Date of Approval: April 12, 2021

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-528

Credelio™ CAT

lotilaner

Chewable Tablet

Cats

The effect of this supplement is to provide for the addition of the indication for the treatment and control of *Ixodes scapularis* (black-legged tick) infestations for one month in cats and kittens 6 months of age and older, and weighing 2.0 pounds or greater.

Sponsored by:

Elanco US Inc.

Executive Summary

Credelio™ CAT (lotilaner) Chewable Tablet is approved for the treatment and control of *Ixodes scapularis* (black-legged tick) infestations for one month in cats and kittens 6 months of age and older, and weighing 2.0 pounds or greater. Credelio™ CAT is already approved to kill 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. Credelio™ CAT is given orally once a month and must be administered with food.

Lotilaner is an ectoparasiticide belonging to the isoxazoline class. The drug selectively inhibits gamma-aminobutyric acid (GABA)-gated chloride channels in fleas and ticks. This inhibition of GABA channels prevents chloride ions from crossing cell membranes, which results in uncontrolled neuromuscular activity in fleas and ticks, causing their death.

Proprietary Name	Established Name	Application Type and Number	Sponsor
Credelio™ CAT	lotilaner	New Animal Drug Application (NADA) 141-528	Elanco US Inc.

Safety and Effectiveness

The sponsor conducted two laboratory studies to show that Credelio™ CAT is effective against *Ixodes scapularis* tick infestations. In each study, cats were experimentally infested with viable, unfed, adult ticks on Day -2, and then weekly after dosing for 4 weeks. On Day 0, cats in the treatment group were given Credelio™ CAT and cats in the control group were mock-dosed (same dosing procedures as the treatment group, but no tablets were administered). Tick counts were performed on Day 3 (72 hours after treatment) and 72 hours after each weekly infestation.

In both studies, Credelio™ CAT was greater than 97% effective at controlling *I. scapularis* tick infestations (reducing the number of live ticks) for 31 days, while cats in the control group remained infested with live ticks at each tick count. Credelio™ CAT was also effective in treating *I. scapularis* tick infestations. Compared to the control cats, treated cats had a significantly higher number of dead ticks for 31 days. No adverse reactions were seen in either study.

At the date of this approval, Credelio™ CAT is approved and marketed in other countries, but is not yet marketed in the United States. FDA evaluated the voluntary reports of adverse events seen in cats in these foreign markets provided by the sponsor. The drug's labeling includes information about these post-approval adverse events. The FOI Summary for the original approval of Credelio™ CAT, dated December 9, 2019, contains a summary of target animal safety studies in cats.

Conclusions

Based on the data submitted by the sponsor for the approval of Credelio™ CAT, FDA determined that the drug is safe and effective when used according to the label.

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 Tablet

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 color-coded packages containing 3 or 6 chewable tablets.

I. Dispensing Status

Prescription (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	NA	Administer the appropriate combination of chewable tablets

NA= not applicable

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.

Credelio™ CAT is also indicated for the treatment and control of *Ixodes scapularis* (black-legged tick) infestations for one month in cats and kittens 6 months of age and older, and weighing 2.0 pounds or greater.

N. Effect of Supplement

This supplement provides for the addition of the indication for the treatment and control of *Ixodes scapularis* (black-legged tick) infestations for one month in cats and kittens 6 months of age and older, and weighing 2.0 pounds or greater.

II. EFFECTIVENESS

The effectiveness of Credelio™ CAT against *Ixodes scapularis* was demonstrated in two laboratory dose confirmation studies, described below. These studies demonstrate that Credelio™ CAT is effective for the treatment and control of *Ixodes scapularis* ticks 72 hours after administration or infestation for 31 days in cats older than 6 months of age.

A. Dosage Characterization

This supplemental approval does not change the previously approved minimum dosage at 2.7 mg/lb (6 mg/kg). The Freedom of Information (FOI) Summary for the original approval of NADA 141-528, dated December 9, 2019, contains dosage characterization information for cats.

