

Date of Approval: June 21, 2017

**FREEDOM OF INFORMATION SUMMARY**  
**SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION**

**NADA 141-338**

**INTERCEPTOR™ PLUS**

**milbemycin oxime/praziquantel**

**Chewable tablets**

**Dog**

This supplement provides for the addition of the treatment and control of adult tapeworm (*Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

**Sponsored by:**

**Elanco US Inc.**

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**I. GENERAL INFORMATION**

**A. File Number**

NADA 141-338

**B. Sponsor**

Elanco US Inc.  
2500 Innovation Way  
Greenfield, IN 46140

Drug Labeler Code: 058198

**C. Proprietary Name**

INTERCEPTOR™ PLUS

**D. Product Established Name**

Milbemycin oxime/praziquantel

**E. Pharmacological Category**

Antiparasitic

**F. Dosage Form**

Chewable tablets

**G. Amount of Active Ingredient**

Each chewable tablet contains:

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

**H. How Supplied**

INTERCEPTOR™ PLUS is available in four strengths, formulated according to the weight of the dog. Each strength is available in color-coded packages of six chewable tablets each. The tablets containing 2.3 mg milbemycin oxime/22.8 mg praziquantel or 5.75 mg milbemycin oxime/57 mg praziquantel are also available in color coded packages of one chewable tablet each.

**I. Dispensing Status**

Rx

## J. Dosage Regimen

INTERCEPTOR™ PLUS should be administered orally, once every month, at the minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime, and 2.28 mg/lb (5 mg/kg) praziquantel. For heartworm prevention, give once monthly for at least 6 months after exposure to mosquitoes.

### Dosage Schedule

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

## K. Route of Administration

Oral

## L. Species/Class

Dogs

## M. Indications

INTERCEPTOR PLUS is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*; and for the treatment and control of adult roundworm (*Toxocara canis*, *Toxascaris leonina*), adult hookworm (*Ancylostoma caninum*), adult whipworm (*Trichuris vulpis*), and adult tapeworm (*Taenia pisiformis*, *Echinococcus multilocularis*, *Echinococcus granulosus*, and *Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

## N. Effect of Supplement

This supplement provides for the addition of the treatment and control of adult tapeworm (*Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

## II. EFFECTIVENESS

### A. Dosage Characterization

This supplemental approval does not change the previously approved dosage. The Freedom of Information (FOI) Summary for the original approval of NADA 141-338, dated June 16, 2012, contains a summary of the dosage characterization information for dogs.

## B. Substantial Evidence

For the Treatment and Control of the Gastrointestinal Cestode *Dipylidium caninum*:

### 1. Laboratory Dose Confirmation and Non-Interference Study NAH-02-0032

**Title:** Efficacy Evaluation Of Flavored Combination Parasiticide Tablets For The Removal Of Natural *Dipylidium caninum* (Tapeworm) Infections In Dogs.

**Study Dates:** August 15, 2002– June 19, 2005

**Study Location:** Bloemfontein, South Africa

#### **Study Design:**

**Objective:** The objectives of the study were to evaluate the effectiveness of a milbemycin oxime and praziquantel combination tablet (non-final formulation) against naturally-acquired adult tapeworm (*D. caninum*) infections in dogs when administered orally; demonstrate that milbemycin oxime and lufenuron do not interfere with the effectiveness of praziquantel against *D. caninum*; and justify the inclusion of praziquantel into the combination.

The study was conducted using the principles of Good Clinical Practices (GCP).

**Study Animals:** Twenty-nine adult dogs (10 males and 19 females) weighing between 12.0 and 42.7 pounds (5.5 and 19.4 kg) and harboring naturally acquired *D. caninum* infections were included in the study.

