

# Credelio Quattro™ Credelio Quattro-CA1™

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

## Flavored Chewable Tablets

For oral use in dogs only

Credelio Quattro-CA1 is conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-619.

### CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

### DESCRIPTION

Credelio Quattro/Credelio Quattro-CA1 (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) are flavored chewable tablets available in five sizes for oral administration to dogs and puppies according to their weight. Each chewable is formulated to provide minimum doses 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).

Lotilaner is a member of the isoxazoline class of parasiticides and the chemical name is 5-[(5S)-4,5-dihydro-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-3-isoxazolyl]-3-methyl-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-2-thiophenecarboxamide.

Moxidectin is a semisynthetic macrocyclic lactone derived from the actinomycete *Streptomyces cyaneogriseus noncyanogenus*. The chemical name for moxidectin is [6R,23E,25S(E)]-5-O-demethyl-28-deoxy-25-(1,3-dimethyl-1-butenyl)-6,28-epoxy-23-(methoxyimino) milbemycin B.

Praziquantel is an isoquinolone anthelmintic with the chemical name 2-(cyclohexylcarbonyl)-1,2,3,6,7,-11b-hexahydro-4H-pyrazino[2,1-a]isoquinolin-4-one.

Pyrantel is a member of the tetrahydropyrimidine family of compounds. Its chemical name is (E)-1,4,5,6-tetrahydro-1-methyl-2-[2-(2-thienyl)vinyl]pyrimidine 4,4'-methylenebis[3-hydroxy-2-naphthoate](1:1).

### INDICATIONS

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), *Rhipicephalus sanguineus* (brown dog tick), and *Haemaphysalis longicornis* (longhorned tick)] for one month in dogs and puppies 8 weeks of age and older, and weighing 3.3 pounds or greater. Credelio Quattro is indicated for the prevention of *Borrelia burgdorferi* infections as a direct result of killing *Ixodes scapularis* vector ticks.

Credelio Quattro-CA1 is indicated for the treatment of infestations caused by New World screwworm (*Cochliomyia hominivorax*) larvae (myiasis) in dogs and puppies 8 weeks of age and older, and weighing 3.3 pounds or greater.

### DOSAGE AND ADMINISTRATION

Credelio Quattro/Credelio Quattro-CA1 is given orally 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).

Credelio Quattro/Credelio Quattro-CA1 must be administered with food (see **Clinical Pharmacology**). Care should be taken to ensure that the dog consumes the complete dose and that part of the dose is not lost or refused. If vomiting occurs within an hour after administration, readminister a new dose of Credelio Quattro/Credelio Quattro-CA1.

### Credelio Quattro:

Credelio Quattro is given once a month. If a dose is missed, give Credelio Quattro immediately and resume a monthly dosing schedule.

### 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

### Heartworm Prevention

Credelio Quattro should be administered year-round at monthly intervals or at least within 1 month of the animal's first seasonal exposure to mosquitoes and continuing until at least 1 month after the dog's last seasonal exposure. If a dose is missed, give Credelio Quattro immediately and resume monthly dosing. When replacing a monthly heartworm preventive product, Credelio Quattro should be given within 1 month of the last dose of the former medication.

### Intestinal Nematode and Cestode Treatment and Control

Credelio Quattro should be administered as a single dose for the treatment of roundworm, hookworm, and tapeworm infections. Monthly use of Credelio Quattro will control any subsequent infections. Dogs may be exposed to and can become infected with gastrointestinal worms throughout the year, regardless of season or climate. Clients should be advised of appropriate measures to prevent reinfection of their dog with intestinal parasites.

### Flea Treatment and Prevention

Treatment with Credelio Quattro should be administered year-round at monthly intervals or started at least 1 month before fleas become active. To minimize the likelihood of flea re-infestation, it is important to treat all dogs and cats within a household with a flea control product.

### Tick Treatment and Control

Treatment with Credelio Quattro can begin at any time of the year. Credelio Quattro should be administered year-round at monthly intervals or started at least 1 month before ticks become active.

### Credelio Quattro-CA1:

#### New World Screwworm (NWS) Myiasis Treatment

A single dose of Credelio Quattro-CA1 is reasonably expected to treat *C. hominivorax* present at the time of treatment. Re-infestation with *C. hominivorax* may occur sooner than one month. Treatment should be used in conjunction with the mechanical removal of larvae (live and dead) remaining in the wound after treatment (see **PRECAUTIONS**).