Minimum Age

Dose confirmation and field studies with lotilaner demonstrate effectiveness against *Ctenocephalides felis* fleas for one month in cats at least 8 weeks of age when dosed at a minimum of 2.7 mg/lb (6 mg/kg).

Pharmacokinetic studies demonstrate that the mean elimination half-life of lotilaner is shorter in young kittens compared to cats aged 6 months and older. This difference in elimination half-life may cause inadequate protection against *Ixodes scapularis* ticks for an entire month in cats less than 6 months of age. However, pharmacokinetic and dose confirmation studies demonstrate effectiveness against *Ixodes scapularis* ticks for one month in cats at least 6 months of age at the minimum lotilaner dose (6 mg/kg).

Therefore, although safety studies support the safety of lotilaner in cats and kittens 8 weeks of age and older, substantial evidence to support a one-month duration of effectiveness for *Ixodes scapularis* (black-legged tick) infestations is only demonstrated in cats and kittens 6 months of age and older.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study ELA1900448: *Ixodes scapularis* ticks

Title: A Blinded, Randomized, Negative Controlled Laboratory Study Assessing the Efficacy of Credelio™ (lotilaner) Tablets for Cats Against Ticks (*Ixodes scapularis*) When Administered Orally at a Minimum Dose of 6 mg/kg. (Study number ELA 1900448)

Study Dates: September 2019 to April 2020

Study Location: Turlock, CA, USA

Study Design:

Objective: Confirm the effectiveness of a single oral dose of at least 6 mg/kg lotilaner for the treatment and control of experimental *Ixodes scapularis* infestations on cats at 72 hours after drug administration or tick infestation for 31 days.

Study Animals: Twenty (6 male and 14 female) cats, 6 months of age or older, weighing between 2.9 and 5.1 kgs.

Experimental Design: Prior to allocation to treatment groups on Day -4, an initial tick infestation and count was conducted to evaluate susceptibility of each cat to experimental infestation (host suitability). Cats were ranked by live tick count (attached and unattached) and randomly allocated within blocks to two groups.

Tick infestations were conducted on Days -2, 7, 14, 21, and 28. At each infestation, each cat was infested with approximately 50 viable, unfed, adult *Ixodes scapularis* (US source) ticks.

Tick counts were performed at 72 hours after drug administration or tick infestation (Days 3, 10, 17, 24, and 31). Ticks were not returned to the cat after counting.

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

Table II. 1: Study ELA1900448; Treatment Groups

Treatment Group	Treatment Day	Treatment (Minimum Dose)	Number and Gender of Animals
1	Day 0	Lotilaner (6 mg/kg)	10 (2 M, 8 F)
2	Day 0	Control (0 mg/kg)	10 (4 M, 6 F)

Drug Administration: On Day 0, the ten cats in the lotilaner group were administered two or three whole chewable tablets, at doses as close as possible to 6 mg/kg without under-dosing. Doses ranged from 6.4 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 (followed by a dose of tap water via syringe).

Measurements and Observations: The primary variable for effectiveness was the tick counts collected from the cats. At each tick count, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted once daily and clinical observations were conducted prior to treatment and at approximately 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. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:

For live tick counts at each time point, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C = the arithmetic mean obtained from the least squares (LS) means of live tick counts for the control group and T = the arithmetic mean obtained from the LS means of live tick counts for the treated group.

For dead tick counts, the formula was reversed as [(T-C)/T] x 100. The comparisons were tested using the two-sided 5% significance level. Untransformed counts were analyzed using analysis of variance, including treatment as a fixed effect and block as a random effect in the model.

Effectiveness for the control indication was determined on the basis of the percent reduction in live tick counts in the treated group compared to the control group.

Results:

At each tick count, all 10 cats in the control group had an adequate tick infestation, defined as a retention rate of at least 25% (i.e., ≥12 live ticks).

