Date of Approval: December 9, 2019

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-528

Credelio™ CAT

lotilaner

Chewable Tablets

Cats

Credelio™ CAT kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) for one month in cats and kittens 8 weeks of age and older, and weighing 2.0 pounds or greater.

Sponsored by:

Elanco US Inc.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-528

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Credelio™ CAT

D. Drug Product Established Name

Lotilaner

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable Tablets

G. Amount of Active Ingredient

Each chewable tablet contains 12 mg or 48 mg lotilaner.

H. How Supplied

Credelio™ CAT is available in two chewable tablet sizes for use in cats: 12 and 48 mg lotilaner. Each chewable tablet size is available in color-coded packages containing 1 chewable tablet. The 48 mg chewable tablet size is also available in a color-coded package containing 6 chewable tablets.

I. Dispensing Status

Rx

J. Dosage Regimen

Credelio™ CAT is given orally once a month, at the minimum dosage of 2.7 mg/lb (6 mg/kg).

Dosage Schedule:

Body Weight	Lotilaner Per Chewable Tablet (mg)	Chewable Tablets Administered
2.0 to 4.0 lbs	12	One
4.1 to 17.0 lbs	48	One
Over 17.0 lbs	Administer the appropriate combination of chewable tablets	

Credelio™ CAT must be administered with food.

K. Route of Administration

Oral

L. Species/Class

Cats

M. Indication

Credelio™ CAT kills adult fleas and is indicated for the treatment and prevention of flea infestations (*Ctenocephalides felis*) for one month in cats and kittens 8 weeks of age and older, and weighing 2.0 pounds or greater.

II. EFFECTIVENESS

The effectiveness of Credelio™ CAT was demonstrated in three laboratory studies and one field study, described below, enrolling a total of 40 laboratory cats and 228 client-owned cats. These studies demonstrate that Credelio™ CAT is effective for the treatment and prevention of flea infestations for one month. The most common adverse reactions from the effectiveness studies were weight loss, tachypnea, vomiting, diarrhea, anorexia, and elevated blood urea nitrogen (BUN).

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 to treat infestations with *Ctenocephalides felis* and *Ixodes ricinus*. The model identified 3.0 mg/kg and 5.5 mg/kg as potential effective doses for *C. felis* and *I. ricinus*, respectively.

The second stage used a laboratory dose determination study to evaluate four dose rates (1.5 mg/kg, 3.0 mg/kg, 6.0 mg/kg, and 12.0 mg/kg) to treat infestations with *Ctenocephalides felis* and *Ixodes ricinus*. The dose determination study supported that lotilaner was effective against *C. felis* and *I. ricinus* at 6 mg/kg for at least 30 days. 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 2.7 mg/lb (6 mg/kg) was selected for lotilaner.

Bioavailability of lotilaner is lower and more variable in the fasted state. Laboratory studies demonstrated that administration of lotilaner in the fed state was required to achieve adequate oral bioavailability. Therefore, dose

confirmation studies to support substantial evidence of effectiveness in cats were conducted under fed conditions.

B. Substantial Evidence

1. Field Effectiveness and Safety Study

   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 2.73 mg/lb (6 mg/kg) to Cats Naturally Infested with Fleas. (Study No. NAH-14-413)

   Study Dates: May 2015 to November 2016

   Study Locations:
   Greenbrier, AR
   San Rafael, CA
   Lake Worth, FL
   West Palm Beach, FL
   Zachary, LA
   Battle Creek, MI
   Nixa, MO
   Springfield, MO
   Portland, OR
   Harleysville, PA
   Columbia, SC
   New Braunfels, TX