### CONTRAINDICATIONS

There are no known contraindications for the use of Credelio Quattro/Credelio Quattro-CA1.

### WARNINGS

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

Keep Credelio Quattro/Credelio Quattro-CA1 in a secure location out of reach of dogs, cats, and other animals to prevent accidental ingestion or overdose.

### PRECAUTIONS

Lotilaner, one of the ingredients in Credelio Quattro/Credelio Quattro-CA1, is a member of the isoxazoline class. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving isoxazoline class drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders.

Prior to administration of Credelio Quattro/Credelio Quattro-CA1, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated with an adulticide to remove adult heartworms. Credelio Quattro/Credelio Quattro-CA1 is not effective against adult *D. immitis*.

The safe use of Credelio Quattro/Credelio Quattro-CA1 in breeding, pregnant, or lactating dogs has not been evaluated.

Effective treatment of NWS myiasis includes removal of the larvae, lesion cleaning with an antiseptic solution and surgical debridement to remove necrotic tissue. Appropriate wound care and pain management should be implemented.

### ADVERSE REACTIONS

In a field safety and effectiveness study, Credelio Quattro was administered to dogs for the prevention of heartworm disease. The study included a total of 372 dogs treated once monthly for up to 11 treatments (191 treated with Credelio Quattro and 181 treated with an active control). Over the 330-day study period, all observations of potential adverse reactions were recorded.

Adverse reactions seen during the field study are summarized in the table below.

#### Dogs with Adverse Reactions in the Field Study

Clinical Sign	Credelio Quattro N=191 Number (Percentage)	Active Control N=181 Number (Percentage)
Diarrhea, with or without blood*	21 (11%)	15 (8.3%)
Vomiting	18 (9.4%)	8 (4.4%)
Lethargy	12 (6.3%)	1 (0.6%)
Anorexia	11 (5.8%)	5 (2.8%)
Dermatitis	10 (5.2%)	8 (4.4%)
Weight Loss	6 (3.1%)	3 (1.7%)
Pruritus (itching)	3 (1.6%)	1 (0.6%)
Alopecia (hair loss)	2 (1.0%)	4 (2.2%)
Seizure	1 (0.5%)	4 (2.2%)
Ataxia	1 (0.5%)	1 (0.6%)
Nystagmus	1 (0.5%)	0 (0.0%)
Anisocoria	1 (0.5%)	1 (0.6%)

\*Four dogs administered Credelio Quattro and five dogs administered the active control had bloody diarrhea.

One geriatric dog receiving Credelio Quattro experienced two episodes of vomiting, ataxia, and nystagmus, 11 days apart, with the first episode occurring two days after the eighth dose. The dog recovered within 24 hours after the first episode and 1 hour after the second episode and completed the study. One dog receiving Credelio Quattro was observed by the investigator to have anisocoria during scheduled physical examinations one month after the ninth dose and one month after the eleventh dose.

In a second U.S. field safety and effectiveness study, Credelio Quattro was administered to 103 dogs with hookworms. Adverse reactions in dogs treated with Credelio Quattro included gastrointestinal signs (diarrhea, emesis) and lethargy.

In a U.S. field study, 165 dogs received a combination of lotilaner, moxidectin, and praziquantel, three of the active ingredients at the same doses as in Credelio Quattro, monthly for up to 11 months. Two dogs with no history of seizures experienced seizures during the study. One of the dogs developed cluster seizures and was removed from the study. Ataxia was also observed in one other dog three days after the first dose.

In a U.S. field study, one dog administered lotilaner alone, a component of Credelio Quattro, was observed with intermittent head tremors within 1.5 hours of administration of vaccines, an ear cleaning performed by the owner, and its first dose of lotilaner. The head tremors resolved within 24 hours without treatment. The owner elected to withdraw the dog from the study.

In an Australian field study, one dog with a history of seizures experienced seizure activity (tremors and glazed eyes) six days after receiving lotilaner alone. The dog recovered without treatment and completed the study. In a U.S. field study, two dogs with a history of seizures received lotilaner alone and experienced no seizures throughout the study.

## CONTACT INFORMATION

For a copy of the Safety Data Sheet (SDS) or to report suspected adverse drug events, contact Elanco US Inc. at 1-888-545-5973.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or <http://www.fda.gov/reportanimalae>.

