

## FREEDOM OF INFORMATION SUMMARY

INTERCEPTOR® (MILBEMYCIN OXIME) FLAVOR TABS™

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 AND IN PUPPIES  
FOUR WEEKS OF AGE OR GREATER AND TWO POUNDS OF BODY WEIGHT OR GREATER

SPONSORED BY CIBA-GEIGY CORPORATION  
ANIMAL HEALTH DIVISION

### 1. **General Information**

New Animal Drug Application Number: Supplement to NADA 140-915

Sponsor: Ciba-Geigy Corporation  
Animal Health Division  
Post Office Box 18300  
Greensboro, NC 27419-8300

Generic Name of Drug: Milbemycin Oxime Tablets

Trade Name: INTERCEPTOR Flavor Tabs

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

### **Effect of Supplement**

Approval of the supplemental NADA will change NADA No. 140-915 by adding indications for the use of INTERCEPTOR (milbemycin oxime) Flavor Tabs in puppies four weeks of age or greater and two pounds of body weight or greater (from greater than eight weeks of age). The supplemental application does not propose any changes in the formulation, dosage forms, manufacturing procedures, recommended dosages or monthly treatment regimen for INTERCEPTOR (milbemycin oxime) Flavor Tabs.

### 2. **Indications for Use**

INTERCEPTOR Flavor Tabs 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 and in puppies four weeks of age or greater and two pounds of body weight or greater.

### 3. **Dosage Form, Route of Administration, and Recommended Dosage**

The ingredients of INTERCEPTOR Flavor Tabs are formulated into various sized tablets to be administered orally (swallow or chew), 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 oxime per 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.

#### 4. **Target Animal Safety and Effectiveness**

The Supplemental New Animal Drug Application for milbemycin oxime tablets contains adequate and well-controlled studies, which demonstrate safety and confirm efficacy in puppies four to eight weeks of age and two pounds of body weight or greater.

##### **Dose Establishment**

No additional dose establishment work was required. The minimum target dose of milbemycin oxime 0.5 mg/kg body weight is established in NADA 140-915 for the currently approved label indications.

##### **Target Animal Safety**

Milbemycin oxime safety in dogs greater than 8 weeks of age is contained in NADA 140-915. To evaluate the safety of milbemycin oxime in younger puppies, two rising dose toxicity studies in puppies beginning at 2 weeks and ending at 8 and 3 weeks of age respectively were performed: one pivotal study (six weeks duration) and one corroborative study (two weeks duration). Both studies were conducted with the final tablet formulation.

Transient neurological signs were observed at elevated milbemycin oxime doses, in 10% of puppies that reacted at 5-9 mg/kg and up to 83% that reacted at doses greater than 15 mg/kg. The severity and duration of the signs increased with elevated milbemycin oxime doses. All animals returned to normal within 48 hours, and in most puppies the clinical signs were gone within six (6) hours irregardless of the puppy's age.

##### **Pivotal Safety Study**

A six week safety study in beagle puppies beginning at 2 weeks of age, given oral doses of milbemycin oxime (as tablets) at dosage levels ranging from 5X to >30X the recommended minimum dose rate (0.5 mg/kg).

Study Site: Liberty Research  
Post Office Box 107  
Route 17C  
Waverly, NY 14892-0107

Study Director: Martin R. Gilman, Ph.D.

Animals: Pure bred Beagle puppies.  
Three groups of 12 puppies each, 6 males + 6 females beginning at 2 weeks of age.  
Control - 1 group of 12 puppies received placebo tablets.

Dosage form: Tablets were combined to achieve the desired dose levels. Group 1 received one 2.3mg tablet, Group 2, three 2.3 mg tablets and Group 3, five 2.3 mg tablets.

Dosage: Control (placebo tablets)

Group 1 - 1X dose range (2.3 mg tablet), average dose received was 2.98 (6X labeled minimum effective dose) mg/kg at 2 weeks to 0.83 mg/kg (1.6X labeled minimum effective dose) at 8 weeks.