   Of the 12 sites, one site (Harleysville, PA) did not enroll any cases. Two sites (Zachary, LA and New Braunfels, TX) did not enroll enough evaluable households for evaluation of effectiveness but were used for evaluation of safety. Therefore, 11 sites were used for safety evaluations, 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 343 client-owned cats from 208 households, with 298 cats completing the study. The enrolled cats ranged in age from 8 weeks to 20 years of age, and 2.0 to 22.2 pounds of body weight. Two hundred and twenty-eight (228) lotilaner-treated cats and 113 active control (topical formulation of fipronil and S-methoprene) cats were evaluated for safety. One hundred and twenty-six (126) lotilaner-treated cats and 62 active control cats 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 cats and at least one cat with a minimum of 5 live fleas. Pregnant or lactating cats were not eligible for enrollment. There were restrictions on the use of medications or products with flea treatment or control activity in any household cat or household premises prior to or during the study period. Dogs 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 cats were randomly allocated to treatment groups in blocks of three, in a ratio of two lotilaner-treated households to one active control household. In a household where more than one cat had at least 5 fleas, a primary cat was selected based on the alphabetical order of each cats' name, and the other cats were designated as supplementary animals. All cats within a household were in the same treatment group and were included in the safety evaluations. Only the primary cats were included in the flea effectiveness evaluations.

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 and owners were not masked.

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

Measurements and Observations: Flea and tick counts were conducted on all cats in each household prior to treatment on Day 0, and then on primary cats on Days 30, 60, and 90. Monthly flea counts from the primary cat in each enrolled household were used to evaluate effectiveness. Clinical signs of FAD were assessed on Days 0, 30, 60, and 90 in all cats in each household that had both a flea count of at least 1, 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, on floor, or in empty bowl. If not consumed, they offered the tablet(s) in a small amount of food or in a treat. If not consumed in food, they placed the tablet(s) in the back of the cat's mouth.

Physical examinations, body weight, and clinical pathology (hematology and serum chemistry) were performed on all cats at enrollment (Day 0) and at premature study exit or scheduled study completion (Day 90). In addition, physical examinations and body weights were performed on primary cats 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 active control-treated cats showed a statistically significant ($p < 0.001$) reduction in fleas from baseline (Day 0; pre-treatment) to the end of the study, with the lotilaner treatment group having ≥ 90% effectiveness (Table II.1).

Table II.1: Field Study NAH-14-413; 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	(24.6)	98.5% (0.4)	100% (0.0)	100% (0.0)
Active control	(25.8)	61.7% (9.7)	75.2% (6.3)	83.2% (3.9)

There were no ticks observed during the study, and therefore no analyses performed.

Improvements in clinical signs of FAD were seen in 95.9% to 100% of cats in the lotilaner treatment group and in 37.5% to 75% of cats in the active control group (Table II.2).

Table II.2: Field Study NAH-14-413; Percent (and Number of Cats) with Improvement in Clinical Signs of Flea Allergy Dermatitis on Day 90

Clinical Sign	Lotilaner	Active Control
Pruritus	95.9% (47 of 49)	61.9% (13 of 21)
Papules	100% (17 of 17)	75.0% (3 of 4)
Erythema	100% (25 of 25)	37.5% (3 of 8)
Alopecia	100% (42 of 42)	50.0% (8 of 16)
Scaling	100% (33 of 33)	68.8% (11 of 16)
Dermatitis/Pyodermatitis	100% (32 of 32)	63.6% (7 of 11)

Cats 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 648 doses of lotilaner chewable tablets administered to 225 cats (Table II.3).

Table II.3: Field Study NAH-14-413; Summary of Lotilaner Chewable Tablet Acceptance

Acceptance Method	Percent of Doses
Free choice (voluntarily taken from hand, on floor, or in empty bowl)	21.1%
Voluntarily with food	25.8%
Placement in the cat's mouth	52.6%
Tablet not accepted	0.5%

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 cats (Table II.4).

Table II.4: Field Study NAH-14-413; Adverse Reactions

Adverse Reaction (AR)	Lotilaner Group: Number (and Percent) of Cats with the AR (n=228)	Active Control Group: Number (and Percent) of Cats with the AR (n=113)
Weight loss	5 (2.2%)	2 (1.8%)
Tachypnea	3 (1.3%)	0 (0.0%)
Vomiting	3 (1.3%)	1 (0.9%)
Diarrhea	2 (0.9%)	0 (0.0%)
Anorexia	2 (0.9%)	0 (0.0%)
Elevated blood urea nitrogen (BUN)*	2 (0.9%)	0 (0.0%)
Elevated serum creatinine*	1 (0.4%)	0 (0.0%)
Elevated alanine aminotransaminase (ALT)	1 (0.4%)	0 (0.0%)

*Two geriatric cats developed mildly elevated BUN (42 to 58 mg/dL; reference range: 14 to 36 mg/dL) during the study. One of these cats, which had suspected pre-existing kidney disease, also developed a mildly elevated serum creatinine (2.5 mg/dL; reference range: 0.6 to 2.4 mg/dL) during the study which returned to normal by the end of the study.