#### **Treatment Groups:**

Table 1: Study NAH-02-0032 Treatment Groups (9 dogs in the control group, 10 dogs in the milbemycin oxime/praziquantel group and 10 dogs in the milbemycin oxime/lufenuron group)

<b>Treatment Group</b>	<b>Milbemycin oxime Dose</b>	<b>Praziquantel Dose</b>	<b>Lufenuron Dose</b>
Milbemycin oxime/praziquantel tablets	0.5 mg/kg	5 mg/kg	0 mg/kg
Control (inert ingredients)	0 mg/kg	0 mg/kg	0 mg/kg
Milbemycin oxime/lufenuron tablets	0.5 mg/kg	0 mg/kg	10 mg/kg

**Drug Administration:** The test and control articles were administered, according to Table 1, once on Day 0, within 30 minutes following ingestion of a meal after an overnight fast. All dogs received the appropriately-sized tablet intended for dogs weighing between 5.0 to 11.4 kg (11 to 25.0 pounds) or

11.8 to 22.7 kg (25.1 to 50 pounds). The actual doses ranged from 5.9 mg/kg to 9.7 mg/kg praziquantel.

**Measurements and Observations:** All dogs were determined to be healthy, with the exception of *D. caninum* infections confirmed by fecal examination, prior to initiation of the study. All dogs were determined to be heartworm negative prior to Day 0. On Day 0, all dogs were observed hourly for six hours post-dosing, then at 8, 10, 12, 18, and 24 hours for evidence of adverse events. Daily observations of general health continued throughout the study. On Day 12, the dogs were euthanized and necropsied for *D. caninum* recovery and enumeration.

**Statistical Methods:**

Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group as compared to the control. Geometric means of tapeworm counts were calculated.

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

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

Statistical significance was assessed using Analysis of Variance (ANOVA; SAS PROC MIXED) of logarithmically transformed worm counts at necropsy with treatment group as a fixed effect. Treatment, sex and the treatment-by-sex interaction were included as classification variables in the ANOVA. Study phase was included as a random effect.

**Results:**

Adequate infection was demonstrated in the control group with six of the nine control dogs, on necropsy, harboring greater than 2 tapeworms. Treatment with milbemycin oxime/praziquantel tablets was 100% effective against naturally-acquired adult *D. caninum* tapeworm infections in dogs (Table 2). The difference in the number of *D. caninum* recovered between the treated and control groups was statistically significant ( $p = 0.0022$ ).

Table 2: Study NAH-02-0032 Results

<b>Treatment Group</b>	<b>Number of Dogs</b>	<b>Geometric Mean of <i>D. caninum</i> Recovered (range)</b>	<b>Percent Effectiveness</b>
Milbemycin oxime / praziquantel tablets	10	0.0 (NA)	100%
Control	9	13.6 (0-315)	NA
Milbemycin oxime/ lufenuron tablets	10	10.0 (1-102)	26.7%

NA=Not applicable

**Adverse Reactions:**

Diarrhea was reported during the study. Diarrhea was observed in two dogs in the control group and five dogs in the milbemycin oxime/praziquantel tablet group. None of the dogs required treatment.

**Conclusion:**

The results of a pharmacokinetics (PK) bridging study (NAH-10-0015) (refer to the Freedom of Information Summary for the original approval of NADA 141-338, dated June 16, 2012) allow for a bridge from the milbemycin oxime/praziquantel tablet formulation used in this study to the final chewable formulation.

This study demonstrates that a single dose of milbemycin/praziquantel tablets was 100% effective against naturally-acquired adult *D. caninum* infections in dogs. The addition of milbemycin oxime and lufenuron does not interfere with the effectiveness of praziquantel against *D. caninum* and justifies the inclusion of praziquantel into the combination.

Therefore, based on the results of this study and those of the PK bridging study (NAH-10-0015), INTERCEPTOR™ PLUS is effective against *D. caninum* infections in dogs. Diarrhea should be considered a potential adverse reaction

2. Laboratory Dose Confirmation Study NAH-14-093

**Title:** Experimental Study to Evaluate the Efficacy of Interceptor Spectrum® for Treatment and Control of *Dipylidium caninum* in Dogs.

**Study Dates:** September 9, 2015- May 27, 2016

**Study Location:** Bloemfontein, South Africa

**Study Design:**

**Objective:** The objective of the study was to evaluate the effectiveness of INTERCEPTOR™ PLUS against experimentally-induced adult *D. caninum* infections in dogs when administered orally.

This study was conducted using principles of OECD Good Laboratory Principles (GLP).