## INFORMATION FOR ANIMAL OWNER

*Echinococcus granulosus* is a tapeworm found in wild canids and domestic dogs. *E. granulosus* can infect humans and cause serious disease (hydatid disease). Owners of dogs living in areas where *E. granulosus* is endemic should be instructed on how to minimize their risk of exposure to this parasite, as well as their dog's risk of exposure. Although Credelio Quattro was 100% effective in laboratory studies in dogs against *E. granulosus*, no studies have been conducted to show that the use of this product will decrease the incidence of hydatid disease in humans.

New World Screwworm (NWS) is a parasitic fly larva that infests open wounds in warm-blooded animals, including pets and people. These infestations can cause severe tissue damage and can be fatal if untreated. Pet owners should regularly inspect their animals for open wounds and signs of infestation, such as visible maggots, an enlarging wound, or a foul odor. If you suspect your pet has an NWS infestation, contact your veterinarian immediately. Early detection and treatment are crucial.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Credelio Quattro contains four active pharmaceutical ingredients, lotilaner, moxidectin, praziquantel, and pyrantel (as pamoate salt).

Lotilaner is an ectoparasiticide belonging to the isoxazoline group. Lotilaner inhibits insect and acarine gamma-aminobutyric acid (GABA)-gated chloride channels. This inhibition blocks the transfer of chloride ions across cell membranes, which results in uncontrolled neuromuscular activity leading to death of insects and acarines. The selective toxicity of lotilaner between insects and acarines and mammals may be inferred by the differential sensitivity of the insects and acarines' GABA receptors versus mammalian GABA receptors.

Moxidectin is an endectocide in the macrocyclic lactone class. Moxidectin acts by interfering with the chloride channel-mediated neurotransmission in the parasite. This results in paralysis and death of the parasite.

Praziquantel's mode of action is not precisely known, but treated tapeworms undergo muscular paralysis accompanied by a rapid influx of calcium ions and the disruption of the tegument.

Pyrantel is a nematocide belonging to the tetrahydropyrimidine class. Pyrantel acts as a depolarizing, neuromuscular-blocking agent in susceptible parasites, causing paralysis and death or expulsion of the parasite.

### Pharmacokinetics

Due to reduced drug bioavailability of lotilaner in the fasted state, Credelio Quattro must be administered with a meal or within 30 minutes after feeding.

Following a single oral administration of Credelio Quattro at the minimum labeled dose in the fed state or a single intravenous administration of 5 mg lotilaner, 0.005 mg moxidectin, 1.25 mg praziquantel, and 1.25 mg pyrantel per kg body weight to Beagle dogs (1.5 to 2.5 years old), the mean oral bioavailability for lotilaner, praziquantel, and pyrantel was 93%, 41%, and 31%, respectively. Bioavailability for moxidectin is not reported due to insufficient data to adequately describe the elimination phase following intravenous administration. For Credelio Quattro, the area under the curve from time of dosing to the time of the last measurable concentration ( $AUC_{last}$ ) was 5970, 1.75, 1.54, and 0.857 mg<sup>h</sup>/L for lotilaner, moxidectin, praziquantel, and pyrantel, respectively.

Peak concentrations ( $C_{max}$ ) of 9070, 15.3, 390, and 122 ng/mL were reached ( $T_{max}$ ) 10, 4.5, 0.75, and 2.5 h after dosing for lotilaner, moxidectin, praziquantel, and pyrantel, respectively. Mean plasma elimination half-lives were 806, 634, 3.64, and 4.87 h for lotilaner, moxidectin, praziquantel, and pyrantel, respectively.

Following nine oral administrations of Credelio Quattro at 1X, 3X, and 5X the maximum labeled dose of 40 mg/kg lotilaner, 0.04 mg/kg moxidectin, 10 mg/kg praziquantel, and 10 mg/kg pyrantel, every 28 days in 8-week-old Beagle dogs, moxidectin and lotilaner area under the curve from time of dosing to the time of the last measurable concentration ( $AUC_{last}$ ) increased approximately in a less than proportional manner, whereas praziquantel  $AUC_{last}$  increased approximately in a more than proportional manner from 1X to 5X after most study doses. Pyrantel  $AUC_{last}$  increased approximately in a proportional manner from 1X to 5X observed after first, sixth, and last doses. Within the 1X group, accumulation was observed between Days 0 and 224 with geometric mean accumulation ratios for  $AUC_{last}$  of 6.2 and 7.9 for lotilaner and moxidectin, respectively. Concentrations of praziquantel and pyrantel prior to each dose were below the limit of quantification.