Conclusion: This study demonstrated that Credelio™ CAT (lotilaner), when used at the labeled dose, was safe and effective for the treatment and prevention of flea infestations in client-owned cats.

2. Laboratory Dose Confirmation Study: Effectiveness (24 Hours) for Fleas

Title: A Blinded, Randomized, Negative Controlled Pivotal Laboratory Study Assessing the Efficacy of Lotilaner Chewable Tablets against Fleas (*Ctenocephalides felis*) when Administered Orally at 6 mg/kg to Cats. (Study No. NAH-13-164)

Study Dates: February 2016 to October 2016

Study Location: Rockwood, TN

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

Objective: Confirm the effectiveness of a single oral dose of at least 6 mg/kg lotilaner for the treatment of experimental adult *C. felis* infestations on cats at 24 hours after treatment or infestation for 36 days.

Study Animals: 16 cats (8 males and 8 females), greater than 11 months of age, weighing between 3.0 and 5.7 kg.

Experimental Design: Prior to allocation to treatment groups on Day -3, an initial flea infestation and count was conducted to evaluate susceptibility of each cat to experimental infestation (host suitability). Cats were ranked by live flea count and randomly allocated within blocks to two groups. Flea infestations were conducted on Days -2, 7, 14, 21, 28, and 35. At each infestation, each cat was infested with approximately 100 ± 5 unfed, adult *C. felis* fleas.

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

Table II.5: Study NAH-13-164; Treatment Groups

Treatment Group	Treatment Day	Treatment (Minimum Dose)	Number and Gender of Animals
1	Day 0	Lotilaner (6 mg/kg)	6 (2 M, 4 F)*
2	Day 0	Control (0 mg/kg)	8 (4 M, 4 F)

*Two cats, out of a total of 8, had potential dosing errors and are not included. These cats completed all study activities, but outcome data were not included in the statistical analyses.

Drug Administration: On Day 0, the eight cats in the lotilaner group were administered one or more whole chewable tablets, at doses as close as possible to 6 mg/kg without under-dosing. Doses ranged from 6.3 to 8.0 mg/kg. The chewable tablets were administered by placement in the back of the cat's mouth approximately 30 minutes after feeding. A dose of tap water was given via syringe to facilitate swallowing. On Day 0, cats in the control group were mock dosed (given a dose of tap water via syringe).

Measurements and Observations: The primary variable for effectiveness was the live flea counts collected from the cats. At each flea count, fleas were removed, and the numbers of live fleas were recorded. General health observations were conducted once daily and clinical observations were conducted prior to treatment and at 30 minutes, 1, 6, and 8 hours post-treatment. Physical examinations were conducted at the beginning of the

study (Day -14). Cats were weighed on Days -14 and -2. Flea counts and health observations were conducted masked to treatment.

Statistical Methods: Percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C)] x 100, where C = arithmetic mean live flea count in the control group and T = arithmetic mean live flea count in the treated group for each time point. The comparisons were tested using the two-sided 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment as a fixed effect and block as a random effect.

Results: At each flea count, a minimum of six cats in each control group had an adequate flea infestation, defined as a retention rate of at least 50% (i.e., at least 50 live fleas).

Lotilaner was 100% effective at 24 hours post-treatment or infestation through Day 36 (Table II.6). On all count days following drug administration, live flea counts between the two groups were significantly different ($p < 0.001$).

Table II.6: Study NAH-13-164; Effectiveness Against *C. felis* at 24 Hours after Infestation

Days After Treatment*	Control Group Arithmetic Mean	Lotilaner Group Arithmetic Mean	Percent Effectiveness
1	74.1	0.0	100%
8	82.6	0.0	100%
15	76.8	0.0	100%
22	77.4	0.0	100%
29	85.6	0.0	100%
36	79.1	0.0	100%

*For Day 1, fleas were applied to the cats on Day -2 and were removed 24 hours after treatment

Adverse Reactions: One cat had a swollen lower lip two days after lotilaner administration that resolved without treatment. This was considered a possible drug hypersensitivity.