Group 2 - 3X dose range (3 X 2.3 mg tablets = 6.9 mg), average dose received was 9.61 mg/kg (19X labeled minimum effective dose) at 2 weeks to 2.66 mg/kg (~5X labeled minimum effective dose) at 8 weeks.

Group 3 - 5X dose range (5 X 2.3 = 11.5 mg tablet), average dose received was 14.72 mg/kg (~29X labeled minimum effective dose) at 2 weeks to 4.41 mg/kg (~9X labeled minimum effective dose) at 8 weeks.

Route of Administration: Orally by tablet, finished dosage form.

Test Duration: Puppies received one dose at 2, 4, 6, and 8 weeks of age.

Pertinent Parameters and Measured: Clinical observations, body weights, hematology and blood chemistry, urine analysis.

#### Results:

A typical, reversible macrolide-induced syndrome was observed at elevated doses of milbemycin oxime. The effects were similar in severity and duration to those observed in older dogs (see Freedom of Information Summary for original NADA 140-915) and were dependent on milbemycin oxime dose. Effects were not age or sex dependent. Two puppies in the 1X group and two in the 3X group exhibited diarrhea. Thirteen puppies in the placebo (1), 3X (4) and 5X (8) groups exhibited neurological signs consisting of trembling, vocalization, and/or ataxia. GGT (gamma glutamyl transferase) was slightly increased in the 3X and 5X groups but not the 1X group. No other adverse side effects were observed during the study.

#### Conclusion:

This toxicity study demonstrated the safety of milbemycin oxime in puppies between four and eight weeks of age or greater and two pounds body weight or greater. There were no animals in the 1X group observed with adverse clinical signs and abnormal clinical chemistry profiles. Animals (2 weeks of age) were observed in the 3X and 5X groups with adverse clinical signs. No clinical signs were seen in the 3X group at 4, 6 or 8 weeks. Puppies four weeks and older had only minor neurological signs in the 5X group. The severity and duration of clinical signs appeared to be dose dependent. Therefore Interceptor is recommended for use in puppies four weeks of age or greater and two pounds of body weight or greater.

#### Corroborative Safety Study

A two week safety study in beagle pups beginning at 2 weeks of age at dosage levels ranging from 5X to >30X the recommended minimum dose rate (0.5 mg/kg).

Study Site: Liberty Research  
Post Office Box 107  
Route 17C  
Waverly, NY 14892-0107

Study Director: Martin R. Gilman, Ph.D.

Animals: - Purebred Beagle puppies.  
- Three groups of 3 puppies each, 5 males and 4 females all from 2 litters beginning at 2 weeks of age. No Control group was used.

Dosage Form: Tablets were combined to achieve the desired dose levels. Group 1 received one 2.3mg tablet, Group 2, three 2.3 mg tablets and Group 3, five 2.3 mg tablets.

Dosage: Group 1 - 1X dose range (2.3 mg tablet), average dose received was 2.98 (6X labeled minimum effective dose) mg/kg at 2 weeks.  
Group 2 - 3X dose range (3 X 2.3 mg tablets = 6.9 mg), average dose received was 9.61 mg/kg (19X labeled minimum effective dose) at 2 weeks.  
Group 3 - 5X dose range (5 X 2.3 mg tablets = 11.5 mg), average dose received was 14.72 mg/kg (~29X labeled minimum effective dose) at 2 weeks.

Route of Administration: Orally by tablet, finished dosage form.

Test Duration: Puppies received one dose at 2 weeks of age on 2 consecutive days and again a single dose 7 days later.

Pertinent Parameters Measured: Clinical observations and body weights.

#### Results:

No effects were observed in groups 1 or 2 (2.3 and 6.9 mg respectively) at any time during the study. Unsteady gait and decreased activity in all animals in group 3 (11.5 mg) following the second and third dosing. Tremors were in 2 of 3 animals in group 3 following the second dosing and all animals following third dosing. One group 3 animal was sensitive to touch following post-dosing. All of the affected animals were normal 24 hours post dosing.

