Date of Approval: January 12, 2023

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-426

BRAVECTO®

(fluralaner)

Chewable tablets

Dogs

This supplement provides for the addition of the indication for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

Sponsored by:

Intervet, Inc.

Executive Summary

BRAVECTO® (fluralaner) chewable tablets are approved for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater. The Asian longhorned tick is a new tick species in the U.S. Not normally found in the Western Hemisphere, these ticks were reported for the first time in the U.S. in 2017.

BRAVECTO® is already approved to 1) kill adult fleas (*Ctenocephalides felis*); 2) treat and prevent flea infestations; and 3) treat and control several types of tick infestations for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater. The drug may be given every 8 weeks in case of potential exposure to *Amblyomma americanum* ticks (lone star ticks). BRAVECTO® should be given with food.

Fluralaner is an ectoparasiticide belonging to the isoxazoline class. The drug inhibits the nervous system of arthropods, such as fleas and ticks. It works by blocking gamma-aminobutyric acid (GABA)- and glutamate-gated chloride channels. Chloride ions are blocked from crossing cell membranes, which results in uncontrolled neuromuscular activity in fleas and ticks, causing their death.

Proprietary Name	Established Name	Application Type and Number	Sponsor
BRAVECTO®	fluralaner	New Animal Drug Application (NADA) 141-426	Intervet, Inc.

Safety and Effectiveness

The sponsor conducted two laboratory studies to show that BRAVECTO® is effective against *H. longicornis* tick infestations in dogs. In each study, dogs were experimentally infested with viable, unfed, adult ticks on Day -2 and then monthly for 3 months. On Day 0, dogs in the treatment group were given BRAVECTO® and dogs in the control group were sham-dosed (same dosing procedures as the treatment group, but no tablets were administered). Tick counts were performed on Day 2 (48 hours after treatment) and 48 hours after each monthly infestation.

In both studies, BRAVECTO® was 100% effective at controlling *H. longicornis* tick infestations (reducing the number of live ticks) for 3 months, while dogs in the control group remained infested with live ticks at each tick count. BRAVECTO® was also effective in treating *H. longicornis* tick infestations. Compared to dogs in the control group, treated dogs had a higher number of dead ticks for 3 months. No adverse reactions were reported in dogs in the treatment group in either study.

The Corrected Freedom of Information (FOI) Summary for the original approval of BRAVECTO®, dated May 25, 2014, contains a summary of target animal safety studies for dogs.

Conclusions

Based on the data submitted by the sponsor for the approval of BRAVECTO®, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-426

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

BRAVECTO®

D. Drug Product Established Name

fluralaner

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

Each chewable tablet ("chew") contains 112.5, 250, 500, 1000, or 1400 mg fluralaner.

H. How Supplied

BRAVECTO® is available in five strengths (112.5, 250, 500, 1000, and 1400 mg fluralaner per chew). Each chew is packaged individually into aluminum foil blister packs sealed with a peelable paper backed foil lid stock. Product may be packaged in 1, 2, or 4 chews per package.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

BRAVECTO® should be administered orally as a single dose every 12 weeks according to the Dosage Schedule below to provide a minimum dose of 11.4 mg/lb (25 mg/kg) body weight.

BRAVECTO® may be administered every 8 weeks in case of potential exposure to *Amblyomma americanum* ticks.

BRAVECTO® should be administered with food.

Dosage Schedule

Body Weight Ranges (lb)	Fluralaner Content (mg)	Chews Administered
4.4 – 9.9	112.5	One
> 9.9 – 22.0	250	One
> 22.0 – 44.0	500	One
> 44.0 – 88.0	1000	One
> 88.0 – 123.0*	1400	One

*Dogs over 123.0 lb should be administered the appropriate combination of chews

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

BRAVECTO® kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*), and the treatment and control of tick infestations [*Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick), *Rhipicephalus sanguineus* (brown dog tick), and *Haemaphysalis longicornis* (Asian longhorned tick)] for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

BRAVECTO® is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for 8 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

N. Effect of Supplement

This supplement provides for the addition of the indication for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

II. EFFECTIVENESS

The effectiveness of BRAVECTO® against *Haemaphysalis longicornis* was demonstrated in two well-controlled laboratory studies described below. These studies demonstrated that BRAVECTO® is effective for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) for 12 weeks in dogs and puppies 6 months of age and older.

