Date of Approval: May 25, 2014

CORRECTED FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-426

BRAVECTO

Fluralaner

Chewable Tablets

Dogs

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)*,* and *Rhipicephalus sanguineus* (brown dog 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.

Sponsored by:

Intervet, Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-426

B. Sponsor

Intervet, Inc.
556 Morris Ave.
Summit, NJ 07901

Drug Labeler Code: 000061

C. Proprietary Name

BRAVECTO

D. 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

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 (see EFFECTIVENESS).

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. Indications

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)*,* and *Rhipicephalus sanguineus* (brown dog 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.

II. EFFECTIVENESS

A. Dosage Characterization

1. Dose Selection

   Various studies conducted with orally and topically administered fluralaner demonstrate a direct relationship between fluralaner dose and duration of effectiveness against fleas and ticks. These studies also indicate that fleas are more susceptible to lower doses of fluralaner than ticks. A 12-week study in

dogs that used a topical formulation of fluralaner at a dose of 10 mg/kg demonstrated 100% effectiveness against fleas versus 51% effectiveness against *Ixodes ricinus* ticks. Pharmacokinetic studies demonstrate that fluralaner has a higher bioavailability when provided by an oral versus topical route of administration. A dose determination study with topical fluralaner at doses ranging from 10 to 40 mg/kg demonstrated that 25 mg/kg provided greater than 90% effectiveness for 12 weeks duration for fleas and *Rhipicephalus sanguineus* ticks. An oral dose of 25 mg/kg was selected for BRAVECTO.

2. Minimum Age

   Dose confirmation studies with fluralaner chews demonstrate effectiveness against *Ctenocephalides felis* fleas and *Ixodes scapularis, Dermacentor variabilis*, and *Rhipicephalus sanguineus* ticks for 12 weeks duration in dogs at least 6 months of age when dosed at 25 mg/kg. However, in a European dose confirmation study in young puppies, fluralaner chews were effective against *R. sanguineus* ticks to Day 30 in 8-week-old Beagle puppies that were dosed once at 41-54 mg/kg. In a Japanese dose confirmation study in young puppies, fluralaner chews were effective against *Haemaphysalis longicornis* ticks to Day 58 in 9-week-old puppies that were dosed once at 25 mg/kg. In contrast, fluralaner chews were effective against *H. longicornis* ticks to Day 86 in dogs that were dosed once at 6.5 to 7.5 months of age at 25 mg/kg.

   Pharmacokinetic studies demonstrate that fluralaner chews have a substantially lower peak plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC), and a shorter plasma elimination half-life ($T_{½}$), in young puppies (8-9 weeks of age) compared to dogs aged 6 months and older, at approximately the same oral dose.

   Therefore, although the margin of safety study supports the safety of BRAVECTO in 8-week old puppies, substantial evidence to support a 12-week duration of effectiveness in dogs less than 6 months of age has not been demonstrated.

B. Substantial Evidence

1. For the Treatment and Prevention of Flea Infestations

   a. Laboratory Dose Confirmation Study S11139-03: Effectiveness for Fleas

      (1) Title/Objective

      Effectiveness of 13.64% w/w fluralaner flavored chewable tablets for dogs at the proposed recommended dose against *Ctenocephalides felis* infestations on dogs

      (2) Location and Dates

      Young Veterinary Research Services, Turlock CA
      January 12, 2013, to May 16, 2013

      (3) Study Design

(a) Study Animals

20 healthy dogs (pure- and mixed-bred, 6 males and 14 females), 2 to 13.6 years of age, and 7.9 to 29.1 kg body weight

(b) Experimental Design

Prior to allocation to treatment groups on Day -7, an initial flea infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked and blocked by live flea count, and one dog from each block was randomly assigned to the untreated control (10 dogs) or the fluralaner (10 dogs) treatment group.

Drug administration was on Day 0. Flea infestations were conducted on Days -2, 28, 56, 84, and 112. At each infestation, each dog was infested with approximately 100 unfed adult fleas.