## EFFECTIVENESS

### Heartworm Prevention

In two well-controlled laboratory studies, a single oral dose of Credelio Quattro was 100% effective in preventing the development of adult *D. immitis* in dogs inoculated with infective larvae 30 days before administration.

In a well-controlled U.S. field study consisting of 156 dogs administered Credelio Quattro and 149 administered an active control for 11 consecutive months, no dogs treated with Credelio Quattro tested positive for heartworm disease. All dogs treated with Credelio Quattro were negative for *D. immitis* antigen and blood microfilariae at study completion on Day 330.

### Intestinal Nematode and Cestode Treatment and Control

In well-controlled laboratory studies, a single dose of Credelio Quattro was  $\geq 97.0\%$  effective against immature adult and adult *Toxocara canis*; adult *Toxascaris leonina*; fourth stage larvae, immature adult, and adult *Ancylostoma caninum*; and adult *Uncinaria stenocephala* infections.

In a 10-day multi-center US field study, 72 dogs administered a single dose of Credelio Quattro and 37 dogs administered a single dose of an active control were evaluable for effectiveness; Credelio Quattro reduced *Ancylostoma caninum* fecal egg counts 99.9% compared to pre-treatment.

In well-controlled laboratory studies, a single dose of Credelio Quattro was 100% effective against *Echinococcus granulosus*. In separate well-controlled laboratory studies, praziquantel alone was 100% effective against *Echinococcus granulosus*, *Dipylidium caninum*, and *Taenia pisiformis*.

### Flea Treatment and Prevention

In a well-controlled laboratory study, Credelio Quattro was 100% effective against adult fleas 24 hours after administration or infestation for 36 days. In a separate laboratory study, lotilaner alone began to kill fleas 4 hours after administration or infestation, with greater than 99% of fleas killed within 8 hours after administration or infestation for 35 days.

In a well-controlled laboratory study, lotilaner alone killed fleas before they could lay eggs, thus preventing subsequent flea infestations for 30 days after the start of treatment of existing flea infestations.

In a well-controlled U.S. field study conducted in households with existing flea infestations of varying severity, flea reductions of 99.5% to 100% were observed over the course of three monthly treatments with lotilaner alone. Dogs with signs of flea allergy dermatitis showed improvement in erythema, papules, scaling, alopecia, dermatitis/pyodermitis, and pruritus as a direct result of eliminating fleas.

### Tick Treatment and Control

In well-controlled laboratory studies, Credelio Quattro was  $\geq 97.1\%$  effective against *Rhipicephalus sanguineus* and *Haemaphysalis longicornis* ticks 48 hours after administration or infestation for 32 days. In well-controlled laboratory studies, lotilaner alone was  $> 97\%$  effective against *Amblyomma americanum*, *Dermacentor variabilis*, *Ixodes scapularis*, and *Rhipicephalus sanguineus* ticks 48 hours after administration or infestation for 30 days.

In a well-controlled European laboratory study, lotilaner alone started killing *Ixodes ricinus* ticks within 4 hours after administration.

In two separate, well-controlled laboratory studies, Credelio Quattro was effective at preventing *Borrelia burgdorferi* infections after dogs were infested with *Ixodes scapularis* vector ticks.

## REASONABLE EXPECTATION OF EFFECTIVENESS

### New World Screwworm (NWS) Myiasis Treatment

A reasonable expectation of effectiveness may be demonstrated based on evidence such as, but not limited to, pilot data in the target species or studies from published literature.

Credelio Quattro-CA1 is conditionally approved pending a full demonstration of effectiveness.

Additional information for Conditional Approvals can be found at [www.fda.gov/animalca](http://www.fda.gov/animalca).

A reasonable expectation of effectiveness for Credelio Quattro-CA1 is based on a study conducted by do Vale et al.<sup>1</sup> that evaluated the effectiveness of Credelio (lotilaner) alone for the treatment of naturally acquired NWS myiasis in dogs in eleven client-owned dogs in Brazil. All dogs received a single oral administration of lotilaner at doses ranging from 23.9 to 40.9 mg/kg body weight, following the dose bands for the approved flea and tick indications. The study did not include a control group.

Dogs were observed at 2- and 6- hours post-treatment for larval expulsion, with remaining dead larvae mechanically removed at 24 hours.