Conclusion: This study demonstrated the effectiveness of Credelio™ CAT (lotilaner) for the treatment of existing flea infestations for 36 days when assessed 24 hours after drug administration or infestation. Drug hypersensitivity should be considered a possible drug-related adverse event.

3. Laboratory Egg Laying Study: Prevention of Flea Infestations

Title: A Blinded, Randomized, Negative Controlled Laboratory Study Assessing the Efficacy of Lotilaner Chewable Tablets against Flea (*Ctenocephalides felis*) Egg Production when Administered Orally at 6 mg/kg to Cats. (Study No. ELA1700178)

Study Dates: August 2017 to March 2018

Study Location: Turlock, CA

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

Objective: Confirm the effectiveness of a single oral dose of at least 6 mg/kg lotilaner for the treatment and prevention of flea infestations for 30 days. Prevention is demonstrated by killing fleas before they can lay eggs.

Study Animals: 20 cats (6 males and 14 females), greater than 10 months of age, weighing between 2.9 and 7.7 kg.

Experimental Design: Prior to allocation to treatment groups on Day -6, an initial flea infestation and count were conducted to evaluate susceptibility of each cat to experimental infestation (host suitability). Cats were ranked by live flea count and randomly allocated within blocks to two groups. Flea infestations were conducted on Days -1, 6, 13, 20, and 29. At each infestation, each cat was infested with approximately 100 ± 5 unfed, adult *C. felis* fleas.

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

Table II.7: Study ELA1700178; Treatment Groups

Treatment Group	Treatment Day	Treatment (Minimum Dose)	Number and Gender of Animals
1	Day 0	Lotilaner (6 mg/kg)	10 (3 M, 7 F)
2	Day 0	Control (0 mg/kg)	10 (3 M, 7 F)

Drug Administration: On Day 0, the eight cats in the lotilaner group were administered one or more whole chewable tablets, at doses as close as possible to 6 mg/kg without under-dosing. Doses ranged from 6.0 to 8.6 mg/kg. The chewable tablets were administered by placement in the back of the cat's mouth approximately 30 minutes after feeding. A dose of tap water was given via syringe to facilitate swallowing. On Day 0, cats in the control group were mock dosed (given a dose of tap water via syringe).

Measurements and Observations: The primary variables for effectiveness were the live flea counts collected from the cats and the flea eggs collected from the cages. At each count, fleas were removed and the numbers of live fleas on the cats and flea eggs collected from the bottom of the cage were recorded. General health observations were conducted once daily and clinical observations were conducted prior to treatment and at 1, 6, and 8 hours post-treatment. Physical examinations were conducted at the beginning of the study (Day -14). Cats were weighed on Day -6. Flea counts, flea egg counts, and health observations were conducted masked to treatment.

Statistical Methods: For the treatment indication, percent effectiveness of the treated group with respect to the control group was calculated using the

formula [(C-T)/C)] x 100, where C = arithmetic mean live flea count in the control group and T = arithmetic mean live flea count in the treated group for each time point. The comparisons were tested using the two-sided 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment as a fixed effect and block as a random effect.

Effectiveness for the prevention indication was concluded if there were essentially zero flea eggs collected from the cages of the treated cats on Day 7 and later (eggs present on Day 1 were not deemed as a lack of effectiveness) and high levels of eggs were collected from the cages of the control cats.

Results: At each flea count, a minimum of six cats in the control group had an adequate flea infestation, defined as a retention rate of at least 50% (i.e., at least 50 live fleas).

Lotilaner was ≥ 99.8% effective at 24 hours post-treatment or infestation through Day 30 (Table II.8). On all count days following drug administration, live flea counts between the two groups were significantly different ($p < 0.0001$).

Lotilaner was also effective at preventing flea egg production (Table II.9).

Table II.8: Study ELA1700178; Effectiveness Against *C. felis* at 24 Hours after Infestation

Days After Treatment*	Control Group Arithmetic Mean	Lotilaner Group Arithmetic Mean	Percent Effectiveness
1	89.7	0.0	100%
7	88.5	0.0	100%
14	90.6	0.1	99.9%
21	84.3	0.1	99.9%
30	86.5	0.2	99.8%

*For Day 1, fleas were applied to the cats on Day -1 and were removed 24 hours after treatment.