(c) Drug Administration

On Day 0, the ten dogs in the fluralaner group were administered one or more whole fluralaner chews, at doses as close as possible to 25 mg/kg without under-dosing. Doses ranged from 25.3 to 29.1 mg/kg per dog. The chews were administered by placement on the back of the dog's tongue (pilling) within 20 minutes after food had been offered.

(d) Measurements and Observations

The primary variable for effectiveness was the counts of live fleas collected from the dogs. At flea counts on Days 2, 30, 58, 86 and 114, fleas were removed and the numbers of live fleas recorded. General health observations were conducted daily and at 1, 3, and 6 hours after drug administration. Dogs were weighed on Day -2. Flea counts and health observations were conducted masked to treatment.

(e) Statistical Methods

A mixed model analysis was used to analyze log-transformed flea counts, with treatment group as a fixed effect at a two-sided 5% significance level. Percent effectiveness against the control was calculated based on geometric means.

(4) Results

At each flea count, there were a minimum of six dogs in the control group that had an adequate infestation, defined as at least 50 live fleas (50% of the infestations of 100 fleas per dog). On all count days following drug administration, live flea counts between the two groups were significantly different ($p \leq 0.001$).

Table 1: Study S11139-00 Effectiveness Against Fleas

Day	Control Group Flea Counts[a]	Fluralaner Group Flea Counts[a]	% Effectiveness
2	74.1	0.0	100
30	49.0	0.0	100
58	67.4	0.0	100
86	69.7	0.0	100
114	70.4	0.5	99.3

[a] Flea counts are geometric means and % effectiveness is based on geometric means.

(5) Adverse Reactions

No adverse reactions were reported in this study.

(6) Conclusion

This study demonstrated the effectiveness of fluralaner for the treatment of existing flea infestations for at least 12 weeks when assessed 48 hours after drug administration or infestation.

b. Field Study S11002-00: Effectiveness for Fleas

(1) Title/Objective

Title: Clinical effectiveness of 13.64% w/w fluralaner flavored chewable tablets for dogs against fleas: a multi-center pivotal field trial

Field Study S11002-00 assessed safety, effectiveness against fleas, signs of flea allergy dermatitis, and palatability.

(2) Investigators and Locations, Study Dates

Jay Butan, DVM Lake Worth, FL	Ken McMillan, DVM Cropwell, AL
Bill Campaigne, DVM Seguin, TX	Jason St. Romain, DVM Zachary, LA
Beth Carroll, DVM Durham, NC	Joel Sailor, DVM Starke, FL
Peter Davis, DVM Augusta, ME	Roger Sifferman, DVM Springfield, MO
Don Dinges, DVM Leawood, KS	Troy Smith, DVM Austin, TX
Michael Doherty, DVM New Braunfels, TX	David Stanley, DVM Gladstone, MO
Sam Geller, VMD Quakertown, PA	John Teeter, DVM Shawnee Mission, KS
Sherwood Gill, DVM Lake Charles, LA	Casey Thomas, DVM Junction City, KS
Greg Griffeth, DVM Philadelphia, PA	Melissa Wiest, DVM O'Fallon, MO

The study was conducted between August 16, 2011, and June 18, 2012

(3) Study Design

(a) Study Animals

294 client-owned dogs from 157 households; 224 dogs (118 households) treated with fluralaner chews and 70 dogs (39 households) treated with a combination of spinosad tablets and amitraz collars

Enrollment eligibility included: households with no more than 5 dogs, at least one dog with a minimum of 10 live fleas, and no other pets that could harbor fleas. There were no breed or gender restrictions, but households with pregnant or lactating dogs were not eligible for enrollment. There were restrictions on the use of medications or products with flea treatment or control activity in any household dogs or household premises prior to or during the study period. The study enrolled 153 females and 141 males, 12 weeks to 15 years of age, and 4.4 to 152 lb body weight. The study included purebred and mixed breed dogs.

