Date of Approval: May 21, 2025

FREEDOM OF INFORMATION (FOI) SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION (NADA)

NADA 141-581

Credelio Quattro™

(lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets)

Dogs

This supplement provides for the addition of the indication for the treatment and control of hookworm (fourth stage larvae, immature adult, and adult *Ancylostoma caninum*) infections in dogs and puppies 8 weeks of age and older, and weighing 3.3 pounds or greater.

Sponsored by:

Elanco US Inc.

Executive Summary

Credelio Quattro™ (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) is approved for the treatment and control of hookworm (fourth stage larvae, immature adult, and adult *Ancylostoma caninum*) infections in dogs and puppies 8 weeks of age and older, and weighing 3.3 pounds or greater.

Credelio Quattro™ is already approved to prevent heartworm disease caused by *Dirofilaria immitis*, and treat and control roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*), hookworm (adult *Uncinaria stenocephala*), and tapeworm (*Dipylidium caninum, Taenia pisiformis,* and *Echinococcus granulosus*) infections. Credelio Quattro™is approved to kill adult fleas and treat and prevent flea infestations (*Ctenocephalides felis*), and treat and control 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 3.3 pounds or greater.

Credelio Quattro™ is a combination antiparasitic drug with four active ingredients and available in five strengths of flavored chewable tablets that are given orally once a month.

Safety and Effectiveness

The sponsor conducted five laboratory studies in young, healthy, male and female, crossbred and purebred (beagle) dogs. Depending on the study, dogs were experimentally infected with *A. caninum* third stage larvae (L3) on Day -7, Day -12, or Day -28. On Day 0, dogs were administered either Credelio Quattro™ or a vehicle control. The vehicle control contained all the inactive ingredients in Credelio Quattro™ but none of the active ingredients. To determine the effectiveness of Credelio Quattro™ against fourth stage larvae (L4), immature adult stage (L5), and adult *A. caninum* infections, worm counts were conducted on Day 5, Day 9, or Day 10, respectively.

Control dogs in all five studies were adequately infected with *A. caninum*. Credelio Quattro™ was at least 99.0% effective against L4, L5, and adult *A. caninum* infections. Some treated and control dogs had regurgitation, vomiting, and diarrhea (with or without blood and/or mucous). All adverse events resolved without treatment.

The sponsor also conducted one clinical field study in client-owned dogs across the United States. Enrolled dogs were healthy and included mixed breed and purebred, intact and neutered, male and female dogs with a range of ages and weights. Dogs were administered either Credelio Quattro™ or an active control containing sarolaner, moxidectin, and pyrantel at home on Day 0. Fecal samples were collected on Days -1 and 10 for qualitative and quantitative fecal egg counts (FEC). From pre-treatment on Day -1 to post-treatment on Day 10, the percent reduction in FEC for *A. caninum* was 99.9% for both Credelio Quattro™ and the active control. A few dogs treated with Credelio Quattro™ had diarrhea, vomiting, flatulence, and lethargy. All adverse events resolved without treatment. The study confirmed that Credelio Quattro™ is effective in a diverse population of dogs under field conditions.

The FOI Summary for the original approval of Credelio Quattro™, dated October 7, 2024, contains a summary of target animal safety studies for dogs.

Conclusions
Based on the data submitted by the sponsor for the approval of Credelio Quattro™, the U.S. Food and Drug Administration (FDA) determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-581

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Credelio Quattro™

D. Drug Product Established Name

lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets

E. Pharmacological Category

Antiparasitic

F. Dosage Form

Chewable tablet

G. Amount of Active Ingredient

Each chewable tablet contains:

56.25 mg lotilaner, 0.056 mg moxidectin, 14.25 mg praziquantel, and 14.25 mg pyrantel*
112.5 mg lotilaner, 0.113 mg moxidectin, 28.5 mg praziquantel, and 28.5 mg pyrantel*
225 mg lotilaner, 0.225 mg moxidectin, 57 mg praziquantel, and 57 mg pyrantel*
450 mg lotilaner, 0.45 mg moxidectin, 114 mg praziquantel, and 114 mg pyrantel*
900 mg lotilaner, 0.9 mg moxidectin, 228 mg praziquantel, and 228 mg pyrantel*