**Study Animals:** Sixteen dogs (12 male and 4 female) between 11-20 months of age and weighing between 29.4 and 54.0 pounds (13.3 and 24.5 kg) were included in the study.

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\* The proprietary name was subsequently changed from Interceptor Spectrum® to INTERCEPTOR™ PLUS.

The dogs were confirmed to be negative for intestinal parasites during acclimation. The dogs were experimentally infested with topical application of fleas infected with United States (US)-derived *D. caninum* on Days 0, 7, 13, 21, 26, 35, 42, 48, and 55. Dogs were also dosed orally with *D. caninum* infected fleas on Days 0, 14, 27, and 56.

Treatment Groups:

Table 3: Study NAH-14-093 Treatment Groups (8 dogs per group)

<b>Treatment Group</b>	<b>Milbemycin oxime Dose</b>	<b>Praziquantel Dose</b>
INTERCEPTOR™ PLUS	0.5 mg/kg	5 mg/kg
Control (untreated)	0 mg/kg	0

Drug Administration: The test article was administered, according to Table 3, once on Day 82, within 30 minutes following ingestion of a meal after an overnight fast. Using a combination of chewable tablet strengths, the dogs were dosed at a minimum target praziquantel dose of 5 mg/kg (2.28 mg/lb). The actual doses ranged from 4.9 mg/kg to 5.2 mg/kg praziquantel.

Measurements and Observations: All dogs were determined to be healthy with negative fecal examination prior to initiation of the study. All dogs were determined to be heartworm negative prior to Day 82. On Day 82, all dogs were observed hourly for four hours for evidence of adverse events. Daily observations of general health occurred throughout the study. On Day 92, the dogs were euthanized and necropsied for *D. caninum* recovery and enumeration.

**Statistical Methods:**

Effectiveness was determined on the basis of the percent reduction in tapeworm counts in the treated group as compared to the control group. Geometric means of tapeworm counts were calculated.

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

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

Statistical significance was assessed using Analysis of Variance (ANOVA; SAS PROC MIXED) of logarithmically transformed worm counts at necropsy with treatment group as a fixed effect.

**Results:**

Adequate infection was demonstrated in the control group with all eight control dogs, on necropsy, harboring greater than 5 tapeworms. Treatment with INTERCEPTOR™ PLUS was 100% effective against adult *D. caninum*



tapeworms in experimentally-infected dogs (Table 4). The difference in the number of *D. caninum* recovered between the treated and control groups were statistically significant ( $p < 0.0001$ ).

Table 4: Study NAH-14-093 Results

<b>Treatment Group</b>	<b>Number of Dogs</b>	<b>Geometric mean of <i>D. caninum</i> Recovered (range)</b>	<b>Percent Effectiveness</b>
INTERCEPTOR™ PLUS	8	0.0 (NA)	100%
Control (untreated)	8	30.7 (8-124)	NA

NA=Not applicable

**Adverse Reactions:**

No test article-related adverse reactions were observed.

**Conclusion:**

INTERCEPTOR™ PLUS, when used at a minimum dose of 5 mg/kg (2.28 mg/lb) praziquantel, was 100% effective against *D. caninum* infections in dogs.

**III. TARGET ANIMAL SAFETY**

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-338 dated June 16, 2012, contains a summary of the target animal safety studies for use in for dogs.

**IV. HUMAN FOOD SAFETY**

This drug is intended for use in dogs. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

**V. USER SAFETY**

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to INTERCEPTOR™ PLUS:

*"Not for use in humans . Keep this and all drugs out of the reach of children."*

**VI. AGENCY CONCLUSIONS**

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that INTERCEPTOR™ PLUS, when used according to the label, is safe and effective for the treatment and control of adult tapeworm (*Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

**A. Marketing Status**

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because the product is indicated for the prevention of heartworm infections (*Dirofilaria immitis*) in dogs, which requires veterinary examination and testing to ensure dogs are negative for adult heartworm disease prior to administration of the product to dogs.

**B. Exclusivity**

This supplemental approval for INTERCEPTOR™ PLUS qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the treatment and control of adult tapeworm (*Dipylidium caninum*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

**C. Supplemental Applications**

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

**D. Patent Information:**

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