(b) Experimental Design

Households were randomly assigned to treatment with fluralaner or control in a ratio of three fluralaner households to one control household. Owners treated dogs in the fluralaner group with fluralaner chews once every 12 weeks for three treatments. The fluralaner group finished the study at Visit 8 on Day 182. Owners treated dogs in the active control group with an amitraz collar on study entry and with spinosad tablets once every 4 weeks for three treatments. The control group finished the study at Visit 4 on Day 84. All dogs within a household were in the same treatment group. A primary dog from each household was randomly selected from dogs with 10 or more live fleas at Visit 1. Only the primary dog was assessed for effectiveness against fleas. Owners administered the treatments and they treated all dogs in the household at the same times.

Investigators, who performed flea allergy dermatitis and safety assessments (physical examinations, clinical pathology result assessments, and adverse event assessments), and personnel that performed flea counts were masked to treatment. Treatment administrators at each study location and Owners were not masked.

(c) Drug Administration

In the fluralaner group, Owners administered fluralaner chews, at labeled doses, on Days 0, 84, and 168. Owners recorded palatability at each dosing. In the control group, Owners applied the amitraz collar at the first visit and administered spinosad tablets at labeled doses on Days 0, 28, and 56.

(d) Measurements and Observations

The primary variable was the difference in live flea counts on the primary dogs on Days 28 (Visit 2), 56 (Visit 3), and 84 (Visit 4) versus pretreatment (Visit 1). Additional variables included progression of signs of flea allergy dermatitis, palatability of fluralaner chews,

physical examinations, and clinical pathology. Statistical analyses were not performed for these additional variables.

(e) Statistical Methods
Log-transformed flea counts were analyzed using a mixed model at two-sided 5% significance level. Percent effectiveness against the pretreatment flea counts was calculated based on geometric means.

(4) Results

For each of Visits 2, 3, and 4, the effectiveness of fluralaner, based on geometric means, was greater than 90%.

Table 2: Field Study S11002-00 Effectiveness against Fleas

Visit	Fluralaner Group	Control Group
Visit 1 Number of Dogs	117	39
Visit 1 Geometric Mean Flea Count	32.2	32.6
Visit 2 Number of Dogs	113	38
Visit 2 Geometric Mean Flea Count	0.1	1.3
Visit 2 Percent Effectiveness	99.7%	96.1%
Visit 3 Number of Dogs	108	34
Visit 3 Geometric Mean Flea Count	0.1	0.2
Visit 3 Percent Effectiveness	99.8%	99.5%
Visit 3 Number of Dogs	106	32
Visit 3 Geometric Mean Flea Count	0.1	0.1
Visit 3 Percent Effectiveness	99.8%	99.6%

Within each treatment group, geometric mean flea counts were significantly different ($p < 0.001$) from Visit 1 at Visits 2, 3, and 4.

At least 80% of the dogs with signs attributed to Flea Allergy Dermatitis (FAD) at Visit 1, and not on medications that could affect the assessment of FAD, had resolution of the signs by Visit 4 at Week 12.

Table 3: Field Study S11002-00 Resolution of Signs of Flea Allergy Dermatitis

FAD Sign	Percent of Fluralaner Group Dogs with the FAD Sign at Visit 1 that was Resolved at Week 12	Percent of Control Group Dogs with the FAD Sign at Visit 1 that was Resolved at Week 12
Erythema	89% (50/56 dogs)	71% (12/17 dogs)
Alopecia	88% (30/34 dogs)	80% (8/10 dogs)
Papules	92% (12/13 dogs)	100% (7/7 dogs)
Scales	80% (16/20 dogs)	89% (8/9 dogs)
Crusts	95% (21/22 dogs)	100% (7/7 dogs)
Excoriation	92% (11/12 dogs)	100% (6/6 dogs)

Dogs with signs of FAD showed improvement in erythema, alopecia, papules, scales, crusts, and excoriation as a direct result of eliminating flea infestations.