#### Conclusion:

This toxicity study indicated the safety of milbemycin in puppies three weeks of age or greater and two pounds body weight or greater.

#### Corroborative Safety and Efficacy Studies (1987-88 & 1989-90 Clinical Trial Data from Puppies Between Two and Eight Weeks of Age)

##### Objective

A multi-location, well-controlled clinical field trial was conducted during 1987-88. The overall objective was to evaluate the safety and efficacy of monthly administration of milbemycin oxime for the prevention of heartworm disease and removal and control of hookworm infection when used under typical veterinary practice conditions. A second clinical field trial was conducted during 1989-90 to evaluate the safety and efficacy of monthly administration of milbemycin oxime for the additional indications of removal and control of roundworms and whipworms when used under typical veterinary practice conditions. Safety and efficacy data from puppies, eight (8) weeks of age and less, enrolled in the 1987-88 and 1989-90 clinical field trials was extracted and analyzed in support of the label change for this supplement to the NADA.

## Methods

Dogs received monthly milbemycin oxime treatments for a total of ten months (11 treatments) in the 1987-88 clinical field trial and for a total of two months (3 treatments) in the 1989-90 clinical field trial.

### Dosage and Administration

Milbemycin oxime tablets were administered orally at the recommended minimum dosage level of 0.5 mg/kg body weight at monthly dosing intervals. The recommended dosing schedule was:

| <u>Body Weight</u> | <u>Content (color code)</u> | <u>No. Tablets per month</u> | <u>Dose Range (mg/kg)</u> |
|--------------------|-----------------------------|------------------------------|---------------------------|
| 2 to 10 lbs.       | 2.30 mg                     | 1 (brown)                    | 0.5 - 2.5 (5X)            |

## Results

### 1987-88 Clinical Field Trial

A total of twelve puppies (6 females and 6 males) from four (4) veterinary hospitals, five to eight weeks of age, received INTERCEPTOR (milbemycin oxime) at the recommended label dose. The hospitals were located in the following states: Florida and South Carolina (Table 3).

Of the twelve puppies enrolled, seven (7) puppies (58.3%) successfully completed the 10-month study regimen. The puppy population breakdown, by breed and sex and by age and weight at the first milbemycin oxime dosing, is given in Table 1.

There were no investigator documented adverse reported reactions. Comments were received from owners, most concerning vomiting, diarrhea, and weight loss. However, these responses were not treatment related as determined by the investigator. Also, diarrhea, vomiting and anorexia are included on the approved label for Interceptor® Flavor Tabs.

One hundred percent (100%) of the seven (7) puppies, six to eight weeks of age at the study initiation, were heartworm free after receiving 10 months of milbemycin oxime at monthly intervals. Eighty-nine percent (89%) of nine (9) puppies were cleared of hookworm (*Ancylostoma caninum*) fecal egg shedding 7-10 days after receiving the first milbemycin oxime treatment. One hundred percent (100%) of the reinfected puppies were cleared 7 to 10 days after each subsequent treatment. Complete control of hookworm infections, as measured by the total number of puppies free of fecal egg shedding, was one hundred percent (100%) after four (4) milbemycin oxime treatments in puppies less than eight weeks of age at study initiation. Additionally six (6) puppies (100%) were cleared of roundworms (*Toxocara canis*) after a single milbemycin treatment.

### 1989-90 Clinical Trial

A total of 19 puppies (7 females and 12 males) from four veterinary hospitals, three to eight weeks of age and enrolled in this field trial, received INTERCEPTOR (milbemycin oxime) at the recommended label dose. The hospitals were located in the following states: Alabama, Florida, Texas and California (Table 3). Of the 19 puppies enrolled, 18 puppies (94.7%) successfully completed the 60-day study regimen. The puppy population breakdown, by breed and sex and by age and weight at the time of first dosing, is given in Table 2.