Table II.9: Study ELA1700178; Effectiveness Against *C. felis* Egg Production at 24 Hours after Infestation

Days After Treatment*	Control Group Arithmetic Mean (Range)	Lotilaner Group Arithmetic Mean (Range)
1	441.7 (205-677)	22.6 (1-46)
7	138.8 (0-276)	0.0 (0)
14	113.4 (0-308)	0.0 (0)
21	94.3 (0-399)	0.1 (0-1)
30	117.2 (0-343)	0.0 (0)

*For Day 1, fleas were applied to the cats on Day -1 and were removed 24 hours after treatment.

Adverse Reactions: One cat regurgitated food approximately 1 hour after lotilaner administration.

Conclusion: This study demonstrated the effectiveness of Credelio™ CAT (lotilaner) for the treatment and prevention of flea infestations for 30 days when assessed 24 hours after drug administration or infestation. Regurgitation should be considered a possible drug-related adverse reaction.

4. Laboratory Dose Confirmation Study: Speed of Kill for Fleas (6 Hours)

   Title: A Randomized, Blinded, Negative Controlled Study to Evaluate the Speed of Kill of Lotilaner Chewable Tablets for Cats against Fleas (*Ctenocephalides felis*) on Cats. (Study No. ELAZA150306)

   Study Dates: March 2016 to October 2016

   Study Location: Bloemfontein, South Africa

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

   Objective: Determine the speed of kill of a single oral dose of at least 6 mg/kg lotilaner against experimental adult *C. felis* infestations on cats after treatment or infestation for 35 days.

   Study Animals: 48 cats (26 males and 22 females), 1.1 to 7.1 years of age, weighing between 2.5 and 5.0 kg.

   Experimental Design: Prior to allocation to treatment groups on Day -16, initial flea infestations on Days -21 and -19 were conducted to evaluate susceptibility of each cat to experimental infestation (host suitability). Cats were ranked by live flea count and randomly allocated within blocks to six groups. Flea infestations were conducted on Days -2, 7, and 14. At each infestation, each cat was infested with approximately 100 ± 5 unfed, adult *C. felis* fleas.

   Flea counts were performed at 4, 6, and 12 hours after drug administration or flea infestation. Fleas were not returned to the cat after counting.

   The study was terminated early when effectiveness of at least 90% was not achieved within 12 hours following infestation on Days 7 and 14. Flea infestations and flea counts were not performed as initially scheduled on Days 21, 28, or 35.

Table II.10: Study ELAZA150306; 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)	4 hours
2	Control (0 mg/kg)	8 (5 M, 3 F)	6 hours
3	Control (0 mg/kg)	8 (3 M, 5 F)	12 hours
4	Lotilaner (6 mg/kg)	8 (4 M, 4 F)	4 hours
5	Lotilaner (6 mg/kg)	8 (4 M, 4 F)	6 hours
6	Lotilaner (6 mg/kg)	8 (6 M, 2 F)	12 hours

Drug Administration: On Day 0, cats in the three lotilaner groups were administered whole chewable tablets at doses as close as possible to 6 mg/kg without under-dosing. Doses ranged from 6.3 to 9.6 mg/kg. The chewable tablets were administered by placement in the back of the cat's mouth approximately 30 minutes after feeding. On Day 0, cats in the control group were sham-treated (mouths opened as if for treatment administration).

Measurements and Observations: The primary variable for effectiveness was the live flea counts collected from the cats. At each flea count, fleas were removed and the numbers of live fleas were recorded. General health observations were conducted daily, and clinical observations were conducted prior to treatment and at 1, 6, and 8 hours post-treatment. Clinical examinations were conducted at the beginning of the study (Day -22) and upon study termination (Day 21). Cats were weighed on Days –22, -14, and 21. Flea counts and health observations were conducted masked to treatment.

Statistical Methods: Percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C)] x 100, where C = arithmetic mean live flea count in the control group and T = arithmetic mean live flea count in the treated group for each time point. The comparisons were tested using the two-sided 5% significance level. The mixed model analysis was used to analyze log-counts, with treatment as a fixed effect and block and room as random effects.