*As pamoate salt

H. How Supplied

Credelio Quattro™ (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) is available in five strengths of flavored chewable tablets formulated according to the weight of the dog. Each chewable tablet size is available in packages of 1, 6, or 12 tablets.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Credelio Quattro™ is given orally once a month, at the minimum dosage of 9 mg/lb (20 mg/kg) lotilaner, 0.009 mg/lb (0.02 mg/kg) moxidectin, 2.28 mg/lb (5 mg/kg) praziquantel, and 2.28 mg/lb (5 mg/kg) pyrantel (as pamoate salt).

Dosing Schedule:

Body Weight (lbs)	Tablets to Administer	Lotilaner per Tablet (mg)	Moxidectin per Tablet (mg)	Praziquantel per Tablet (mg)	Pyrantel* per Tablet (mg)
3.3 - 6	1	56.25	0.056	14.25	14.25
6.1 - 12	1	112.5	0.113	28.5	28.5
12.1 - 25	1	225	0.225	57	57
25.1 - 50	1	450	0.45	114	114
50.1 - 100	1	900	0.9	228	228
>100	Administer the appropriate combination of tablets				

* As pamoate salt

K. Route of Administration

Oral

L. Species

Dogs

M. Indication

Credelio Quattro™ is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis* and for the treatment and control of roundworm (immature adult and adult *Toxocara canis* and adult *Toxascaris leonina*), hookworm (fourth stage larvae, immature adult, and adult *Ancylostoma caninum* and adult *Uncinaria stenocephala*), and tapeworm (*Dipylidium caninum, Taenia pisiformis,* and *Echinococcus granulosus*) infections. Credelio Quattro™ 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 3.3 pounds or greater.

N. Effect of Supplement

This supplement provides for the addition of the indication for the treatment and control of hookworm (fourth stage larvae, immature adult, and adult *Ancylostoma caninum*) infections in dogs and puppies 8 weeks of age and older, and weighing 3.3 pounds or greater.

II. EFFECTIVENESS

The effectiveness of Credelio Quattro™ was demonstrated in five well-controlled laboratory studies and one supportive clinical field safety and effectiveness study described below. The clinical field safety and effectiveness study confirmed the product effectiveness in a diverse population of dogs.

A. Dosage Characterization

This supplemental approval does not change the previously approved dose of 9 mg/lb (20 mg/kg) of lotilaner, 0.009 mg/lb (0.02 mg/kg) of moxidectin, 2.28 mg/lb (5 mg/kg) of praziquantel, and 2.28 mg/lb (5 mg/kg) of pyrantel (as pamoate salt), given orally once a month. The FOI Summary for the original approval of NADA 141-581, dated October 7, 2024, contains dosage characterization information for dogs.

B. Substantial Evidence

1. Laboratory Dose Confirmation Study Against Fourth Stage Larvae and Immature Adult *Ancylostoma caninum.*

   Title: Dose Confirmation Efficacy Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel, and Pyrantel Pamoate Administered Orally to Dogs for the Treatment of Immature (L4 and Immature Adult) *Ancylostoma caninum*. (Study No. ELA210524)

   Study Dates: September 2, 2021 to June 30, 2022

   Study Location: Rockwood, TN

   Study Design:

   Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of fourth stage larvae and immature adult *A. caninum* in experimentally infected dogs.

   Study Animals: Thirty-two beagle dogs (16 male and 16 female), 8 to 12 months of age, weighing between 6.2 and 12.1 kg.

   Experimental Design: On Day -7, each dog was orally inoculated with approximately 300 infective *A. caninum* L3 larvae. On Day -3, dogs were randomized into treatment groups of eight dogs each using a completely randomized design. On Day 5 post-treatment, Group 1 and 2 dogs were humanely euthanized and necropsied for recovery and counting of *A. caninum*. On Day 9 post-treatment, Group 3 and 4 were humanely euthanized and necropsied for recovery and counting of *A. caninum*. The study was conducted in accordance with Good Clinical Practice (GCP) guidelines.

