Date of Approval: January 19, 2018

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-494

Credelio™

lotilaner

Chewable Tablets

Dogs

CREDELIO kills adult fleas and is indicated for the treatment of flea infestations *(Ctenocephalides felis)* and the treatment and control of tick infestations [*Amblyomma americanum* (lone star tick*), Dermacentor variabilis* (American dog tick)*, Ixodes scapularis* (black-legged 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.

Sponsored by:

Elanco US, Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 141-494

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Credelio™

D. Product Established Name

Lotilaner

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable Tablets

G. Amount of Active Ingredient

Each chewable tablet contains 56.25 mg, 112.5 mg, 225 mg, 450 mg, or 900 mg lotilaner.

H. How Supplied

CREDELIO is available in five chewable tablet sizes for use in dogs: 56.25, 112.5, 225, 450, and 900 mg lotilaner. Each chewable tablet size is available in color-coded packages of 1 or 6 chewable tablets.

I. Dispensing Status

Rx

J. Dosage Regimen

CREDELIO is given orally once a month, at the minimum dosage of 9 mg/lb (20 mg/kg).

Dosage Schedule:

Body Weight	Lotilaner Per Chewable Tablet (mg)	Chewable Tablets Administered
4.4 to 6.0 lbs	56.25	One
6.1 to 12.0 lbs	112.5	One
12.1 to 25.0 lbs	225	One
25.1 to 50.0 lbs	450	One
50.1 to 100.0 lbs	900	One
Over 100.0 lbs	Administer the appropriate combination of chewable tablets	

CREDELIO must be administered with food.

K. Route of Administration

Oral

L. Species/Class

Dogs

M. Indication

CREDELIO kills adult fleas and is indicated for the treatment of flea infestations *(Ctenocephalides felis)* and the treatment and control of tick infestations [*Amblyomma americanum* (lone star tick*), Dermacentor variabilis* (American dog tick)*, Ixodes scapularis* (black-legged 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.

II. EFFECTIVENESS

A. Dosage Characterization

A two-stage approach was used for dosage characterization. The first stage used a dose-exposure-response relationship model based on pharmacokinetic/ pharmacodynamic (PK/PD) data from pilot studies to calculate the optimal dose. The model identified *Rhipicephalus sanguineus* and *Amblyomma americanum* as the two least sensitive ticks and demonstrated that *Ctenocephalides felis* was susceptible to much lower doses of lotilaner.

The second stage used a laboratory dose determination study to evaluate four dose rates (10 mg/kg, 15 mg/kg, 20 mg/kg, and 25 mg/kg) against *Rhipicephalus sanguineus* and *Amblyomma americanum*. The dose determination study suggested that lotilaner was effective against *R. sanguineus* and *A. americanum* at all four tested doses. Other pilot pharmacokinetic and effectiveness studies demonstrated variable bioavailability of lotilaner and, in one study, a decreased duration of effectiveness against *A. americanum* at the 15 mg/kg dose. Based on collective results from the dose-exposure-response modeling and simulations, pilot PK and effectiveness studies, and the dose determination study, a minimum dose of 9 mg/lb (20 mg/kg) was selected for lotilaner.

Bioavailability of lotilaner is lower and more variable in the fasted state. Laboratory studies demonstrated reduced duration of effectiveness in fasted dogs compared to fed dogs and that administration of lotilaner in the fed state was required to achieve adequate oral bioavailability and effectiveness. Therefore, dose confirmation studies to support substantial evidence of effectiveness in dogs were conducted under fed conditions.

B. Substantial Evidence

1. Field Effectiveness and Safety Study NAH-13-076

Title:

A randomized, blinded, positive controlled, field study to evaluate the efficacy and safety of lotilaner chewable tablets administered orally at a minimum dose of 20 mg/kg to dogs naturally infested with fleas.

Study Dates:

April 14, 2014 to October 16, 2015

Study Locations:

San Rafael, CA
Commerce, GA
Lake Worth, FL
Zachary, LA
Battle Creek, MI
Springfield, MO
Portland, OR
Harleysville, PA
Columbia, SC
Irving, TX
New Braunfels, TX

Of the 11 sites, one site (Irving, TX) did not enroll any cases. One site (Commerce, GA) did not enroll enough evaluable households for evaluation of effectiveness, but was used for evaluation of safety. Therefore, ten sites were used for safety evaluation, while nine sites were used for assessing effectiveness.

Study Design:

The study was conducted in accordance with good clinical practice (GCP) guidelines.

Objective:
The primary objectives were to assess the effectiveness and safety of lotilaner against natural infestations of fleas under field conditions. Secondary objectives were to assess improvement in the clinical signs of flea allergy dermatitis (FAD), palatability, and tick counts.

