Credelio Quattro™

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

Flavored Chewable Tablets
For oral use in dogs only

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

DESCRIPTION
Credelio Quattro (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 *Streptomycetes 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 (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.

DOSAGE AND ADMINISTRATION
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). Credelio Quattro 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. 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.

CONTRAINDICATIONS
There are no known contraindications for the use of Credelio Quattro.

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 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, 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, 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 is not effective against adult *D. immitis*.

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

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 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.

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*h/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 ≥ 97.0% effective against immature adult and adult *Toxocara canis*, adult *Toxascaris leonina,* and adult *Uncinaria stenocephala* infections.

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 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/pyodermatitis, and pruritus as a direct result of eliminating fleas.

Tick Treatment and Control

In well-controlled laboratory studies, Credelio Quattro was ≥ 97.1% effective against *Rhipicephalus sanguineus* 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.

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 (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).

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Manufactured for: Elanco US Inc, Greenfield, IN 46140

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