Eighteen of nineteen (94.7%) puppies (3 to 8 weeks of age) were cleared of roundworm (*Toxocara canis*) fecal egg shedding after the first milbemycin oxime treatment, and 100% of dogs were cleared after each subsequent treatment. Total (100%) control of all roundworm infections was established in the puppy population after two (2) milbemycin oxime treatments. There were no adverse reactions noted during the study.

The number (%) of puppies (3 to 8 weeks of age) cleared of hookworm (*Ancylostoma caninum*) fecal egg shedding was 100%, 7 to 10 days after each milbemycin oxime treatment. Control of hookworm infections was 91.7% after two (2) milbemycin oxime treatments. One puppy out of the twelve that completed the trial was shedding hookworm eggs at each monthly recheck, presumably due to reinfection (the prepatent period of *A. Caninum* is 14-21 days).

Although whipworm infection is not considered a disease of young puppies and the prepatent period is greater than eight weeks six cases were diagnosed as positive for whipworms upon initial exam. All were fecal negative at the 7-10 day recheck and remained free of whipworms throughout the remainder of the trial. Control of whipworm infection was 100%.

Tabulated Data from 1987-88 & 1989-90 Clinical Trials

Data from the 1987-88 and 1989-90 clinical trials is presented individually and then combined in the total calculation.

Total puppies (2-8 weeks of age) cleared of nematode fecal egg shedding over total number of puppies in the group after a single milbemycin oxime treatment or free of heartworms at study end:

|                 | Heartworm Prevention | Hookworm Removal | Roundworm Removal | Whipworm Removal |
|-----------------|----------------------|------------------|-------------------|------------------|
| 1987-88 Results | 7/7                  | 8/9              | (6/6)             |                  |
| 1989-90 Results |                      | <u>12/12</u>     | <u>18/19</u>      | <u>(6/6)</u>     |
| Total           | = 7/7                | = 20/21          | = 18/19           |                  |
| X 100%          | = 100%               | = 95.2%          | = 94.7%           |                  |

( ) data is supportive only and was not included in the Total calculation.

Control of nematode infections (% puppies cleared of fecal egg shedding) by study end:

|                 | Hookworm Control | Roundworm Control |
|-----------------|------------------|-------------------|
| 1987-88 Results | 6/6              |                   |
| 1989-90 Results | <u>11/12</u>     | <u>18/18</u>      |
| Total           | = 17/18          | = 18/18           |
| X 100%          | = 94.4%          | = 100%            |

Conclusions

The data in this supplement establishes the safety and confirms the efficacy of milbemycin oxime administered one time for the removal of intestinal nematode infections in puppies four to eight weeks of age. In addition, monthly administration of milbemycin oxime was safe and effective in the control of intestinal nematode infections and in the prevention of heartworm infections in puppies four to eight weeks of age.

6. **Human Safety**

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

## 7. Agency Conclusions

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

According to the Center' supplemental approval policy (21 CFR 514.106), this is a Category II change. This supplement provides for the use of milbemycin oxime in dogs four weeks of age or greater and two pounds of body weight or greater. This approval did require a reevaluation of the safety and effectiveness data in the parent application and evaluation of new target animal safety data submitted in the supplemental application.

Under section 512(c)(2)(F)(iii) of the Federal Food, Drug, and Cosmetic Act (FFDCA), this approval qualifies for THREE years of marketing exclusivity beginning on the date of approval because the supplemental application contains reports of new clinical or field investigations (other than bioequivalence studies) essential to the approval of the application and conducted or sponsored by the applicant. The three years of marketing exclusivity applies only to new weight (two pounds or greater) and age (4 weeks of age or greater) specifications for which the supplemental application was approved. This exclusivity period will expire three years from the date of the approval letter.

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 hookworm, roundworm and/or whipworm infection. In addition, professional expertise is required to determine the existence of heartworm infection, and to then properly treat existing heartworm infection prior to starting treatment with Interceptor ® (milbemycin oxime) flavor tabs in a prevention program.