Study Animals:
The study enrolled 312 client-owned dogs from 180 households, with 259 dogs completing the study. The study enrolled dogs ranging in age from 8 weeks to 16 years of age, and 4.4 to 143 pounds of body weight. One hundred and ninety-eight (198) lotilaner-treated dogs and 86 afoxolaner-treated (control) dogs were evaluated for safety. One hundred and eleven (111) lotilaner-treated dogs and 50 afoxolaner-treated dogs were included in the assessment of effectiveness for at least one time point (Day 30, 60, and/or 90).

Enrollment eligibility included households with no more than three dogs and at least one dog with a minimum of 10 live fleas. 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 dog or household premises prior to or during the study period. Cats in the household were treated with a commercially available flea adulticide, once monthly for the duration of the study.

Experimental Design:
Households having one to three dogs were randomly allocated to treatment groups in blocks of three, in a ratio of two lotilaner households to one control (afoxolaner) household. In a household where more than one dog had ≥ 10 fleas, a primary dog was selected based on the alphabetical order of each dogs' name, and the other dogs were designated as supplementary animals. All dogs within a household were in the same treatment group and were included in the safety evaluations. Only the primary dogs were included in the effectiveness evaluations.

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

Drug Administration:
Owners administered lotilaner or afoxolaner at labeled doses to their dogs on, or within three days of Days 0, 30, and 60. All dogs in the household were treated at the same time. Owners were instructed to administer the products within 30 minutes of feeding. Owners assessed the palatability of both products after each administration.

Measurements and Observations:
Flea and tick counts were conducted on all dogs in each household prior to treatment on Day 0, and then on primary dogs on Days 30, 60, and 90. Monthly flea counts from the primary dog in each enrolled household were used to evaluate effectiveness. Clinical signs of FAD were assessed on Days 0, 30, 60, and 90 in all dogs in each household that had both a flea count ≥ 10 and one or more clinical signs of FAD on Day 0.

Palatability was assessed at each dose administration by the owners first offering the tablet(s) by hand for 90 seconds. If not consumed, they offered the tablet(s) in an empty bowl for 90 seconds. If not consumed they offered the tablet(s) in food for 90 seconds, and if not consumed in food, they placed the tablet(s) in the back of the dog's mouth.

Physical examinations, body weight, and clinical pathology (hematology, serum chemistry and urinalysis) were performed in all dogs at enrollment (Day 0) and at premature study exit or scheduled study completion (Day 90). In addition, physical examinations and body weights were performed in primary dogs on Days 30 and 60.

Statistical Methods:

Percent effectiveness of each treated group with respect to the baseline was calculated using the formula [(B - A)/B] x 100, where B = geometric mean live flea count prior to dosing (Day 0) and A = geometric mean live flea count post-dosing (Day 30, 60, or 90). The comparisons were tested using the two-sided 5% significance level. The mixed model analysis was used to analyze log-transformed counts, with visit day as a fixed effect, and site and subject-within-site as random effects.

Results:

Both lotilaner- and afoxolaner-treated dogs showed a statistically significant ($p < 0.001$) reduction in fleas from baseline (Day 0; pre-treatment) to the end of the study, and both showed ≥ 90% effectiveness (Table II.1).

Table II.1: Field Study NAH-13-076 Effectiveness Against Fleas- Percent Reduction (and Geometric Mean) of Live Flea Count Compared to Baseline (Day 0)

Treatment Group	Day 0 (pre-treatment)	Day 30	Day 60	Day 90
Lotilaner	(42.3)	99.5% (0.2)	100% (0.0)	100% (0.0)
Afoxolaner	(41.8)	98.4% (0.7)	99.7% (0.1)	99.9% (0.0)

There were an insufficient number of dogs with pre-existing and subsequent tick infestations to derive any conclusions on effectiveness against ticks.

Improvements in clinical signs of FAD were seen in 90.6% to 100% of dogs treated with lotilaner and in 100% of dogs treated with afoxolaner (Table II.2).

Table II.2: Field Study NAH-13-076 Percent (and Number) of Dogs with Improvement in Clinical Signs of Flea Allergy Dermatitis on Day 90

Clinical Sign	Lotilaner	Afoxolaner
Pruritus	97.6% (40 of 41)	100% (25 of 25)
Papules	100% (12 of 12)	100% (6 of 6)
Erythema	95.1% (39 of 41)	100% (21 of 21)
Alopecia	90.6% (29 of 32)	100% (15 of 15)
Scaling	95.2% (20 of 21)	100% (8 of 8)
Dermatitis/ Pyodermatitis	100% (23 of 23)	100% (7 of 7)

Dogs with signs of FAD showed improvement in pruritus, papules, erythema, alopecia, scaling, and dermatitis/pyodermatitis as a direct result of eliminating the fleas.