Table II.1. Study ELA210524; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs	Day of Worm Count
1	Control (vehicle)	0 mg/kg	8 (4M, 4F)	5
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	8 (4M, 4F)	5
3	Control (vehicle)	0 mg/kg	8 (6M, 2F)	9
4	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	8 (2M, 6F)	9

Drug Administration: On Day 0, the dogs in the Credelio Quattro™ groups were administered one or more chewable tablets, at doses as close as possible to the minimum indicated dose without under-dosing. Moxidectin doses ranged from 0.02 to 0.027 mg/kg and pyrantel doses ranged from 5 mg/kg to 7.5 mg/kg. The dogs in the control groups were administered a vehicle control. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the *A. caninum* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment, and at 1, 2, 4, and 8 hours after treatment. Physical examinations and qualitative fecal examinations were conducted on Day -13 or -12. Dogs were weighed on Day -13 and -3. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *A. caninum* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. Two models were constructed: one with data from Groups 1 and 2 to determine the effectiveness against the L4 stage of *A. caninum*, and a second model with data for Groups 3 and 4 to determine the effectiveness of treatment against the immature adult stage of *A. caninum*. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using geometric mean through back-transformation of the Least Squares (LS) mean estimated from the model.

Percent Effectiveness = 100 × (C - T) / C

Where C = Geometric mean number of worms in the control group.
T = Geometric mean number of worms in the treatment group.

Results: All eight dogs in both of the control groups had an adequate infection, defined as ≥ 5 *A. caninum* worms present at necropsy.

Credelio Quattro™ was 99.0% effective against experimentally induced fourth stage larvae *A. caninum* infections (Table II.2), and was 99.8% effective against experimentally induced immature adult *A. caninum* infections in dogs (Table II.3). Mean worm counts between the treatment and respective control groups were statistically significantly different ($p<0.0001$).

Table II.2. Study ELA210524; Effectiveness Against Fourth Stage Larvae *A. caninum*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control (vehicle)	40 – 214	116.8	NA
Credelio Quattro™	0 – 12	1.1	99.0%

Table II.3. Study ELA210524; Effectiveness Against Immature Adult *A. caninum*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control (vehicle)	26 – 242	125.3	NA
Credelio Quattro™	0 – 2	0.3	99.8%

Adverse Reactions: Regurgitation, vomiting, and diarrhea (with or without blood and/or mucous) were observed in treated and control dogs. All events resolved without treatment.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of fourth stage larvae and immature adult *A. caninum* in dogs.

2. Laboratory Dose Confirmation Study Against Fourth Stage Larvae *Ancylostoma caninum*.

Title: Dose Confirmation Efficacy Laboratory Study Using Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel, and Pyrantel Pamoate Administered Orally to Dogs for the Treatment of Immature (L4) *Ancylostoma caninum*. (Study No. ELA210539)

Study Dates: November 17, 2022 to January 12, 2024

Study Location: Bloemfontein, South Africa

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of fourth stage larvae *A. caninum* in experimentally infected dogs.

Study Animals: Sixteen crossbred or purebred (beagle) dogs (8 male and 8 female), 9 to 11 weeks of age, weighing between 4.3 and 6.6 kg.

Experimental Design: On Day -7, each dog was orally inoculated with approximately 300 infective *A. caninum* L3 larvae. On Day -1, dogs were randomized into treatment groups of eight dogs each using a completely randomized design. On Day 5 post-treatment, dogs were humanely euthanized and necropsied for recovery and counting of *A. caninum*. The study was conducted in accordance with GCP guidelines.

Table II.4. Study ELA210539; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control (vehicle)	0 mg/kg	8 (4M, 4F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	8 (4M, 4F)

Drug Administration: On Day 0, the eight dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at doses as close as possible to the minimum indicated dose without under-dosing. Moxidectin doses ranged from 0.02 to 0.03 mg/kg and pyrantel doses ranged from 5.09 mg/kg to 7.5 mg/kg per dog. The eight dogs in the control group were administered a vehicle control. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the *A. caninum* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment, and at 1, 2, 4, and 8 hours after treatment. Physical examinations and qualitative fecal examinations were conducted on Day -14. Dogs were weighed on Day -14 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *A. caninum* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using

geometric mean through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C - T) / C
Where C = Geometric mean number of worms in the control group.
T = Geometric mean number of worms in the treatment group.