Owners recorded palatability information for 559 doses of fluralaner chews administered. Owners first offered fluralaner chews by hand. If not consumed, they offered the chews in food, and if not consumed they placed the chews in the back of dog's mouths. Dogs voluntarily consumed 80.7% of the doses offered within five minutes of offering.

Table 4: Field Study S11002-00 Palatability of Fluralaner Chews

Type of Dose Offering for Assessment of Palatability	Percent of Doses
Free choice and consumed within 1 minute of offering	74.4%
Free choice and consumed between 1 and 5 minutes of offering	6.3%
With food or other treat	12.5%
Placement in the dog's mouth (pilling)	5.9%
Owner unable to dose	0.9%

(5) Adverse Reactions

There were no serious adverse reactions in any of the dogs treated with fluralaner chews or control.

Table 5: Field Study S11002-00 Adverse Reactions

Adverse Reaction (AR)	Fluralaner Group: Percent of Dogs with the AR During the 182-Day Study (n=224 dogs)	Control Group: Percent of Dogs with the AR During the 84-Day Study (n=70 dogs)
Emesis	7.1%	14.3%
Decreased Appetite	6.7%	0.0%
Diarrhea	4.9%	2.9%
Lethargy	5.4%	7.1%
Polydipsia	1.8%	4.3%
Flatulence	1.3%	0.0%

(6) Conclusion

This study demonstrated that fluralaner was safe and effective for the treatment of flea infestations when administered once every 12 weeks to client-owned dogs.

c. Laboratory Dose Confirmation Study S11453-00: Simulated Home Environment for Fleas

(1) Title/Objective

Effectiveness of 13.64% w/w fluralaner flavored chewable tablets for dogs at their proposed recommended doses for the control of *Ctenocephalides felis* in a simulated home environment for dogs

(2) Location and Dates

Young Veterinary Research Services, Turlock CA
April 17, 2012, to August 21, 2012

(6) Conclusion

This study demonstrated the effectiveness of fluralaner for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* ticks for 8 weeks when assessed at 72 hours after drug administration or infestation.

i. Laboratory Dose Confirmation Study S13080-01: *Amblyomma americanum* Ticks

(1) Title/Objective

Effectiveness of 13.64% w/w fluralaner flavored chewable tablets for dogs at the proposed recommended dose against wild caught *Amblyomma americanum* ticks on dogs

(2) Location and Dates

Young Veterinary Research Services, Turlock CA
April 13, 2013, to July 18, 2013

(3) Study Design

(a) Study Animals

20 healthy dogs (pure- and mixed-bred, 11 males and 9 females), 1.3 to 11.1 years of age, and 7.8 to 39.6 kg body weight

(b) Experimental Design

Prior to allocation to treatment groups on Day -6, an initial tick infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked and blocked by live tick count, and one dog from each block was randomly assigned to the untreated control (10 dogs) or the fluralaner (10 dogs) treatment group.

Drug administration was on Day 0. Tick infestations were conducted on Days -2, 28, 55, and 83. At each infestation, each dog was infested with approximately 50 adult, unfed *A. americanum* ticks (approximate 50:50 ratio of male to female ticks).

(c) Drug Administration

On Day 0, the ten dogs in the fluralaner group were administered one or more whole fluralaner chews, at doses as close as possible to 25 mg/kg without under-dosing. Doses ranged from 25.3 to 34.2 mg/kg per dog. The chews were administered by placement on the back of the dog's tongue (pilling) within 20 minutes after food had been offered.

(d) Measurements and Observations

The primary variables for effectiveness were the counts of live ticks collected from the dogs. At tick counts on Days 2, 30, 58 and 86, 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 after drug administration. Dogs were weighed on Day -2. Tick counts and health observations were conducted masked to treatment.

(e) Statistical Methods

A mixed model analysis was used to analyze log-transformed tick counts, with treatment group as a fixed effect at a two-sided 5% significance level. Percent effectiveness against the control was calculated based on geometric means.