Results: At the 6- and 12-hour flea counts on Day 0, a minimum of six cats in each of the control groups had an adequate flea infestation, defined as a retention rate of at least 50% (i.e. at least 50 live fleas). At the 4-hour flea

count on Day 0, only five cats in the control group had an adequate infestation. Furthermore, because the study was terminated early, effectiveness conclusions were only possible for the immediate (6- and 12-hour) post-treatment effectiveness on Day 0.

Lotilaner was 67.5% and 98.1% effective at 6- and 12-hours post-treatment, respectively (Table II.11). Live flea counts between the two groups and the respective control group were significantly different on Day 0 ($p = 0.0148$ and $p < 0.0001$ at 6 and 12 hours, respectively). On Days 7 and 14, the percent effectiveness ranged from 22.6% (6 hours post-infestation) to 87.5% (12 hours post-infestation).

Table II.11: Study ELAZA150306; Effectiveness Against *C. felis* at 6 and 12 Hours after Treatment on Day 0*

Hours After Treatment	Control Group Arithmetic Mean	Lotilaner Group Arithmetic Mean	Percent Effectiveness
6	63.5	20.6	67.5%
12	72.9	1.4	98.1%

*For Day 0, fleas were applied to the cats on Day -2

Adverse Reactions: There were no adverse reactions during the study.

Conclusion: This study demonstrated that Credelio™ CAT (lotilaner) starts killing fleas 6 hours after drug administration, with greater than 98% of fleas killed within 12 hours after administration.

III. TARGET ANIMAL SAFETY

The safety of Credelio™ CAT was demonstrated in two laboratory studies described below. In the margin of safety study (NAH-14-083), which included groups of cats administered elevated lotilaner doses, possible drug-related effects included decreased dry food consumption, decreased body weight, vomiting, neutropenia, elevations in BUN, lymphoid depletion of the thymus, and tubular regeneration of the kidneys. In an exploratory (pilot) margin of safety study, possible drug-related effects included chronic, unilateral renal infarcts. Coupled with the findings in the margin of safety studies and the field study, renal changes may be a possible drug-related change. These safety studies, in combination with the safety information collected in the effectiveness studies, demonstrate the safety of Credelio™ CAT when used according to the label.

A. Margin of Safety Study

Title: Pivotal Eight-Month Target Animal Safety Study of Lotilaner in 8-Week-Old Cats. (Study no. NAH-14-083)

Study Dates: December 31, 2014 to May 25, 2016

Study Location: Mattawan, Michigan

Study Design: The study was conducted in accordance with the Good Laboratory Practice (GLP) regulations (21 CFR 58).

Objective: To evaluate the safety of lotilaner chewable tablets in eight-week-old cats when administered orally once every four weeks for eight months.

Study Animals: 32 healthy cats (16 male and 16 female), approximately 8 weeks of age, weighing between 0.6 kg to 1.0 kg (1.3 to 2.2 lbs).

Experimental Design: Cats were randomized to one of four groups (0X, 1X, 3X, and 5X) of eight cats per group (four per sex). The lotilaner chewable tablets were administered orally every four weeks for eight months (Days 1, 29, 57, 85, 113, 141, 169, and 197) at doses of 23.5 to 33.8 mg/kg (1X), 71.6 to 87.0 mg/kg (3X), and 123.5 to 137.4 mg/kg (5X). The control group (0X) was sham dosed.

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

Drug Administration: All cats were fed prior to dose administration. The amount of lotilaner chewable tablets administered was based on the body weight of each animal. Each animal received 3 to 5 mL of tap water following each dose. The control group was sham dosed and received 3 to 5 mL of tap water in the same manner as the treated groups.

Measurements and Observations: General observations were performed twice daily on all cats. Detailed clinical observations were performed on Days -13, -2, the day prior to dosing, at 8 hours (± 1 hour) post-dose on each dosing day and once weekly thereafter, and on Day 225. Body weights were measured and recorded on Days -14, -12, -9, -7, -5, -2, prior to randomization (Day -1), and at least once weekly (the day prior to dosing and on days with physical/neurological examinations and detailed clinical observations). A complete physical and neurological examination was conducted on Days -6, 7, 35, 63, 91, 119, 147, 175, 203, and 224. Ophthalmoscopic examinations were conducted on Days -4, 99, and 211. An electrocardiographic (ECG) examination was performed pretest (Day-6), and on Days 59, 143, 199, and 224. Food consumption was measured and recorded daily and reported weekly, starting with Day -7.