Results: All eight dogs in the control group had an adequate infection, defined as ≥5 *A. caninum* worms present at necropsy**.**

Credelio Quattro™ was 99.8% effective against experimentally induced fourth stage larvae *A. caninum* infections (Table II.5). Mean worm counts between the treatment and control groups were statistically significantly different ($p<0.0001$).

Table II.5. Study ELA210539; Effectiveness Against Fourth Stage Larvae *A. caninum*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control (vehicle)	110 – 233	168.8	NA
Credelio Quattro™	0 – 3	0.4	99.8%

Adverse Reactions: No treatment-related adverse reactions were observed in the study.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of fourth stage larvae *A. caninum* in dogs.

3. Laboratory Dose Confirmation Study Against Immature Adult *Ancylostoma caninum*.

Title: Dose Confirmation Efficacy Laboratory Study Using Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel, and Pyrantel Pamoate Administered Orally to Dogs for the Treatment of Immature Adult (L5) *Ancylostoma caninum*. (Study No. ELA210611)

Study Dates: December 07, 2022 to January 12, 2024

Study Location: Bloemfontein, South Africa

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of immature adult *A. caninum* in experimentally infected dogs.

Study Animals: Fifteen beagle dogs (12 male and 3 female), 8 to 11 weeks of age, weighing between 2.8 and 7.3 kg.

Experimental Design: On Day -12, each dog was orally inoculated with approximately 300 infective *A. caninum* L3 larvae. On Day -1, dogs were

randomized into treatment groups using a completely randomized design. On Day 5 post-treatment, dogs were humanely euthanized and necropsied for recovery and counting of *A. caninum*. The study was conducted in accordance with GCP guidelines.

Table II.6. Study ELA210611; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control (vehicle)	0 mg/kg	7* (6M, 1F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	8 (6M, 2F)

*One dog had been removed prior to randomization due to medical reasons.

Drug Administration: On Day 0, the eight dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at doses as close as possible to the minimum indicated dose without under-dosing. Moxidectin doses ranged from 0.02 to 0.03 mg/kg and pyrantel doses ranged from 5.09 mg/kg to 7.5 mg/kg per dog. The seven dogs in the control group were administered a vehicle control. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the *A. caninum* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment, and at 1, 2, 4, and 8 hours after treatment. Physical examinations and qualitative fecal examinations were conducted on Day -19. Dogs were weighed on Day -19 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *A. caninum* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using geometric mean through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C - T) / C
Where C = Geometric mean number of worms in the control group.
T = Geometric mean number of worms in the treatment group.

Results: All seven dogs in the control group had an adequate infection, defined as ≥5 *A. caninum* worms present at necropsy.

Credelio Quattro™ was 100% effective against experimentally induced immature adult *A. caninum* infections (Table II.7). Mean worm counts between the treatment and control groups were statistically significantly different ($p<0.0001$).

Table II.7. Study ELA210611; Effectiveness Against Immature Adult *A. caninum*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control (vehicle)	210 – 312	256.4	NA
Credelio Quattro™	0	0	100%

Adverse Reactions: No treatment-related adverse reactions were observed in the study.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of immature adult *A. caninum* in dogs.

4. Laboratory Dose Confirmation Study Against Adult *Ancylostoma caninum*.

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel, and Pyrantel Pamoate when Administered Orally for the Treatment, and Control of Adult *Ancylostoma Caninum* in Experimentally Infected Dogs. (Study No. ELA210573)

Study Dates: February 28, 2022 to January 09, 2023

Study Location: Athens, GA

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *A. caninum* in experimentally infected dogs.

Study Animals: Twenty beagle dogs (11 male and 9 female), 13 to 14 weeks of age, weighing between 4.7 and 7.3 kg.

Experimental Design: On Day -28, each dog was orally inoculated with approximately 300 infective *A. caninum* L3 larvae. On Day -1, dogs were randomized into treatment groups of ten dogs each using a completely randomized design. On Day 10 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *A. caninum*. The study was conducted in accordance with GCP guidelines.

