Date of Approval: November 25, 2024

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-532

BRAVECTO® 1-MONTH

(fluralaner)

Chewable tablet

Dogs

This supplement provides for the addition of the indication for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

Sponsored by:

Intervet, Inc.

Executive Summary

BRAVECTO® 1-MONTH (fluralaner) chewable tablets are approved for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater. The Asian longhorned tick is a new tick species in the United States (U.S.). Not normally found in the Western Hemisphere, these ticks were reported for the first time in the U.S. in 2017.

BRAVECTO® 1-MONTH is already approved to 1) kill adult fleas (*Ctenocephalides felis*); 2) treat and prevent flea infestations; and 3) treat and control tick infestations [*Ixodes scapularis* (black-legged tick), *Dermacentor variabilis* (American dog tick), and *Rhipicephalus sanguineus* (brown dog tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater. The drug is also already approved to treat and control *Amblyomma americanum* (lone star tick) infestations for one month in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater.

BRAVECTO® 1-MONTH is an antiparasitic drug that is available in five strengths of chewable tablets that are given orally once a month.

Safety and Effectiveness

The sponsor conducted two laboratory studies to show that BRAVECTO® 1-MONTH is effective against *H. longicornis* tick infestations in puppies 8 weeks of age and older. In each study, dogs were experimentally infested with viable, unfed, adult ticks on Day -2 and then weekly for one month. On Day 0, dogs in the treated group were given BRAVECTO® 1-MONTH 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 weekly infestation.

In both studies, BRAVECTO® 1-MONTH was greater than 99% effective at controlling *H. longicornis* tick infestations (reducing the number of live ticks) for one month, while dogs in the control group remained infested with live ticks at each tick count. BRAVECTO® 1-MONTH was also effective at treating *H. longicornis* tick infestations (increasing the number of dead ticks) for one month. Compared to dogs in the control group, treated dogs had a higher number of dead ticks. No adverse reactions were reported in dogs in the treatment group in either study.

The FOI Summary for the original approval of BRAVECTO® 1-MONTH dated July 9, 2020, contains a summary of target animal safety studies for dogs.

Conclusions

Based on the data submitted by the sponsor for the approval of BRAVECTO® 1-MONTH, the Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-532

B. Sponsor

Intervet, Inc.
126 E Lincoln Ave.
Rahway, NJ 07065

Drug Labeler Code: 000061

C. Proprietary Name

BRAVECTO® 1-MONTH

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 45, 100, 200, 400, or 560 mg of fluralaner

H. How Supplied

BRAVECTO® 1-MONTH is available in five strengths (45, 100, 200, 400, and 560 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, 3, or 4 chews per package.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

BRAVECTO® 1-MONTH should be administered orally as a single dose monthly according to the **Dosage Schedule** below to provide a minimum dose of 4.5 mg/lb (10 mg/kg) fluralaner.

BRAVECTO® 1-MONTH should be administered with food.

Dosage Schedule

Body Weight Ranges (lb)	Fluralaner Content (mg)	Chews Administered
4.4 – 9.9	45	One
>9.9 – 22.0	100	One
>22.0 – 44.0	200	One
>44.0 – 88.0	400	One
>88.0 – 123.0*	560	One

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

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

BRAVECTO® 1-MONTH 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 one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

BRAVECTO® 1-MONTH is also indicated for the treatment and control of *Amblyomma americanum* (lone star tick) infestations for one month 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 one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

II. EFFECTIVENESS

The effectiveness of BRAVECTO® 1-MONTH against *Haemaphysalis longicornis* was demonstrated in two well-controlled laboratory studies, described below. These studies demonstrated that BRAVECTO® 1-MONTH is effective for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

A. Dosage Characterization

This supplemental approval does not change the previously approved dose of 4.5 mg/lb (10 mg/kg) body weight given as a single oral administration monthly. The FOI

Summary for the original approval of NADA 141-532 dated July 9, 2020, contains dosage characterization information for dogs.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study

Title: Effectiveness of 5.46% w/w Fluralaner Chewable Tablets for Dogs at the Proposed Recommended Dose Against *Haemaphysalis longicornis* Ticks on Puppies. (Study No. S20185-00)

Study Dates: January 6, 2021 to June 30, 2022

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the effectiveness of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg) for the treatment and control of *H. longicornis* infestations on growing puppies, starting at 8 weeks of age.