The lotilaner group had greater than 97% reduction in live tick counts at 72 hours following treatment or infestation through Day 31 (Table II.2). On all count days following drug administration, live tick counts between the two groups were statistically significantly different ($p < 0.0001$). The lotilaner group had significantly higher numbers of dead ticks 72 hours following treatment or infestation through Day 31 (Table II.3). On all count days following drug administration, dead tick counts between the two groups were statistically significantly different ($p < 0.0001$).

Table II. 2: Study ELA1900448; Live Tick Counts and Effectiveness Against *I. scapularis* 72 Hours After Administration or Infestation

Days After Treatment	Control Group LS Mean	Lotilaner Group LS Mean	Percent Effectiveness
3	37.4	0.0	100%
10	38.9	0.2	99.5%
17	38.5	0.2	99.5%
24	42.4	1.1	97.4%
31	38.6	0.5	98.7%

Table II. 3: Study ELA1900448; Dead Tick Counts 72 Hours After Administration or Infestation

Days After Treatment	Control Group LS Mean	Lotilaner Group LS Mean
3	0.0	24.5
10	0.2	26.2
17	0.1	23.8
24	0.2	25.1
31	0.1	19.4

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

Conclusion: This study demonstrated the effectiveness of a single oral dose of lotilaner for the control (reduced live ticks) and treatment (increased dead ticks) of *Ixodes scapularis* in cats > 6 months of age for 31 days when assessed 72 hours after administration or infestation.

2. Laboratory Dose Confirmation Study ELA2000181: *Ixodes scapularis* ticks

Title: A Blinded, Randomized, Negative Controlled Laboratory Study Assessing the Efficacy of Credelio™ (lotilaner) Tablets for Cats Against Ticks (*Ixodes scapularis*) When Administered Orally at a Minimum Dose of 6 mg/kg. (Study number ELA 2000181)

Study Dates: March 2020 to June 2020

Study Location: Waverly, NY, USA

Study Design:

Objective: Confirm the effectiveness of a single oral dose of at least 6 mg/kg lotilaner for the treatment and control of experimental *Ixodes scapularis* infestations on cats at 72 hours after drug administration or tick infestation for 31 days.

Study Animals: Nineteen (17 male and 2 female) cats, 6 months of age or older, weighing between 3.2 and 8.0 kg.

Experimental Design: Prior to allocation to treatment groups on Day -4, an initial tick infestation and count was conducted to evaluate susceptibility of each cat to experimental infestation (host suitability). Cats were ranked by live tick count (attached and unattached) and randomly allocated within blocks to two groups.

Tick infestations were conducted on Days -2, 7, 14, 21, and 28. At each infestation, each cat was infested with approximately 50 viable, unfed, adult *Ixodes scapularis* (US source) ticks.

Tick counts were performed at 72 hours after drug administration or tick infestation (Days 3, 10, 17, 24, and 31). Ticks were not returned to the cat after counting.

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

Table II. 4: Study ELA2000181; Treatment Groups

Treatment Group	Treatment Day	Treatment (Minimum Dose)	Number and Gender of Animals
1	Day 0	Lotilaner (6 mg/kg)	9* (8 M, 1 F)
2	Day 0	Control (0 mg/kg)	10 (9 M, 1 F)

* One cat in the lotilaner group was removed from the study on Day 0 because it was fractious and unable to be restrained.

Drug Administration: On Day 0, the nine cats in the lotilaner group were administered two or three whole chewable tablets at doses as close as possible to 6 mg/kg without under-dosing. Doses ranged from 6.4 to 7.7 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 (followed by a dose of tap water via syringe).

Measurements and Observations: The primary variable for effectiveness was the tick counts collected from the cats. At each tick count, ticks were removed, and the numbers of live and dead ticks were recorded. General health observations were conducted once daily and clinical observations were conducted prior to treatment and at approximately 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. Tick counts and health observations were conducted masked to treatment.