Table II.8. Study ELA210573; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control (vehicle)	0 mg/kg	10 (6M, 4F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	10 (5M, 5F)

Drug Administration: On Day 0, the 10 dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at doses as close as possible to the minimum indicated dose without under-dosing. Moxidectin doses ranged from 0.02 to 0.03 mg/kg and pyrantel doses ranged from 5.1 mg/kg to 7.5 mg/kg per dog. The 10 dogs in the control group were administered a vehicle control. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the *A. caninum* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment and at 1, 2, 4, and 8 hours after treatment. Physical examinations and qualitative fecal examinations were conducted on Day -33. Fecal egg count examinations were performed on Day -4, -2, and 10. Dogs were weighed on Day -34 or -33 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *A. caninum* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using geometric mean through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C - T) / C
Where C = Geometric mean number of worms in the control group.
T = Geometric mean number of worms in the treatment group.

Results: All 10 dogs in the control group had an adequate infection, defined as ≥ 5 *A. caninum* worms present at necropsy.

Credelio Quattro™ was 100% effective against experimentally induced adult *A. caninum* infections in dogs (Table II.9). Mean worm counts between the control group and the Credelio Quattro™ group were statistically significantly different ($p<0.0001$).

Table II.9. Study ELA210573; Effectiveness Against Adult *A. caninum*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control (vehicle)	202 – 270	227.3	NA
Credelio Quattro™	0	0	100%

Adverse Reactions: Three dogs treated with Credelio Quattro™ and two control dogs were observed with diarrhea 1 to 8 hours after dosing. Vomitus was observed for one dog treated with Credelio Quattro™. All events resolved without treatment.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of adult *A. caninum* infections in dogs.

5. Laboratory Dose Confirmation Study Against Adult *Ancylostoma caninum*.

Title: Dose Confirmation Laboratory Study of Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel, and Pyrantel Pamoate when Administered Orally for the Treatment, and Control of Adult *Ancylostoma Caninum* in Experimentally Infected Dogs. (Study No. ELA220857)

Study Dates: February 24, 2023 to May 13, 2024

Study Location: Bloemfontein, South Africa

Study Design:

Objective: Confirm the effectiveness of a single oral dose of Credelio Quattro™ for the treatment and control of adult *A. caninum* in experimentally infected dogs.

Study Animals: Sixteen crossbred or purebred (beagle) dogs (10 male and 6 female), 9 to 11 weeks of age, weighing between 4.7 to 8.6 kg.

Experimental Design: On Day -28, each dog was orally inoculated with approximately 300 infective *A. caninum* L3 larvae. On Day -1, dogs were randomized into treatment groups of eight dogs each using a completely randomized design. On Day 10 post-treatment, all dogs were humanely euthanized and necropsied for recovery and counting of *A. caninum*. The study was conducted in accordance with GCP guidelines.

Table II.10. Study ELA220857; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Number and Sex of Dogs
1	Control (vehicle)	0 mg/kg	8 (5M, 3F)
2	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	8 (5M, 3F)

Drug Administration: On Day 0, the 8 dogs in the Credelio Quattro™ group were administered one or more chewable tablets, at doses as close as possible to the minimum indicated dose without under-dosing. Moxidectin doses ranged from 0.02 to 0.03 mg/kg and pyrantel doses ranged from 5.09 mg/kg to 7.5 mg/kg per dog. The 8 dogs in the control group were administered a vehicle control. All dogs were administered tablets orally in a fed state.

Measurements and Observations: The primary variable for effectiveness was the *A. caninum* worm counts collected from the dogs. General health observations were conducted at least once daily. Clinical observations were conducted prior to treatment and at 1, 2, 4, and 8 hours after treatment. Physical examinations and qualitative fecal examinations were conducted on Day -36 or -35. Fecal egg count examinations were performed on Day -3, -2, and 10. Dogs were weighed on Day -36 or -35 and -1. Worm counts and health observations were conducted masked to treatment.