Study Animals: Eighteen healthy puppies (pure and mixed breed; 10 males and 8 females), 7.6 to 9 weeks of age, and 2.9 to 4.6 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -1, puppies were randomly assigned to the untreated control group or the fluralaner treatment group. 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, 7, 14, 21, and 28. At each infestation, each puppy was infested with approximately 50 adult, unfed *H. longicornis* ticks (United States source). Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 9, 16, 23, and 30, 48 hours after tick infestations. Ticks were not returned to the puppy after counting.

Drug Administration: On Day 0, the nine puppies in the fluralaner group were administered one whole fluralaner chewable tablet, at doses as close as possible to 10 mg/kg without under-dosing. Doses ranged from 10 to 19.6 mg/kg per puppy. The chewable tablets were administered by placement on the back of the puppy's tongue (pilling) within 20 minutes after food had been offered. Puppies in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the puppies. At tick counts on Days 2, 9, 16, 23, and 30, 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. Puppies were weighed on Day -1 for dose calculations. Tick counts and health observations were conducted 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, all 9 puppies 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 puppy).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following drug administration or infestation for 30 days (infestations on Day 28) 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.1: S20185-00 *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	19.9	0	100
9	36.1	0	100
16	27.6	0	100
23	27.7	0.1	99.6
30	30.6	0	100

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

On Days 2, 9, 16, and 30, following drug administration, dead tick counts for the fluralaner group were higher than those in the control group.

Table II.2: S20185-00 *H. longicornis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
2	0.1	14.6
9	0	0.8
16	0.4	4.2
23	0.7	0.6
30	0	0.1

*Tick counts are arithmetic means.

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

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

2. Laboratory Dose Confirmation Study

Title: Effectiveness of 5.46% w/w Fluralaner Chewable Tablets for Dogs at the Proposed Recommended Dose Against *Haemaphysalis longicornis* Ticks on Puppies. (Study No. S21138-00)

Study Dates: August 3, 2021 to August 30, 2022

Study Location: Waverly, NY

Study Design:

Objective: To confirm the effectiveness of fluralaner chewable tablets at the recommended minimum dose (10 mg/kg) for the treatment and control of *H. longicornis* infestations on growing puppies, starting at 8 weeks of age.

Study Animals: Twenty healthy puppies (Beagles; 11 males and 9 females), 7.4 to 8.3 weeks of age, and 2 to 3 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -5, puppies were randomly assigned to the untreated control group or the fluralaner treatment group. 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, 7, 14, 21, and 28. At each infestation, each puppy was infested with approximately 50 adult, unfed *H. longicornis* ticks. Tick counts were performed on Day 2, 48 hours after drug administration, and on Days 9, 16, 23, and 30, 48 hours after tick infestations. Ticks were not returned to the puppy after counting.

Drug Administration: On Day 0, the 10 puppies in the fluralaner group were administered one whole fluralaner chewable tablet, at doses as close as possible to 10 mg/kg without under-dosing. Doses ranged from 15 to 21.2 mg/kg per puppy. The chewable tablets were administered by placement on the back of the puppy's tongue (pilling) within 20 minutes after food had been offered. In the fluralaner group, five puppies consumed part of their meal and five puppies consumed none of their meal prior to drug administration. Puppies in the control group were sham-dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the puppies. At tick counts on Days 2, 9, 16, 23, and 30, 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. Puppies were weighed on Day -1 for dose calculations. Tick counts and health observations were conducted 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 9 of the 10 puppies 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 puppy).

The fluralaner group had greater than 90% reduction in live tick counts at 48 hours following drug administration or infestation for 30 days (infestations on Day 28) 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: S21138-00 *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	22.9	0	100
9	26.7	0	100
16	21.2	0	100
23	27.6	0	100
30	24	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: S21138-00 *H. longicornis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
2	2.5	6
9	0.1	2.6
16	0.1	3
23	1.3	1.6
30	0.4	1.5

*Tick counts are arithmetic means.

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

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

III. TARGET ANIMAL SAFETY

FDA did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-532 dated July 9, 2020, contains a summary of target animal safety studies 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, FDA 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® 1-MONTH:

Warnings:

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® 1-MONTH, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above.

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 and to monitor for and respond to adverse reactions.

B. Exclusivity

This supplemental approval for BRAVECTO® 1-MONTH 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 one month in dogs and puppies 8 weeks of age and older, and weighing 4.4 pounds or greater.

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval did not require a reevaluation of certain safety or effectiveness data in the application.

D. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.