Date of Approval: September 3, 2019

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 141-494

Credelio™

Lotilaner

Chewable Tablets

Dogs

This supplement provides for the addition of the indication for the prevention of flea infestations (*Ctenocephalides felis*) 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 and prevention 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.

N. Effect of Supplement

This supplement provides for the addition of the indication for the prevention of flea infestations (*Ctenocephalides felis*) for one month in dogs and puppies 8 weeks of age and older, and 4.4 pounds of body weight or greater.

II. EFFECTIVENESS

A. Dosage Characterization

This supplemental approval does not change the previously approved 9 mg/lb (20 mg/kg) dose, given orally once a month. The Freedom of Information (FOI) Summary for the original approval of NADA 141-494, dated January 19, 2018, contains dosage characterization information for dogs.

B. Substantial Evidence

The effectiveness of Credelio™ for the prevention of flea infestations was demonstrated in one laboratory and one field study. Laboratory study ELA1700480 demonstrated that Credelio™ killed fleas before they could lay eggs. The field effectiveness and safety study (NAH-13-076), as described in the Freedom of Information (FOI) Summary for the original approval (NADA 141-494), demonstrated that Credelio™ was safe and effective for the treatment and prevention of flea infestations for one month when administered to client-owned dogs.

1. Laboratory Egg Laying Study ELA1700480: Prevention of Flea Infestations

Title:

A blinded, randomized, negative controlled laboratory study using a flavored isoxazoline tablet administered orally to dogs to assess the efficacy against experimentally induced adult flea (*Ctenocephalides felis*) infestations and the impact on egg production

Study Dates:

October 2017 to August 2018

Study Location:

Greenbrier, AR

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 20 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 dogs (9 males and 11 females), 13 to 28 months of age, weighing between 7.0 kg and 13.6 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 two groups. Flea infestations were conducted on Days -1, 6, 13, 20, and 29. At each infestation, each dog was infested with approximately 100 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 dog after counting.

Table II.1: Study ELA1700480 Treatment Groups

Treatment Group	Treatment Day	Treatment (Minimum Dose)	Number and Gender of Animals
1	Day 0	0 mg/kg (Vehicle)	10 (3 M, 7 F)
2	Day 0	20 mg/kg	10 (6 M, 4 F)

Drug Administration:
On Day 0, the ten dogs in the lotilaner group were administered one or more whole chewable tablets, at doses as close as possible to 20 mg/kg without under-dosing. Doses ranged from 20.2 to 25.9 mg/kg per dog. The chewable tablets were administered by placement in the back of the dog's mouth approximately 30 minutes after feeding. Dogs administered the vehicle control tablets received the same number of tablet(s) as lotilaner tablet(s) for the same bodyweight.

Measurements and Observations:
The primary variables for effectiveness were the live flea counts collected from the dogs and the flea eggs collected from the cages. At each flea count, fleas were removed and the numbers of live fleas on the dogs and flea eggs collected from the bottom of the cage were recorded. General health observations were conducted twice daily and clinical observations were conducted prior to treatment and at 1, 2, 4, and 8 hours post-treatment. Physical examinations were conducted at the beginning of the study (Day -13). Dogs were weighed on Day -6. Flea counts, flea egg counts, and health observations were conducted masked to treatment group.

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 group 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 dogs 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 dogs.

Results:
At each flea count, a minimum of six dogs 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 100% effective at 24 hours (Table II.2) post-treatment or post-infestation through Day 30. 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.3).

Table II.2: Study ELA1700480 Effectiveness Against *C. felis* 24 Hours After Infestation

Days After Treatment*	Control Group Arithmetic Mean	Lotilaner Group Arithmetic Mean	Percent Effectiveness
1	91.4	0.0	100%
7	92.6	0.0	100%
14	92.9	0.0	100%
21	93.1	0.0	100%
30	87.8	0.0	100%

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

Table II.3: Study ELA1700480 Effectiveness Against *C. felis* Egg Production 24 Hours after Infestation

Days After Treatment*	Control Group Arithmetic Mean (Range)	Lotilaner Group Arithmetic Mean (Range)
1	527.0 (281-809)	13.9 (0-48)
7	139.2 (0-281)	0.0 (0)
14	163.1 (0-289)	0.0 (0)
21	188.0 (0-376)	0.0 (0)
30	154.5 (0-338)	0.0 (0)

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

Adverse Reactions:

There were no adverse reactions reported during the study.

Conclusion:

This study demonstrated the effectiveness of lotilaner for the treatment and prevention of flea infestations for 30 days when assessed 24 hours after drug 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 141-494, dated January 19, 2018, contains a summary of target animal safety studies for dogs.

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. Keep CREDELIO 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™, when used according to the label, is safe and effective for the prevention of flea infestations (*Ctenocephalides felis*) 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

This supplemental approval for Credelio™ 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 prevention of flea infestations (*Ctenocephalides felis*) indication.

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 Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.