Statistical Methods: The experimental unit was the individual dog. The log-transformed *A. caninum* worm counts were analyzed using a linear mixed model with treatment group as a fixed effect. The treatment effect was tested at a two-sided 5% significance level. Percent effectiveness was calculated by using geometric mean through back-transformation of the LS mean estimated from the model.

Percent Effectiveness = 100 × (C - T) / C
Where C = Geometric mean number of worms in the control group.
T = Geometric mean number of worms in the treatment group.

Results: All 8 dogs in the control group had an adequate infection, defined as ≥ 5 *A. caninum* worms present at necropsy.

Credelio Quattro™ was 99.9% effective against experimentally induced adult *A. caninum* infections in dogs (Table II.11). Mean worm counts between the control group and the Credelio Quattro™ group were statistically significantly different ($p<0.0001$).

Table II.11. Study ELA220857; Effectiveness Against Adult *A. caninum*

Treatment	Worm Counts: Range	Worm Counts: Geometric Mean	Percent Effectiveness
Control	32 – 190	83.8	NA
Credelio Quattro™	0 - 1	0.1	99.9%

Adverse Reactions: No treatment-related adverse reactions were observed in the study.

Conclusion: This study demonstrated the effectiveness of Credelio Quattro™ for the treatment and control of adult *A. caninum* infections in dogs.

6. Field Safety and Effectiveness Study

Title: A Field Study to Evaluate the Effectiveness and Safety of Orally Administered Flavored Chewable Tablets Containing Lotilaner, Moxidectin, Praziquantel, and Pyrantel Pamoate in the Treatment of Naturally Occurring Gastrointestinal Nematode Infections in Dogs. (Study No. ELA221321)

Study Dates: March 9, 2023 to October 14, 2024

Study Locations: Dogs were enrolled from 17 sites in the United States:

Barnwell, SC
Battle Creek, MI
Bristol, CT
Cincinnati, OH
Crescent Springs, KY
Dover, NH
Elgin, SC
Kimberling City, MO
Muncy, PA
Nashville, TN
Plaquemine, LA
Purdy, MO
Quakertown, PA
Springfield, MO
Virginia Beach, VA
Yorktown, VA
Zachary, LA

Study Design:

Objective: Evaluate the effectiveness and field safety of Credelio Quattro™ for the treatment and control of Gastrointestinal (GI) nematode infections in client-owned dogs.

Study Animals: One hundred and fifty five client-owned mixed breed and purebred intact and neutered male and female dogs, 8 weeks to 9.9 years of age, and weighing between 1.8 and 41.9 kg were enrolled in the study. There

were no breed or sex restrictions, but dogs intended for breeding, and pregnant and lactating dogs were not eligible for enrollment. Dogs were confirmed healthy prior to enrollment. Dogs that had a serious health condition that would interfere with the objectives of the study were excluded from enrollment. Only one dog per household could enroll in the study. Dogs were included in the evaluation of field safety if they received at least one dose of Credelio Quattro™ or the active control product. One hundred and three dogs administered Credelio Quattro™ and 52 dogs administered the active control were evaluated for safety. Seventy-two dogs administered Credelio Quattro™ and 37 dogs administered the active control were included in the effectiveness evaluation.

Experimental Design: The study was a randomized, masked, multicenter, active control study. The study used a randomized block design based on the order of enrollment of the individual dogs on a per-site basis. The study compared Credelio Quattro™ to an orally administered active control containing sarolaner, moxidectin, and pyrantel (as pamoate salt). The clinical investigators and other personnel conducting safety assessments and effectiveness measurements were masked to treatment. The treatment dispensers and dog owners at each study location were not masked (due to product packaging, labeling, and instructions). The study was conducted in accordance with GCP guidelines.

Table II.12. Study ELA221321; Treatment Groups

Treatment Group	Treatment	Minimum Dose	Total Dogs Per Group (Effectiveness Evaluable Dogs)
1	Credelio Quattro™	20 mg/kg lotilaner + 0.02 mg/kg moxidectin + 5 mg/kg praziquantel + 5 mg/kg pyrantel (as pamoate salt)	103 (72)
2	Active Control	1.2 mg/kg sarolaner + 0.024 mg/kg moxidectin + 5 mg/kg pyrantel (as pamoate salt)	52 (37)

Drug Administration: Dog owners administered Credelio Quattro™ or the active control to the dog in the dog's home environment once on Day 0. The dog owners were instructed to administer Credelio Quattro™ within 30 minutes of a meal (or with food), and the active control product with or without food according to the product label.