(4) Results

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

The fluralaner group had greater than 90% reduction in live tick counts at 72 hours following treatment or infestation at 8 weeks (infestation on Day 55), but failed to demonstrate greater than 90% effectiveness beyond 8 weeks.

On all count days following drug administration, live tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table 27: *A. americanum* S13080-01 Live Tick Count Effectiveness

Day for Tick Counts	Control Group Live Tick Counts[a]	Fluralaner Group Live Tick Counts[a]	% Effectiveness
2	44.0	0.3	99.4
30	30.3	1.1	96.3
58	31.6	0.7	97.7
86	25.5	4.2	83.6

[a] Tick counts are geometric means and % effectiveness is based on geometric means.

On all count days following drug administration, dead tick counts for the fluralaner group were significantly different from the control group ($p < 0.001$).

Table 28: *A. americanum* S13080-01 Dead Tick Count Results

Day for Tick Counts	Control Group Dead Tick Counts[a]	Fluralaner Group Dead Tick Counts[a]
2	0	24.4
30	0	13.3
58	0	12.0
86	0	6.8

[a] Tick counts are geometric means.

(5) Adverse Reactions

No adverse reactions were reported in this study.

(6) Conclusion

This study demonstrated the effectiveness of fluralaner for the control (reduced live ticks) and treatment (increased dead ticks) of *A. americanum* ticks for 8 weeks when assessed at 72 hours after drug administration or infestation, but failed to demonstrate greater than 90% effectiveness beyond 8 weeks.

III. TARGET ANIMAL SAFETY

A. Margin of Safety Study D009\11-001

1. Title/Objective

Title: Target animal safety study in pups when administered 13.64% w/w fluralaner flavored chewable tablets for dogs orally on three occasions 56 days apart

Study D009\11-001 assessed the safety of fluralaner chews following oral administration at doses of up to 1X, 3X, and 5X the maximum label dose (up to 56, 168, and 280 mg/kg) to dogs three times at eight-week intervals.

2. Location and Dates

Charles River Laboratories Preclinical Services Ireland Ltd.
Glenamoy, Co. Mayo, Ireland
July 26, 2011, to February 7, 2012

3. Study Design

a. Study Animals
32 healthy weaned puppies (Beagles, 16 male and 16 female), 54 to 62 days of age, and 2.0 to 3.6 kg body weight

b. Experimental Design

Dogs were randomized to one of four treatment groups of eight dogs per group (four per sex) within sex by body weight. Dogs were either administered fluralaner chews at up to 56, 168, and 280 mg/kg (1X, 3X, and 5X the maximum label dose) three times at eight-week intervals (Study Days 0, 56, and 112) or were untreated (control group).

c. Drug Administration

The dogs were fed prior to oral administration of fluralaner chews.

d. Measurements and Observations

Clinical observations were made twice daily and at 1, 2, 3, 4, and 8 hours after oral administration of fluralaner chews on Study Days 0, 56, and 112. Body weight was recorded weekly. Individual food consumption was recorded daily. Blood samples were collected for clinical pathology (hematology, coagulation profile, clinical chemistry, adrenocorticotrophic hormone, and acute phase (C-reactive) protein) on Days -14, 8, 50, 106, and 162; and for plasma fluralaner concentrations on Study Days -5, 2, 7, 14, 28, 55, 58, 63, 70, 84, 111, 114, 119, 126, 140, and 167. Urine samples were collected

overnight for urinalysis on Days -6/5, 7/8, 49/50, 105/106, and 161/162. All dogs were euthanized on Day 168 and underwent full gross necropsy, organ weight, and histopathological evaluation. Except for histopathological evaluation, measurements and observations were conducted masked to treatment.

4. Statistical Methods

Hematology, clinical chemistry, ACTH, coagulation, C-reactive protein, numerical urinalysis variables, food consumption, and body weight were analyzed using a repeated measured mixed model analysis of covariance. Pre-treatment measurement was included as a covariate. Organ weights were analyzed using a mixed model analysis of variance.