Samples for clinical pathology evaluations (hematology, serum chemistry, coagulation, and urinalysis) were collected on Days -8 (Day -5 for urinalysis and Day -1 for coagulation), 8, 28, 36, 56, 64, 84, 92, 112, 120, 140, 148, 168, 176, 196, 204, and 223. Blood samples for plasma lotilaner concentrations were collected pre-dose on Days -1, 29, 57, 85, 113, 141, 169, and 197; 4 hours post-dose on Days 1 and 113; 24 hours post-dose on Days 2, 30, 58, 86, 114, 142, 170, and 198; and 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 all tissues from all cats.

Statistical Methods: Body weights, ECGs, 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 physical and neurologic examinations and gross pathology. Dry food consumption was significantly lower in male cats (1X, 3X, and 5X groups) compared to control cats ($p < 0.10$). Body weights of male cats in the 3X group were significantly lower ($p < 0.05$) than those of the control male cats.

One female cat in the 3X group died on Day 143 while anesthetized to obtain an ECG. She had no abnormal clinical observations, physical examinations, ophthalmoscopic examinations, ECG, or gross pathology findings. She was one of three cats in the 3X group that had neutropenia (neutrophil count: 2040 to 2700/µL; low end of normal: approximately 2800/µL) at Day 28 and from Days 84 to 140. Her blood urea nitrogen (BUN) was elevated at 39 mg/dl (normal: 13-36 mg/dl) on Day 36. Histopathological evaluation showed mild unilateral tubular regeneration in the kidneys.

Throughout the study, vomiting occurred on the day of dosing in seven cats (two cats in the control group, one cat in the 1X group, one cat in the 3X group, and three cats in the 5X group). Outside of dosing days, there were occasional episodes of vomiting in all groups.

One female cat in the 5X group had electrical alternans on the final ECG.

Neutrophils were significantly decreased ($p < 0.05$) in cats in all groups administered lotilaner compared to control cats, at multiple time points, including the cat in the 3X group that died on Day 143 while anesthetized. Five and four cats in the 3X and 5X groups, respectively, had neutropenia (neutrophil count: 750-2710/µL; low end of normal: approximately 2800/µL) at 25% or more of the time points. One female cat in the 3X group had unilateral chorioretinitis on both the Day 99 and Day 211 ophthalmoscopic examinations. This cat also had neutropenia (neutrophil count: 1450-2710/µL; low end of normal: approximately 2800/µL) at more than 50% of the time points. No abnormalities were found on gross or histopathological evaluation of the eye or optic nerve.

From Days 28 to 92, two and three female cats in the 3X and 5X groups, respectively, had elevations in blood urea nitrogen (BUN) at least at one time point (37-43 mg/dL; high end of normal: 36 mg/dL). On Days 56 and 64, two cats in the 5X group had elevated alkaline phosphatase (ALP) (191-243 U/L; high end of normal: approximately 174 U/L).

Histopathological examination of the kidneys showed minimal, usually unilateral, tubular regeneration in three cats in the control group, three cats in the 1X group, six cats in the 3X group, and three cats in the 5X group. Histopathological examination of the thymus showed minimal to mild generalized lymphoid

depletion in one cat in the control group, one cat in the 1X group, four cats in the 3X group, and one cat in the 5X group. These histological changes correlated with a significant decrease ($p < 0.05$) in the weight of the thymus in males in the 3X group. Four of the five cats in the two high-dose groups (3X and 5X) with minimal generalized lymphoid depletion of the thymus also had neutropenia at 25% or more of the time points.

Blood concentrations of lotilaner confirmed systemic exposure in all cats administered lotilaner, although the exposure was less than dose proportional. Peak lotilaner concentrations were observed in most cats at the 24-hour sampling point following oral administration of the maximum labeled dose (26 mg/kg). Cats three months of age had a shorter elimination half-life (average of 7.5 days) than the cats at seven months of age (average of 32 days).

