

Date of Approval: August 9, 2022

FREEDOM OF INFORMATION SUMMARY
SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-459

BRAVECTO[®]

(fluralaner topical solution)

Cats

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 cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

Sponsored by:

Intervet, Inc.

Executive Summary

BRAVECTO® (fluralaner topical solution) is approved for the treatment and control of *Haemaphysalis longicornis* (Asian longhorned tick) infestations for 12 weeks in cats and kittens 6 months of age and older, and weighing 2.6 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® is already approved to kill adult fleas (*Ctenocephalides felis*); treat and prevent flea infestations; and treat and control *Ixodes scapularis* (black-legged tick) infestations for 12 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater. The drug is also approved to treat and control *Dermacentor variabilis* (American dog tick) infestations for 8 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

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 topical solution	New Animal Drug Application (NADA) 141-459	Intervet, Inc.

Safety and Effectiveness

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

In both studies, BRAVECTO® was greater than 95% effective at controlling *H. longicornis* tick infestations (reducing the number of live ticks) for 3 months, while cats 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 cats in the control group, treated cats had a higher number of dead ticks following infestation for 3 months. No adverse reactions were reported in cats in the treatment group in either study.

The Freedom of Information (FOI) Summary for the original approval of BRAVECTO®, dated July 20, 2016, contains a summary of target animal safety studies for cats.

Other Safety Information

Fluralaner, the active ingredient in BRAVECTO®, is in the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and

seizures. Neurologic adverse reactions have been reported even in cats without a history of neurologic disorders. The drug should be used with caution in cats with a history of neurologic disorders.

The safety of BRAVECTO® has not been established in breeding, pregnant, and lactating cats.

The labeling for BRAVECTO® includes safety information for people who handle the drug. People, including children, should not touch the application site for 2 hours after the dose is given.

Conclusions

Based on the data submitted by the sponsor for the approval of BRAVECTO®, the 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 141-459

B. Sponsor

Intervet, Inc.
2 Giralda Farms
Madison, NJ 07940

Drug Labeler Code: 000061

C. Proprietary Name

BRAVECTO®

D. Drug Product Established Name

Fluralaner topical solution

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Solution

G. Amount of Active Ingredient

Each milliliter contains 280 mg of fluralaner

H. How Supplied

BRAVECTO® is available in three strengths for use in cats (112.5, 250, and 500 mg fluralaner per tube). Each tube is packaged individually in a pouch. Product may be supplied in 1 or 2 tubes per carton.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

BRAVECTO® should be administered topically as a single dose every 12 weeks according to the **Dosage Schedule** below to provide a minimum dose of 18.2 mg/lb (40 mg/kg) body weight.

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

Dosage Schedule:

Body Weight Ranges (lb)	Fluralaner content (mg/tube)	Tube Administered
2.6 – 6.2	112.5	One
>6.2 – 13.8	250	One
>13.8 – 27.5*	500	One

*Cats over 27.5 lb should be administered the appropriate combination of tubes.

K. Route of Administration

Topical

L. Species/Class

Cats

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 *Ixodes scapularis* (black-legged tick) and *Haemaphysalis longicornis* (Asian longhorned tick) infestations for 12 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

BRAVECTO® is also indicated for the treatment and control of *Dermacentor variabilis* (American dog tick) infestations for 8 weeks in cats and kittens 6 months of age and older, and weighing 2.6 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 cats and kittens 6 months of age and older, and weighing 2.6 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) infestations for 12 weeks in cats and kittens 6 months of age and older, and weighing 2.6 pounds or greater.

A. Dosage Characterization

This supplemental approval does not change the previously approved dosage of 18.2 mg/lb (40 mg/kg) fluralaner given every 8-12 weeks as a single topical application. The FOI Summary for the original approval of NADA 141-459 dated July 20, 2016, contains dosage characterization information for cats.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study

Title: Evaluation of the Effectiveness of BRAVECTO® Topical Solution for Cats (fluralaner) against Experimental Infestations of *Haemaphysalis longicornis* in Cats. (Study No. S19248-00)

Study Dates: May 2020 to November 2021

Study Location: Waverly, NY

Study Design:

Objective: To confirm the effectiveness of fluralaner topical solution at the recommended minimum dose (40 mg/kg fluralaner) for the treatment and control of *H. longicornis* infestations on cats.

Study Animals: 20 healthy cats (domestic shorthair; 5 males and 15 females), 1.4 to 3.4 years of age, and 2.5 to 9.1 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -4, an initial *H. longicornis* infestation and count was conducted to evaluate susceptibility of each cat to experimental infestation (host suitability). Cats were randomly assigned to the untreated control group (10 cats) or the fluralaner group (10 cats). 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 cat was infested with approximately 50 adult, unfed female *H. longicornis* ticks. To prevent grooming, Elizabethan collars were placed on cats prior to each infestation and, with the exception of Day 0, remained on until tick counts were completed. Following the infestation on Day -2, the collars were removed on Day 0, prior to treatment, to prevent the collars from interfering with the topical treatment. Tick counts were conducted on Day 2, 48 hours after drug administration, and on Days 30, 60, and 90, 48 hours after infestation. Ticks were not returned to the cats after counting.