5. Results

There were no clinically-relevant, treatment-related effects on physical examinations, body weights, food consumption, clinical pathology (hematology, clinical chemistries, coagulation profiles and urinalysis), gross pathology, histopathology, or organ weights.

Diarrhea, mucoid and bloody feces were the most common observations in this study, occurring at a similar incidence in the treated and control groups. Five of the twelve treated dogs that experienced one or more of these signs did so within 6 hours of the first dosing. One dog in the 3X group was observed to be dull, inappetent, with evidence of bloody diarrhea, vomiting and weight loss beginning five days following the first dose. One dog in the 1X group vomited food four hours following the first dose.

Plasma concentrations of fluralaner confirmed systemic exposure of all treated dogs although the exposure was less than dose proportional. Dogs achieved steady-state fluralaner concentrations by the third treatment period.

6. Conclusion

The oral administration of fluralaner chews at up to 280 mg/kg on three occasions eight weeks apart was well-tolerated in dogs. Potential treatment-related effects include diarrhea, mucoid and bloody feces, and vomiting.

B. Reproductive Safety Study 671596

1. Title/Objective

Title: 13.64% w/w fluralaner flavored chewable tablets for dogs: target animal reproductive safety study in the dog by oral administration

Study 671596 assessed the effects of fluralaner chews on reproductive performance and offspring viability in dogs following oral administration at doses of up to 3X of the maximum label dose (up to 168 mg/kg).

2. Location and Dates

Charles River Laboratories Preclinical Services Edinburgh Ltd.
Tranent, Scotland
June 28, 2011, to May 22, 2012

3. Study Design

   a. Study Animals

      40 adult, intact, reproductively-sound dogs (Beagles, 20 male and 20 female), 2 to 6 years of age, and 7.2 to 15.7 kg body weight

      The dogs were healthy and had a breeding history of at least four pups weaned in at least two of the three previous litters with no congenital malformations in any pup.

   b. Experimental Design

      Dogs were randomized to two treatment groups of 20 dogs per group (ten per sex) based on animal ID number and blocked by same parent. The treated dogs were administered fluralaner chews at up to 168 mg/kg (3X the maximum label dose of 56 mg/kg) for three to four doses at 8-week intervals, starting approximately 12 weeks (males) or 4 weeks (females) prior to expected mating. The females continued to be dosed at 8-week intervals until weaning of the pups, and the males were treated until the females had littered. The control dogs remained untreated.

   c. Drug Administration

      The dogs were fed prior to oral administration of fluralaner chews.

   d. Measurements and Observations

      Clinical observations were made twice daily and at 1, 2, 3, 4, and 8 hours after treatment on Days 1, 57, 113, 169, and 226. Body weight was recorded weekly for adult dogs and pups. Food consumption was recorded daily for adults. Blood samples were collected from adult dogs for clinical pathology (hematology, coagulation profile, and clinical chemistry) during acclimation; and for plasma fluralaner concentrations 1, 3, 7, 14, and 28 days after each dose, unless necropsy occurred first. Reproductive performance (including monthly semen analysis) and litter data was also assessed. All surviving pups and adult females were euthanized between Days 50 and 71 of lactation, and adult male dogs were euthanized 1 to 6 weeks after pups were born. Gross necropsy and organ weights were assessed in all dogs, and histopathological examination was performed on selected tissues including reproductive organs and any tissues with gross lesions. Except for histopathological evaluation, measurements and observations were conducted masked to treatment.

4. Statistical Methods

   Pre-mating adult body weight and food consumption (for each sex separately) and sperm assessment were analyzed using a repeated measures mixed model analysis of covariance. Pre-treatment measurement was included as a covariate. Average puppy weight of litters and organ weights of adults were analyzed using a mixed model analysis of variance.

5. Results

   All females that were bred in this study became pregnant and were allowed to litter normally. Two total litter losses occurred in the control group and one in the fluralaner-treated group.