Owners recorded acceptance information for 567 doses of lotilaner chewable tablets, administered to 198 dogs. There were no reports of unsuccessful dosing (Table II.3).

Table II.3: Field Study NAH-13-076 Summary of Lotilaner Chewable Tablet Acceptance

Acceptance Method	Percent of Doses
Free choice (hand & empty bowl) (%)	80.4%
With food (%)	13.6%
Placement in the dog's mouth (%)	6.0%
Tablet not accepted (%)	0.0%

Adverse Reactions:

Evaluation of safety was completed over the 90-day period through in-clinic physical examinations, clinical pathology, and owner reporting of abnormalities for both primary and supplementary dogs (Table II.4).

Table II.4: Field Study NAH-13-076 Adverse Reactions

Adverse Reaction (AR)	Lotilaner Group: Number (and Percent) of Dogs with the AR (n=198)	Afoxolaner Group: Number (and Percent) of Dogs with the AR (n=86)
Weight loss	3 (1.5%)	2 (2.3%)
Polyuria	2 (1.0%)*	0 (0.0%)
Diarrhea	2 (1.0%)	2 (2.3%)
Elevated blood urea nitrogen (BUN)	2 (1.0%)*	0 (0.0%)
Elevated creatinine	1 (0.5%)*	0 (0.0%)
Elevated potassium	1 (0.5%)*	0 (0.0%)
Elevated phosphorus	1 (0.5%)*	0 (0.0%)
Dyspnea	1 (0.5%)	0 (0.0%)
Polyphagia	1 (0.5%)	0 (0.0%)

*Two geriatric dogs developed mildly elevated BUN (34 to 54 mg/dL; reference range: 6 to 31 mg/dL) during the study. One of these dogs also developed polyuria and a mildly elevated potassium (6.5 mEq/L; reference range: 3.6 to 5.5 mEq/L) and phosphorous (6.4 mg/dL; reference range: 2.5 to 6.0 mg/dL). The other dog also developed a mildly elevated creatinine (1.7 to 2.0 mg/dL; reference range: 0.5 to 1.6 mg/dL) and weight loss. One additional dog in the lotilaner group also developed polyuria.

In addition, one dog experienced intermittent head tremors within 1.5 hours of administration of vaccines, an ear cleaning performed by the owner, and its first dose of lotilaner. The head tremors resolved within 24 hours without treatment. The owner elected to withdraw the dog from the study.

Two dogs with a history of seizures received lotilaner and had no reported seizures throughout the study.

Conclusion:

This study demonstrated that lotilaner, when used at the labeled dose, was safe and effective for the treatment and prevention of flea infestations when administered to client-owned dogs.

2. Laboratory Dose Confirmation Study NAH-13-145: Effectiveness and Speed of Kill (12 and 24 Hours) for Fleas

Title:

A randomized, blinded, negative controlled pivotal laboratory efficacy study of lotilaner for the treatment and speed of kill against experimental infestations of *Ctenocephalides felis* on dogs.

Study Dates:

May 12, 2015 to September 16, 2015

Study Location:

Rockwood,TN

Study Design:

The study was conducted in accordance with good laboratory practice (GLP) regulations.

Objective:
Confirm the effectiveness of a single oral dose of at least 20 mg/kg lotilaner for the treatment of experimental adult *C. felis* infestations on dogs at 12 and 24 hours after treatment or infestation for 35 days.

Study Animals:
32 Beagles (15 males and 17 females), greater than 6 months of age, weighing between 6.8 and 12.0 kg.

Experimental Design:
Prior to allocation to treatment groups on Day -6, an initial flea infestation and count was conducted to evaluate susceptibility of each dog to experimental infestation (host suitability). Dogs were ranked by live flea count and randomly allocated within blocks to four groups. Flea infestations were conducted on Days -1, 7, 14, 21, 28, and 35. At each infestation, each dog was infested with approximately 100 ± 5 unfed, adult *C. felis* fleas.

Flea counts were performed at 12 and 24 hours after drug administration or flea infestation. Fleas were not returned to the dog after counting.