TABLE 1

WELL-CONTROLLED CLINICAL FIELD TRIAL OF PUPPIES  
BY BREED, AGE AND WEIGHT

| Case No.      | Breed      | Sex   | Age at Initiation (Days)                       | Weight at Study Initiation (Ozs.)                 |
|---------------|------------|---|--|---|
| PASSMAN 059   | Shep. Mix  | F   | 6.14 Weeks (43)                                | 5.25 lbs. (84)                                    |
| PASSMAN 065*  | Aust. Shep | M   | 7.14 Weeks (50)                                | 9.5 lbs. (152)                                    |
| PASSMAN 070*  | Dachshund  | F   | 7 Weeks (49)                                   | 3 lbs. (48)                                       |
| RAAB 053*     | Pit Bull   | M   | 8 Weeks (56)                                   | 7.2 lbs.(115.20)                                  |
| RAAB 062      | Shep. Mix  | M   | 5 Weeks (35)                                   | 4.7 lbs. (75.20)                                  |
| SMITH 003     | Mix        | F   | 5.28 Weeks (37)                                | 5.37 lbs. (85.92)                                 |
| SMITH 029     | Mix        | M   | 8 Weeks (56)                                   | 10.37 lbs.(165.92)                                |
| SMITH 052*    | Mix        | F   | 6 Weeks (42)                                   | 3.37 lbs. (53.92)                                 |
| SMITH 053*    | Mix        | F   | 6 Weeks (42)                                   | 2.5 lbs. (40.00)                                  |
| SMITH 059     | Mix        | M   | 6 Weeks (42)                                   | 5.37 lbs. (85.92)                                 |
| THOMPSON 060* | Lab/Husky  | F   | 6.85 Weeks (48)                                | 10.1lbs. (161.60)                                 |
| THOMPSON 061  | Lab/Husky  | M   | 6.85 Weeks (48)                                | 10.1lbs. (161.60)                                 |
|               |            | <b>Total of<br/>6 Males<br/>and 6<br/>Females</b> | <b>Average Age: 6.52<br/>Weeks(45.66 days)</b> | <b>Average Weight: 6.40<br/>lbs. (102.44 oz.)</b> |

\*Puppies that completed the ten week study.