There were no clinically-relevant, treatment-related effects on the body weights, food consumption, reproductive performance, semen analysis, litter data, gross necropsy (adult dogs), or histopathology findings (adult dogs and puppies). One treated and one control dog experienced diarrhea on the day of dosing, and one adult treated dog suffered a seizure during the course of the study (46 days after the third dose). Abnormal salivation was observed on 17 occasions: in six treated dogs (11 occasions) after dosing and four control dogs (6 occasions).

The following abnormalities were noted in 7 pups from 2 of the 10 dams in only the treated group during gross necropsy examination: limb deformity (4 pups), enlarged heart (2 pups), enlarged spleen (3 pups), and cleft palate (2 pups). During veterinary examination at Week 7, two pups from the control group had inguinal testicles, and two and four pups from the treated group had inguinal and cryptorchid testicles, respectively. No undescended testicles were observed at the time of necropsy (Days 50 to 71).

Plasma concentrations of fluralaner confirmed systemic and continuous exposure of all treated dogs throughout the study period.

6. Conclusion

The repeated oral administration of fluralaner at a dose of up to 168 mg/kg was well tolerated in reproducing dogs. In adult dogs, potential treatment-related effects include seizures, diarrhea and salivation after dosing. In puppies, potential treatment–related effects include limb deformity, enlarged heart and spleen, and cleft palate.

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 and 21 CFR part 514. The data demonstrate that BRAVECTO, when used according to the label, is safe and effective for killing adult fleas and 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)*,* and *Rhipicephalus sanguineus* (brown dog tick)] for 12 weeks in dogs and puppies 6 months of age and older, and weighing 4.4 pounds or greater. BRAVECTO is also safe and effective 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.

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:

BRAVECTO, as approved in our approval letter qualifies for FIVE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act because this is the first time we are approving this active ingredient in a new animal drug.

C. Patent Information:

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

VII. Appendix 1: Details of Correction

In the Results section for Reproductive Safety Study 671596, the timing of the seizure experience by one adult treated dog was corrected from 46 days after the second dose to 46 days after the third dose. The correction was made on June 13, 2017.

The original text for the Results section:

5. Results

All females that were bred in this study became pregnant and were allowed to litter normally. Two total litter losses occurred in the control group and one in the fluralaner-treated group.

There were no clinically-relevant, treatment-related effects on the body weights, food consumption, reproductive performance, semen analysis, litter data, gross necropsy (adult dogs), or histopathology findings (adult dogs and puppies). One treated and one control dog experienced diarrhea on the day of dosing, and one adult treated dog suffered a seizure during the course of the study (46 days after the second dose). Abnormal salivation was observed on 17 occasions: in six treated dogs (11 occasions) after dosing and four control dogs (6 occasions).

The following abnormalities were noted in 7 pups from 2 of the 10 dams in only the treated group during gross necropsy examination: limb deformity (4 pups), enlarged heart (2 pups), enlarged spleen (3 pups), and cleft palate (2 pups). During veterinary examination at Week 7, two pups from the control group had inguinal testicles, and two and four pups from the treated group had inguinal and

cryptorchid testicles, respectively. No undescended testicles were observed at the time of necropsy (Days 50 to 71).

Plasma concentrations of fluralaner confirmed systemic and continuous exposure of all treated dogs throughout the study period.

Corrected text for the Results section:

5. Results

All females that were bred in this study became pregnant and were allowed to litter normally. Two total litter losses occurred in the control group and one in the fluralaner-treated group.

There were no clinically-relevant, treatment-related effects on the body weights, food consumption, reproductive performance, semen analysis, litter data, gross necropsy (adult dogs), or histopathology findings (adult dogs and puppies). One treated and one control dog experienced diarrhea on the day of dosing, and one adult treated dog suffered a seizure during the course of the study (46 days after the third dose). Abnormal salivation was observed on 17 occasions: in six treated dogs (11 occasions) after dosing and four control dogs (6 occasions).

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Plasma concentrations of fluralaner confirmed systemic and continuous exposure of all treated dogs throughout the study period.