Table II.5: Study NAH-13-145 Treatment Groups

Treatment Group	Treatment (Minimum Dose)	Number and Gender of Animals	Time of Post-Treatment or Infestation Flea Count
1	Control (0 mg/kg)	8 (4 M, 4 F)	12 hours
2	Control (0 mg/kg)	8 (3 M, 5 F)	24 hours
3	Lotilaner (20 mg/kg)	8 (5 M, 3 F)	12 hours
4	Lotilaner (20 mg/kg)	7 (2 M, 5 F)*	24 hours

* One dog, out of a total of 8, was underdosed and is not included. This dog completed all study activities, but outcome data were not included in statistical analyses.

neurological examination was conducted on Days -7, 5, 35, 63, 91, 119, 147, 175, 203, and 224. Ophthalmoscopic examinations were conducted on Days -6, 99, and 211. An electrocardiographic examination was performed pretest (Day -8), and on Days 59, 143, 199, and 222. Food consumption was measured and recorded daily and reported weekly, starting with Day 1.

Samples for clinical pathology evaluations (hematology, serum chemistry, coagulation, and urinalysis) were collected on Days -6 (Day -9 for urinalysis), 8, 29, 36, 57, 64, 85, 92, 113, 120, 141, 148, 169, 176, 197, 204, and 223. Blood samples for blood lotilaner concentrations were collected on Day -1; 6 and 24 hours post-dose on Days 1 and 113; pre-dose and 24 hours post-dose on Days 29, 57, 85, 141, 169, and 197; and once on Days 4, 8, 15, 22, 116, 120, 127, 134, 200, 204, 211, 218, and 225.

Necropsy examinations and organ weight determination were performed on Day 225. Histopathologic examination was performed on tissues from all dogs.

Except for histopathological evaluation, measurements and observations were conducted masked to treatment.

Statistical Methods:

Body weights, electrocardiograms, food consumption, and clinical pathology (hematology, serum chemistry, coagulation, and urinalysis) were analyzed by repeated measures analysis of covariance (RMANCOVA). The pre-dose value closest to first dosing was used as the covariate. Organ weights (absolute weights and absolute weights relative to body and brain weights) and pharmacokinetic parameters were analyzed by analysis of variance (ANOVA).

Results:

There were no clinically relevant, treatment-related effects on clinical observations, physical and neurological examinations, body weights, food consumption, electrocardiograms, clinical pathology (serum chemistries, hematology, coagulation profiles, and urinalysis), gross or microscopic pathology, and organ weights. One male dog in the 5X group had bilateral corneal opacities at the final ophthalmoscopic examination. The minimal microscopic changes in the corneas included increased mitotic figures in the epithelial cells of both eyes, focal hyperplasia of the epithelium of one eye, and focal acute inflammation near the limbus in one eye. A direct relationship of the corneal changes to the drug could not be determined.

Blood concentrations of lotilaner confirmed systemic exposure of all treated dogs although the exposure was less than dose proportional at 5X. Following oral administration of 43 mg/kg (approximately 1X the maximum labeled dose), peak lotilaner concentrations were achieved between 6 hours and 3 days in dogs 2 months of age and between 1 and 7 days in dogs 10 months of age. Dogs 2 months of age had a shorter elimination half-life (average of 9.6 days) than at 10 months of age (average of 28.4 days).

Conclusion:

The study supports the safe use of lotilaner chewable tablets in dogs when used at the labeled dose and duration.

B. Foreign Experience

(Study numbers: NAH-13-077, NAH-13-078, NAH-14-358, NAH-14-360, and INT-13-006)

In a single arm field study conducted in Australia, one dog with a history of seizures experienced seizure activity, characterized as tremors and glazed eyes, six days after receiving lotilaner. The signs resolved without treatment and the dog completed the 60-day study.

In another single arm field study conducted in Australia, a 10-year-old mixed breed dog died 33 days after receiving lotilaner. The dog was withdrawn from the study 16 days after receiving lotilaner due to pruritus secondary to a suspected harvest mite infestation. The dog was treated with a topical ectoparasiticide containing pyrethrin, piperonyl butoxide, and N-ocytl bicycloheptene dicarboximide. The dog died seventeen days later. The dog exhibited vomiting, excessive thirst, and lethargy for a couple of days prior to death. The cause of death is unknown.

In three well-controlled field studies conducted in Europe (Germany, Hungary, Portugal, and Spain), seven dogs experienced episodes of vomiting within 2 days after lotilaner administration and two dogs experienced diarrhea within 3 days after lotilaner administration.

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 Credelio™:

Not for human use. 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 Credelio™, when used according to the label, is safe and effective for killing adult fleas and for the treatment of flea infestations *(Ctenocephalides felis)* and the treatment and control of tick infestations [*Amblyomma americanum* (lone star tick*), Dermacentor variabilis* (American dog tick)*, Ixodes scapularis* (black-legged 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.

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.

B. Exclusivity

Credelio™, 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 FD&C Act because this is the first time we are approving this active ingredient in a new animal drug application submitted under section 512(b)(1) of the FD&C Act.

C. Patent Information:

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