TABLE 2

**WELL-CONTROLLED CLINICAL FIELD TRIAL -  
BREAKDOWN OF PUPPIES BY BREED, AGE AND WEIGHT**

| <b>Case No.</b> | <b>Breed</b>    | <b>Sex</b>             | <b>Age at Initiation<br/>(Days)</b>       | <b>Weight at Study<br/>Initiation (Ozs.)</b>       |
|-----------------|-----------------|------------------------|---|--|
| HUNT/COLLEY 048 | Mix             | M                      | 8 Weeks (56)                              | 7 lbs. (112)                                       |
| HUNT/COLLEY 049 | Mix             | M                      | 8 Weeks (56)                              | 8 lbs. (128)                                       |
| LEGG 002        | Collie          | M                      | 8 Weeks (56)                              | 7 lbs. (112)                                       |
| LEGG 010        | Cocker/Shih Tzu | F                      | 6 Weeks (42)                              | 2 lbs. ( 32)                                       |
| STOCKS 001*     | Dachshund       | M                      | 7 Weeks (49)                              | 2.25 lbs. ( 36)                                    |
| STOCKS 003      | Poodle/Shih Tzu | F                      | 7 Weeks (49)                              | 2.75 lbs. ( 44)                                    |
| STOCKS 010      | Chow            | M                      | 6 Weeks (42)                              | 8 lbs. (128)                                       |
| STOCKS 013      | Aust. Shep. Mix | F                      | 8Weeks (56)                               | 7.5 lbs. (120)                                     |
| STOCKS 014      | Min. Schnauzer  | F                      | 7 Weeks (49)                              | 3.75 lbs. ( 60)                                    |
| UTGARD 021      | Mix             | M                      | 4.5 Weeks (31.5)                          | 4 lbs. ( 64)                                       |
| UTGARD 031      | Pit Bull        | M                      | 3 Weeks (21)                              | 5 lbs. ( 80)                                       |
| UTGARD 032      | Pit Bull        | F                      | 3 Weeks (21)                              | 3.5 lbs. ( 56)                                     |
| UTGARD 033      | Pit Bull        | M                      | 3Weeks (21)                               | 3.8 lbs. ( 60.80)                                  |
| UTGARD 071      | Rottweiler      | M                      | 7Weeks (49)                               | 9.62 lbs. (153.92)                                 |
| UTGARD 073      | Terrier Mix     | F                      | 6 Weeks (42)                              | 4 lbs. ( 64)                                       |
| UTGARD 101      | Rottweiler      | M                      | 8Weeks (56)                               | 4.75 lbs. ( 76)                                    |
| UTGARD 102      | Rottweiler      | F                      | 8 Weeks (56)                              | 5.12lbs. ( 81.92)                                  |
| UTGARD 108      | Cocker Spaniel  | M                      | 8 Weeks (56)                              | 7.5 lbs. (120)                                     |
| UTGARD 121      | Mixed Terrier   | M                      | 6 Weeks (42)                              | 3.25 lbs. ( 52)                                    |
| <b>Total</b>    |                 | 12 Males/<br>7 Females | Average Age:<br>44.76 days(6.39<br>weeks) | Average Weight:<br>5.20 + 2.24 lbs.<br>(83.19 oz.) |

\*Puppy did not complete the 60 day study.

**TABLE 3**

**LOCATION, NAME AND ADDRESS OF CLINICAL INVESTIGATORS**

| <b>MT-14-00-87</b>  | <b>MT-147-00-89</b>  |
|---|--|
| <p data-bbox="418 373 526 405"><b><u>Florida:</u></b></p> <p data-bbox="289 407 656 531">Dr. Denny Passman<br/>Port St. Lucie Animal Hospital<br/>6148 South Federal Highway<br/>Fort Pierce, FL 34982</p> <p data-bbox="305 564 641 688">Dr. James P. Raab<br/>Tri-County Animal Hospital<br/>1807 Okeechobee Road<br/>Fort Pierce, FL 33450</p> <p data-bbox="354 722 591 846">Dr. Perry Smith<br/>Trail Animal Clinic<br/>6464 SW 8th Street<br/>Miami, FL 33144</p> <p data-bbox="370 879 574 911"><b><u>South Carolina:</u></b></p> <p data-bbox="295 913 649 1037">Dr. Susan B. Thompson<br/>The Pet Vet Veterinary Clinic<br/>307 Mill Street<br/>Mt. Pleasant, SC 29464</p> | <p data-bbox="980 342 1110 373"><b><u>Alabama:</u></b></p> <p data-bbox="896 375 1195 499">Dr. Jere Colley<br/>Opelika Animal Hospital<br/>1615 2nd Avenue<br/>Opelika, AL 36801</p> <p data-bbox="974 533 1117 564"><b><u>California:</u></b></p> <p data-bbox="867 567 1224 690">Dr. Kenneth E. Stocks<br/>San Joaquin Veterinary Clinic<br/>4333 North Blackstone<br/>Fresno, CA 93704</p> <p data-bbox="987 724 1101 756"><b><u>Florida:</u></b></p> <p data-bbox="857 758 1230 882">Dr. Herbert M. Utgard<br/>Dade Animal Hospital<br/>175 NW 167th Street<br/>North Miami Beach, FL 33169</p> <p data-bbox="1000 915 1088 947"><b><u>Texas:</u></b></p> <p data-bbox="841 949 1247 1073">Dr. Walter Legg<br/>Lewisville North Animal Hospital<br/>121 Degan<br/>Lewisville, TX 75067</p> |