Drug Administration: On Day 0, fluralaner topical solution was applied to 10 cats in the fluralaner group at doses as close as possible to 40 mg/kg fluralaner. Fluralaner doses ranged from 39.6 to 40.3 mg/kg per cat. Hair at the administration site was parted, and the topical solution was applied to the skin in one spot at the base of the skull. Cats in the control group were sham dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the cats. 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 1-, 3-, and 6-hours following drug administration. Treatment site observations were conducted on Days 1, 2, 3, 7, and 14. Cats 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 cats 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 cat).

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). 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: Study S19248-00; *H. longicornis* Live Tick Count Results

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
2	17.4	0.0	100
30	32.9	0.0	100
60	24.0	0.0	100
90	23.7	1.1	95.4

*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.2: Study S19248-00; *H. longicornis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
2	0.6	2.7
30	0.2	12.2
60	0.8	4.3
90	0.3	8.0

*Tick counts are arithmetic means.

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

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

2. Laboratory Dose Confirmation Study

Title: Evaluation of the Effectiveness of BRAVECTO® Topical Solution for Cats (fluralaner) against Experimental Infestations of *Haemaphysalis longicornis* in cats. (Study No. S19249-00)

Study Dates: May 2020 to July 2021

Study Location: Bloemfontein, South Africa

Study Design:

Objective: To confirm the effectiveness of fluralaner topical solution at the recommended minimum dose (40 mg/kg fluralaner) for the treatment and control of *H. longicornis* infestations on cats.

Study Animals: 20 healthy cats (mixed breed; 7 males and 13 females), 1.7 to 6.8 years of age, and 2.3 to 4.5 kg body weight.

Experimental Design: Prior to allocation to treatment groups on Day -5, an initial *H. longicornis* infestation and count was conducted to evaluate susceptibility of each cat to experimental infestation (host suitability). Cats were randomly assigned to the untreated control group (10 cats) or the fluralaner group (10 cats). 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 cat was infested with approximately 50 adult, unfed female *H. longicornis* ticks. To prevent grooming, Elizabethan collars were placed on cats prior to each infestation and, with the exception of Day 0, remained on until tick counts were completed. Following the infestation on Day -2, the collars were removed on Day 0, prior to treatment, to prevent the collars from interfering with the topical treatment. Tick counts were conducted on Day 2, approximately 48 hours after drug administration, and on Days 30, 60, and 90, approximately 48 hours after infestation. Ticks were not returned to the cats after counting.

Drug Administration: On Day 0, fluralaner topical solution was applied to 10 cats in the fluralaner group at doses as close as possible to 40 mg/kg fluralaner. Fluralaner doses ranged from 39.6 to 40.3 mg/kg per cat. Hair at the administration site was parted, and the topical solution was applied to the skin in one spot at the base of the skull. Cats in the control group were sham dosed.

Measurements and Observations: The primary variable for effectiveness was the counts of live ticks collected from the cats. 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. Treatment site observations were conducted on Days 1, 2, 3, 7, and 14. Cats 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: On Days 30, 60, and 90, at least 7 cats 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 cat). On Day 2, only three of the 10 control cats were adequately infested. The inadequate infestation was attributed to grooming behavior of the cats, who had their Elizabethan collars removed following dosing and not replaced until the subsequent infestations. Therefore, the Day 2 tick counts were considered invalid and not included in the determination of effectiveness.

The fluralaner group had a greater than 90% reduction in live *H. longicornis* tick counts at 48 hours following infestation on Days 30, 60, and 90. On Days 30, 60, and 90 following drug administration, live tick counts for the fluralaner group were significantly different ($P < 0.0001$) from the control group.

Table II.3: Study S19249-00; *H. longicornis* Live Tick Count Results

Day for Tick Counts	Control Group Live Tick Counts*	Fluralaner Group Live Tick Counts*	Percent Effectiveness
30	34.8	0.0	100
60	20.4	0.2	99.0
90	21.6	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 the control group.

Table II.4: Study S19249-00; *H. longicornis* Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts*	Fluralaner Group Dead Tick Counts*
30	0.0	3.2
60	0.4	1.6
90	0.1	3.9

*Tick counts are arithmetic means.

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

Conclusion: This study demonstrated the effectiveness of fluralaner topical solution for the control (reduced live ticks) and treatment (increased dead ticks) of *H. longicornis* from Days 30 to 90 when assessed at 48 hours after infestation.

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 141-459 dated July 20, 2016, contains a summary of target animal safety studies for cats.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. 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®:

Human Warnings:

Not for human use. Keep this and all drugs out of the reach of children.

Do not contact or allow children to contact the application site until 2 hours post application.

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. Avoid contact with skin and eyes. If contact with eyes occurs, then flush eyes slowly and gently with water. **If wearing contact lenses, eyes should be rinsed first, then remove contact lenses and continue rinsing, then seek medical advice immediately. Wash hands and contacted skin thoroughly with soap and water immediately after use of the product. If the product accidentally contacts skin and a sticky residue persists after washing, rubbing alcohol (70% isopropyl alcohol) can be applied to the area to remove the residue.**

The product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

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 cats and kittens 6 months of age and older, and weighing 2.6 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 monitor for and respond to adverse reactions in cats, and to define the appropriate treatment interval (8 or 12 weeks) based on the species of ticks the cat 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 cats and kittens 6 months of age and older, and weighing 2.6 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.