	Lhasa Apso

Number of Animals	**Breed**
2	Mastiff
6	Miniature Schnauzer
2	Misc. Hounds
1	Misc. Non-Sporting Breeds
5	Misc. Toy Breeds
68	Mixed Breed
11	Pointer
1	Pomeranian
2	Poodle
2	Rhodesian Ridgeback
8	Rottweiler
4	Staffordshire Bull Terrier (Pit Bull)
1	Standard Schnauzer
3	Toy Poodle
3	Yorkshire Terrier
220	Total

Table 4: Effects of Milbemycin Oxime on Removal and Control of Adult Roundworm and Whipworm Infections in Dogs During Clinical Field Trials

Investigator/ Location	**Treatment**	**Number of Dogs Completing Study 1**	**Roundworm Infections/ Number Cured 2**	**Whipworm Infections/ Number Cured**
Colley/ Alabama	Milbemycin oxime	25	22/22	23/23
	Filaribits Plus(TM)	24	23/20	22/103
Legg/Texas	Milbemycin oxime	15	5/5	10/10
	Filaribits Plus(TM)	14	3/3	11/11

Investigator/ Location	**Treatment**	**Number of Dogs Completing Study 1**	**Roundworm Infections/ Number Cured 2**	**Whipworm Infections/ Number Cured**
Stocks/ California	Milbemycin oxime	9	9/9	0/0
	Filaribits Plus(TM)	8	8/8	0/0
Utgard/Florida	Milbemycin oxime	62	48/48	52/52
	Filaribits Plus(TM)	63	56/55	37/37
Totals	Milbemycin oxime	111	84/84 =100%	85/85= 100%
	Filaribits Plus(TM)	109	90/86 = 96%	70/58 = 83%

1 Number of dogs is fewer than total number of infections because some dogs had multiple infections; i.e.; 133 A treatment dogs, 193 A treatment parasite cases.

2 "Cured" means no eggs or proglottids found at final fecal examination.

3 Clinical control was achieved in all cases but low number of eggs were found at final fecal examination for 12 dogs. This is a hyperendemic whipworm area.

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.