The study demonstrated 100% overall effectiveness (expulsion plus larvicidal activity) against *Cochliomyia hominivorax* larvae at 24 hours, with larval expulsion rates of 80.5% and 93% at 2 and 6 hours, respectively. The mean larvicidal effectiveness was 41.1% at 24 hours, suggesting that the overall effectiveness at 24 hours was primarily driven by larval expulsion rather than direct killing.

The extrapolation of effectiveness data from Credelio to Credelio Quattro-CA1 is supported by use of the same approved lotilaner dose (minimum 20 mg/kg) for both products and non-interference data from the original approval of Credelio Quattro.

**Palatability:** In the U.S. field study, which included 552 doses administered to 191 dogs, dogs voluntarily consumed 59.8% of Credelio Quattro doses from an empty bowl, on the floor, or when offered by hand, and an additional 28.4% of doses when offered with food. The administration of 11.8% of doses required placement of the chewable tablet in the back of the dog's mouth. All doses were administered within 30 minutes of a meal.

#### **TARGET ANIMAL SAFETY**

##### **Margin of Safety**

Credelio Quattro was administered orally at 0X, 1X, 3X, and 5X the maximum labeled doses at 28-day intervals for nine treatments to 32 healthy, 8-week-old Beagle puppies. Dogs in the control group received placebo. Credelio Quattro-related clinical chemistry findings included increased bile acids in two of the 3X dogs. Minimal mononuclear cell infiltration of the liver was noted microscopically in five control dogs, two 1X dogs, three 3X dogs, and five 5X dogs. One control dog, one 1X dog, two 3X dogs, and none of the 5X dogs also had minimal extramedullary hematopoiesis. Credelio Quattro-related clinical observations included a dose-dependent increase in discolored feces, diarrhea, and vomiting. All dogs recovered without treatment. Hypersalivation associated with vomiting on the day of dosing occurred in two of the 5X dogs.

##### **Avermectin Sensitive Collie Safety**

Credelio Quattro was administered orally at 0X, 1X, 2X, and 5X the maximum labeled dose at 28-day intervals for three treatments to 32 healthy, avermectin sensitive Collie dogs. Dogs in the control group received a vehicle control. One dog in each of the control, 2X, and 5X groups had transient mild depression. Salivation and vomiting was observed in a dose-dependent manner in the 1X, 2X, and 5X groups. Diarrhea, with or without blood, was observed in all groups, including controls, and resolved without treatment.

##### **Heartworm Positive Safety**

Credelio Quattro was administered orally at 0X, 1X, and 3X the maximum labeled dose at 28-day intervals for three treatments to 24 healthy, Beagle dogs with patent adult heartworm infections and circulating microfilariae. Dogs in the control group received placebo. Diarrhea and/or vomiting occurred in all dogs in the 3X group at various times up to 12 hours post-dose. Diarrhea occurred in fewer dogs in the 1X and control groups. All dogs experiencing post-dose gastrointestinal issues recovered without treatment. Hypersensitivity reactions (e.g., anaphylaxis, shock, collapse, respiratory distress, or depression) were not observed in any dog.

##### **Field Safety**

In a well-controlled field study, Credelio Quattro was used concurrently with other medications such as vaccines, antimicrobials, anthelmintics, antiemetics, steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs), anesthetics, and analgesics. No adverse reactions were associated with the concurrent use of Credelio Quattro and other medications.

##### **HOW SUPPLIED**

Credelio Quattro/Credelio Quattro-CA1 (lotilaner, moxidectin, praziquantel, and pyrantel chewable tablets) is available in five strengths of flavored chewable tablets formulated according to the weight of the dog (see **Dosage and Administration**). Each chewable tablet size is available in packages of 1, 6, or 12 tablets.

##### **STORAGE INFORMATION**

Store at 15-25°C (59-77°F). Excursions permitted between 5 and 40°C (41 and 104°F).

<sup>1</sup> do Vale TL, Costa AR, Miranda LM, Silva GF, Silva NCS, Lima TB, Chaves DP, Sager H, Lasmar PVF, Costa-Junior LM. Efficacy of lotilaner against myiasis caused by *Cochliomyia hominivorax* (Diptera: Calliphoridae) in naturally infested dogs. *Parasit Vectors*. 2023;16(1):86.

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Manufactured for: Elanco US Inc, Indianapolis, IN 46221

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