Measurements and Observations: The primary variable for effectiveness was FEC reduction from pre-treatment to post-treatment. Physical examinations, including body weight measurements, were performed on all dogs prior to treatment on Day 0 and 10. Fecal samples were collected on Day -1 and 10 for qualitative and quantitative FEC.

Statistical Methods: The primary assessment of effectiveness for Credelio Quattro™ was based on FEC reduction from pre-treatment to post-treatment. Separate statistical analyses were conducted in both the IVP (investigational veterinary product) and the CP (control product) for all parasite species with ≥10 evaluable cases. Log-transformed egg counts were analyzed using linear mixed models with time point as a fixed effect and subject as a random effect. Percent reduction was calculated by using geometric means through back-transformation of the LS means estimated from the model. Effectiveness for a specific parasite species was concluded when the following conditions were met: 1) ≥95% reduction in mean percent FEC, compared to pre-treatment FEC, in the IVP treatment group for that parasite species, and 2) significant difference (two-sided 5% significance level) between pre- and post-treatment FEC. FEC reduction for other GI nematodes identified with at least 10 evaluable cases would also be analyzed, but only *T. canis* and *A. caninum* had the minimum number of evaluable cases.

Results: The percent reduction in FEC for *A. caninum* was 99.9% for both the IVP and the CP (Table II.13)

Table II.13. Summary of Pre- and Post-Treatment FEC on Day 10 by Parasite

Parasite	Treatment Group	Pre-treatment, mean* (range)	Post-treatment, mean* (range)	% Reduction	p-value
T. canis	Credelio Quattro™N = 33	109.4 (10 – 1901)	1.4 (0 – 136)	98.7	<0.0001
T. canis	Active control N = 11	33.1 (10 – 100)	1.1 (0 -198)	96.6	0.0001
A. caninum	Credelio Quattro™ N = 52	99.9 (10 – 5019)	0.1 (0 – 22)	99.9	<0.0001
A. caninum	Active control N = 27	86.3 (10 – 1393)	0.1 (0 – 15)	99.9	<0.0001

*geometric mean

Adverse Reactions: One hundred and three dogs administered Credelio Quattro™ and 52 dogs administered the active control product were evaluated for safety. Two dogs treated with Credelio Quattro™ and one control dog were observed with diarrhea within 1 day after dosing. Two dogs vomited, three dogs had flatulence, and one dog had lethargy within 1 day after treatment with Credelio Quattro™. All events resolved without treatment.

Conclusions: This study demonstrated that Credelio Quattro™ is safe and effective for the treatment and control of hookworm (*A. caninum*) infections under field conditions.

III. TARGET ANIMAL SAFETY

The Center for Veterinary Medicine did not require target animal safety studies for this supplemental approval. The FOI Summary for the original approval of NADA 141-581, dated October 7, 2024, 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 Quattro™:

Not for use in humans. Keep this and all drugs out of the reach of children. Wash hands after handling. If accidentally ingested, seek medical attention immediately.

Keep Credelio Quattro™ in a secure location out of the 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 Quattro™, when used according to the label, is safe and effective for the effect of supplement in the General Information Section above.

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 the product is indicated for the prevention of heartworm infections (*Dirofilaria immitis*) in dogs, which requires veterinary examination and testing to ensure dogs are negative for adult heartworm disease prior to administration of the product to dogs.

B. Exclusivity

This supplemental approval for Credelio Quattro™ 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 indication, “for the treatment and control of hookworm (fourth stage larvae, immature adult, and adult *Ancylostoma caninum*) infections in dogs and puppies 8 weeks of age and older, and weighing 3.3 pounds or greater.”

C. Supplemental Applications

This supplement is a Category II supplement as defined in (21 CFR 514.106(b)(2)). This supplemental approval did not require a reevaluation of certain safety or effectiveness data in the application.

D. Patent Information

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