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage of 11.4 mg/lb (25 mg/kg) body weight given as a single administration every 12 weeks for fleas and ticks (*Ixodes scapularis*, *Dermacentor variabilis*, *Rhipicephalus sanguineus*). BRAVECTO® may also be administered every 8 weeks

in case of potential exposure to *Amblyomma americanum*. The Corrected Freedom of Information (FOI) Summary for the original approval of NADA 141-426 dated May 25, 2014, contains dosage characterization information for dogs.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study

   Title: Effectiveness of 13.64% w/w Fluralaner Chewable Tablets for Dogs at the Recommended Dose Against *Haemaphysalis longicornis* Ticks on Dogs. (Study No. S19250-00)

   Study Dates: May 13, 2020 to November 4, 2021

   Study Location: Waverly, NY

   Study Design:

   Objective: To confirm the effectiveness of fluralaner chewable tablets at the recommended minimum dose (25 mg/kg) for the treatment and control of *H. longicornis* infestations on dogs.

   Study Animals: 20 healthy dogs (Beagles; 9 males and 11 females), 2.3 to 7.5 years of age, and 7.2 to 14.6 kg body weight.

   Experimental Design: Prior to allocation to treatment groups on Day -3, an initial tick infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were randomly assigned to the untreated control group (10 dogs) or the fluralaner group (10 dogs). The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

   Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 58, and 88. At each infestation, each dog was infested with approximately 50 adult, unfed female *H. longicornis* ticks. Tick counts were conducted on Day 2, 48 hours after drug administration, and on Days 30, 60, and 90, 48 hours after tick infestations. Ticks were not returned to the dogs after counting.

   Drug Administration: On Day 0, the 10 dogs in the fluralaner group were administered two whole fluralaner chewable tablets, at doses as close as possible to 25 mg/kg without under-dosing. Doses ranged from 27.3 to 35.9 mg/kg per dog. The chewable tablets were administered by placement on the back of the dog's tongue (pilling). Drug administration was to have occurred within 20 minutes after food had been offered. However, drug administration for several dogs occurred outside of this 20-minute window. None of the dogs in the fluralaner group consumed food prior to drug administration. Dogs in the control group were sham-dosed.

   Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 60, and 90, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1-, 3-, and 6-hours following drug administration. Dogs were

weighed on Day -2 for dose calculations. Tick counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A linear mixed model analysis with treatment group as a fixed effect was used to analyze live tick counts at each evaluation time point. The test of treatment effect was performed at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on least squares means.

Results: At each tick count day, at least 7 of the 10 dogs in the control group had an adequate infestation, defined as at least 13 live *H. longicornis* ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live *H. longicornis* tick counts at 48 hours following drug administration or infestation for 90 days (infestation on Day 88) compared to the control group. On all count days following drug administration, live tick counts for the fluralaner group were significantly different ($p \leq 0.0002$) from the control group.

Table II.1. Study S19250-00 *H. longicornis* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
2	20.2	0.0	100
30	18.4	0.0	100
60	16.1	0.0	100
90	13.9	0.0	100

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On Days 2, 30, and 90 following drug administration, dead tick counts for the fluralaner group were higher than those in the control group.

Table II.2. Study S19250-00 *H. longicornis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
2	0.1	0.9
30	0.6	1.4
60	0.3	0.3
90	0.6	1.7

*Tick counts are arithmetic means.

Adverse Reactions: No adverse reactions were reported in this study.

Conclusions: This study demonstrated the effectiveness of fluralaner for the control (reduced live ticks) and treatment (increased dead ticks) of *H. longicornis* for 90 days when assessed at 48 hours after drug administration or infestation.