Conclusion: The study supports the safe use of Credelio™ CAT (lotilaner) chewable tablets in cats when used at the labeled dose and duration. Decreased dry food consumption, decreased body weight, vomiting, neutropenia, elevations in BUN, lymphoid depletion of the thymus, and tubular regeneration of the kidneys are possible drug-related effects.

B. Pilot Margin of Safety Study

Title: Safety of Lotilaner in 8-Week-Old Kittens. (Study no. S11362)

Study Design: The objective of this study was to evaluate the safety of lotilaner after oral administration to 8-week-old cats at 30 mg once per month (low dose group; 12.1 to 54.7 mg/kg) and 30 mg three consecutive days per month (high dose group; total of 90 mg over three days; total dose: 36.3 to 161.3 mg/kg) for 84 days. The study was not conducted in accordance with the GLP regulations and did not utilize the final formulation of the drug product.

The study included 26 healthy cats (13 male and 13 female), approximately 8 weeks of age. Cats were randomized to one of three groups (negative control, low dose, and high dose). The control group had ten cats (five per sex). The groups administered lotilaner had eight cats per group (four per sex).

Results: There were no clinically-relevant, treatment-related effects on clinical observations, physical examinations, ophthalmic examinations, body weights, electrocardiograms (ECGs), or food consumption. One cat each in the low (received 12.1 to 32.7 mg/kg) and high (received 36.6 to 108.6 mg/kg) dose group had unilateral renal infarcts of chronic duration. The cat in the low dose group with the renal infarcts also had a mildly elevated BUN on Days 31 and 59 (37 and 41 mg/dl, respectively; normal: 14 -36 mg/dl). The cat in the high dose group had a normal BUN throughout the study. Similar renal infarcts were not present in any of the control cats.

Conclusion: The chronic, unilateral renal infarcts in this study, coupled with renal tubular regeneration seen in study number NAH-14-083, suggest that renal changes may be a possible drug-related change.

C. Foreign Experience

(Study numbers: NAH-15-198, NAH-15-197, NAH-14-248, and YAR-12-043)

In a single arm field study conducted in Australia in cats with flea infestations, four cats receiving lotilaner were noted to have pruritus within 24 hours of dosing, and four cats were noted to have hyperactivity/restlessness, agitation, and/or aggression within 48 hours of dosing. Two cats from the same household were noted by the owner to have twitching and lethargy within 24 hours of dosing and pruritus 7 days after dosing.

In another single arm field study conducted in Australia in cats with flea infestations, two cats receiving lotilaner were noted to have pruritus and irritability within 24 hours of dosing and another cat had pruritus 7 days after dosing. One cat was noted to have lethargy, and one had diarrhea within 24 hours of dosing.

In a well-controlled field study conducted in Europe (France and Spain) in cats with flea infestations, two cats receiving lotilaner were noted to have pruritus within 24 hours of dosing. One of these cats was also noted to be nervous and restless. Another cat was noted to be restless and two cats were noted to have lethargy within 24 hours of dosing.

In a laboratory palatability study conducted in Australia, 20 cats were dosed 15 mg/kg of a granule non-final formulation of lotilaner on Days 0, 2, 4, 14, 16, and 18. On Day -5, all cats had an elevated blood urea nitrogen (BUN) (mean: 7.29 mmol/L; reference range: 3.33-5.00 mmol/L). The BUN elevation further increased on Day 9 (mean: 9.08 mmol/L), then returned to baseline levels on Day 20 (mean: 6.66 mmol/L).

The following adverse event was reported voluntarily during post-approval use of the product in cats in foreign markets: A one-year-old cat received lotilaner orally and an ivermectin ear gel in the ears. Vomiting and anorexia were reported three days after dosing. The cat was hospitalized five days after dosing and icterus, hemolytic anemia, and elevated alanine aminotransaminase (ALT) were reported. The next day, the cat was reported to be comatose and died the following day (seven days after dosing).

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 Credelio™ CAT:

Not for human use. Keep this and all drugs out of the reach of children. Keep CredelioTM CAT in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

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™ CAT, 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*) for one month in cats and kittens 8 weeks of age and older, and weighing 2.0 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™ CAT, as approved in our approval letter, qualifies for THREE years of marketing exclusivity beginning as of the date of our approval letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act because the sponsor submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of Credelio™ CAT.

C. Patent Information

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