Statistical Methods:

For live tick counts at each time point, percent effectiveness of the treated group with respect to the control group was calculated using the formula [(C-T)/C] x 100, where C = the arithmetic mean obtained from the least squares (LS) means of live tick counts for the control group and T = the arithmetic mean obtained from the LS means of live tick counts for the treated group.

For dead tick counts, the formula was reversed as [(T-C)/T] x 100. The comparisons were tested using the two-sided 5% significance level. Untransformed counts were analyzed using analysis of variance, including treatment as a fixed effect and block as a random effect in the model.

Effectiveness for the control indication was determined on the basis of the percent reduction in live tick counts in the treated group compared to the control group.

Results:

At each tick count, all 10 cats in the control group had an adequate tick infestation, defined as a retention rate of at least 25% (i.e., ≥ 12 live ticks).

The lotilaner group had greater than 99% reduction in live tick counts at 72 hours following treatment or infestation through Day 31 (Table II.5). On all count days following drug administration, live tick counts between the two groups were statistically significantly different ($p < 0.0001$). The lotilaner group had significantly higher numbers of dead ticks 72 hours following treatment or infestation through Day 31 (Table II.6). On all count days following drug administration, dead tick counts between the two groups were statistically significantly different ($p < 0.0001$).

Table II. 5: Study ELA2000181; Live Tick Counts and Effectiveness Against *I. scapularis* 72 Hours After Administration or Infestation

Days After Treatment	Control Group LS Mean	Lotilaner Group LS Mean	Percent Effectiveness
3	32.4	0.0	100%
10	35.6	0.1	99.6%
17	36.2	0.0	100%
24	41.8	0.3	99.2%
31	38.4	0.3	99.1%

Table II. 6: Study ELA2000181; Dead Tick Counts 72 Hours After Administration or Infestation

Days After Treatment	Control Group LS Mean	Lotilaner Group LS Mean
3	2.3	26.1
10	1.8	26.3
17	1.8	25.3
24	1.0	24.6
31	1.4	23.6

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

Conclusion: This study demonstrated the effectiveness of a single oral dose of lotilaner for the control (reduced live ticks) and treatment (increased dead ticks) of *Ixodes scapularis* in cats > 6 months of age for 31 days when assessed 72 hours after administration or infestation.

III. TARGET ANIMAL SAFETY

CVM did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-528, dated December 9, 2019, contains a summary of target animal safety studies for the use of Credelio™ CAT in cats. However, voluntary post-approval adverse event reports from foreign markets were evaluated for this approval.

Foreign Market Experience

The following adverse events were reported voluntarily during post-approval use of the product in cats in foreign markets: hyperactivity, pruritus, tachypnea, dyspnea, lethargy, vomiting, anorexia, hyperthermia, hypersalivation, tachycardia, mydriasis, tremors, ataxia, seizures, hepatopathy, anaphylactic reactions resulting in death, pancreatitis, immune mediated hemolytic anemia, and glomerulopathy.

The following adverse events were reported in pregnant and nursing cats. Five 3- to 4-week-old nursing kittens from two litters died within three days of the queens receiving lotilaner. One litter of two kittens was weak and hypothermic the day after the queen received lotilaner, and later died. The other litter of three kittens was found dead two to three days after the queen received lotilaner. One cat with confirmed early pregnancy was back in estrus a few days after receiving lotilaner. Another pregnant cat prematurely delivered four kittens the day after receiving lotilaner; two kittens were stillborn (one had a cleft palate), one died within one hour of birth after nursing, and the fourth died two weeks later.

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 Credelio™ 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 the treatment and control of *Ixodes scapularis* (black-legged tick) infestations for one month in cats and kittens 6 months of age and older, and weighing 2.0 pounds or greater.

A. Marketing Status

This product may be dispensed only by or on the 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

This supplemental approval for Credelio™ CAT qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to the treatment and control of *Ixodes scapularis* (black-legged tick) infestations that is approved in the supplemental application.

C. Supplemental Applications

This supplemental NADA did not require a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(1)).

D. Patent Information

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