2. Laboratory Dose Confirmation Study

Title: Effectiveness of 13.64% w/w Fluralaner Chewable Tablets for Dogs at the Proposed Recommended Dose Against *Haemaphysalis longicornis* Ticks on Dogs. (Study No. S19251-00)

Study Dates: May 13, 2020 to July 28, 2021

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the effectiveness of fluralaner chewable tablets at the recommended minimum dose (25 mg/kg) for the treatment and control of *H. longicornis* infestations on dogs.

Study Animals: 20 healthy dogs (Beagles and mongrels; 7 males and 13 females), 1.7 to 7.2 years of age, and 10.5 to 17.9 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -3, an initial *H. longicornis* infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were randomly assigned to the untreated control group (10 dogs) or the fluralaner group (10 dogs). The study was conducted in accordance with GCP guidelines.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 58, and 88. At each infestation, each dog was infested with approximately 50 adult, unfed female *H. longicornis* ticks (United States source). Tick counts were conducted on Day 2, 48 hours after drug administration, and on Days 30, 60, and 90 after tick infestations. Ticks were not returned to the dogs after counting.

Drug Administration: On Day 0, the 10 dogs in the fluralaner group were administered two or three whole fluralaner chewable tablets, at doses as close as possible to 25 mg/kg without under-dosing. Doses ranged from 25.2 to 31.7 mg/kg per dog. The chewable tablets were administered by placement on the back of the dog’s tongue (pilling) within 20 minutes after food had been offered. Dogs in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 60, and 90, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted daily, and at approximately 1-, 3-, and 6-hours following drug administration. Dogs were weighed on Day -2 for dose calculations. Tick counts and health observations were conducted by individuals masked to treatment.

Statistical Methods: A linear mixed model analysis with treatment group as a fixed effect was used to analyze live tick counts at each evaluation time point. The test of treatment effect was performed at a two-sided 5% significance level. Percent effectiveness against the control group was calculated based on least squares means.

Results: At each tick count day, at least 7 dogs in the control group had an adequate infestation, defined as at least 13 live ticks (25% of the infestations of 50 ticks per dog).

The fluralaner group had greater than 90% reduction in live *H. longicornis* tick counts at 48 hours following drug administration or infestation for 90 days (infestation on Day 88) compared to the control group. On all count days following drug administration, live tick counts for the fluralaner group were significantly different ($p < 0.0001$) from the control group.

Table II.3. Study S19251-00 *H. longicornis* Live Tick Count and Percent Effectiveness

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
2	30.4	0.0	100
30	20.1	0.0	100
60	20.4	0.0	100
90	18.8	0.0	100

*Tick counts are least squares means. Percent effectiveness is based on least squares means.

On all count days following drug administration, dead tick counts for the fluralaner group were higher than those in the control group.

Table II.4. Study S19251-00 *H. longicornis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
2	0.0	3.6
30	0.7	1.5
60	0.0	1.2
90	0.0	0.4

*Tick counts are arithmetic means.

Adverse Reactions: No adverse reactions were reported in this study.

Conclusions: This study demonstrated the effectiveness of fluralaner for the control (reduced live ticks) and treatment (increased dead ticks) of *H. longicornis* for 90 days when assessed at 48 hours after drug administration or infestation.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The Corrected FOI Summary for the original approval of NADA 141-426 dated May 25, 2014 contains a summary of target animal safety studies for use of BRAVECTO® chewable tablets in dogs at an oral dose of 25.5 mg/lb (56 mg/kg) administered every eight weeks.

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 BRAVECTO®:

Not for human use. Keep this and all drugs out of the reach of children. Keep the product in the original packaging until use, in order to prevent children from getting direct access to the product. Do not eat, drink or smoke while handling the product. Wash hands thoroughly with soap and water immediately after use of the product.

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 BRAVECTO®, when used according to the label, is safe and effective for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

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 professional expertise is required to advise dog owners regarding use in breeding dogs, to monitor for and respond to adverse reactions, and to define the appropriate treatment interval (8 vs. 12 weeks) based on the species of ticks the dog is likely to encounter.

B. Exclusivity

This supplemental approval for BRAVECTO® 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 indication for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

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 Green Book Reports in the Animal Drugs @ FDA database.