

  
**Credelio**<sup>®</sup>  
(lotilaner)

# DISCOVER TOUGH TICK AND FLEA CONTROL **FOR DOGS AND PUPPIES**



**Elanco**

# FAST-ACTING, SUSTAINED EFFICACY AGAINST TICKS AND FLEAS

## LOTILANER: CHOSEN OUT OF 1,000 COMPOUNDS STUDIED

There are plenty of isoxazoline tick and flea medications on the market. You've heard their names. You may have even prescribed some of them to your patients.

### WHY LOTILANER:

- **Handpicked for its efficacy and safety profile** from over 1,000 isoxazoline compounds studied<sup>1</sup>
- **Extra-purified** for more efficient drug delivery<sup>1</sup>
- **100x more potent** *in vitro* against ticks and fleas than its removed, inactive component<sup>1</sup>
- **Strongly binds to tick and flea receptors** *in vitro* with no activity on dogs' receptors<sup>2</sup>

## LOTILANER HAS LONGER HALF-LIFE

Half-life comparison of isoxazoline compounds

Brand Name	Isoxazoline compound	5	10	15	20	25	30
Credelio® (lotilaner)	Lotilaner <sup>1</sup>	[Sustained high blood levels for 30 days]					
Bravecto® (fluralaner) 3-Month Chew	Fluralaner <sup>3</sup>	[Sustained high blood levels for ~15 days]					
NexGard® (afoxolaner)	Afoxolaner <sup>4</sup>	[Sustained high blood levels for ~15 days]					
Simparica Trio® (sarolaner, moxidectin, and pyrantel chewable tablets)	Sarolaner <sup>5</sup>	[Sustained high blood levels for ~10 days]					

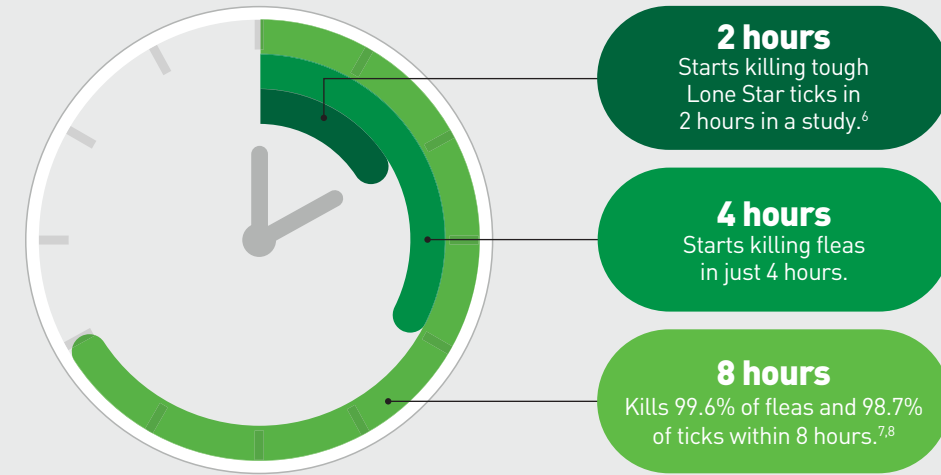
The clinical significance of half-life data has not been established.

Lotilaner reaches **peak absorption in only 2 hours** and maintains high, sustained blood levels for the entire month.<sup>1</sup>

## IMPORTANT SAFETY INFORMATION

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

## ACTS FAST AGAINST TICKS AND FLEAS



**CREDELIO PROVIDES SUSTAINED EFFICACY AGAINST TICKS AND FLEAS THROUGHOUT THE ENTIRE MONTH — NO DROP-OFF.**<sup>9,10</sup>

## QUICK FLEA CONTROL IS CRITICAL



### KILLS FLEAS BEFORE THEY CAN LAY EGGS

Killing fleas fast enough before they can lay eggs is crucial to clearing and preventing infestations. In a controlled laboratory study after 24 hours, Credelio completely eliminated egg shedding for 30 days.<sup>11</sup>



### REDUCES FLEA SALIVARY ANTIGEN LOAD

By killing biting fleas quickly, Credelio can help relieve flea allergy dermatitis (FAD).<sup>7,12</sup>



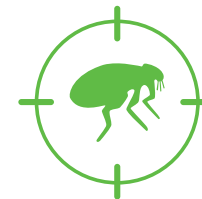
### HELPS REDUCE PRURITUS AND SKIN LESIONS

After only one dose, Credelio reduced pruritus and skin lesions with no need for steroids due to its fast flea kill.<sup>12</sup>



### REAL WORLD SUCCESS

In a high flea-pressure field study based out of Florida, dogs with fleas and their homes were flea-free after only 2 monthly doses.<sup>12</sup>




### SUPPORTS A FLEA-FREE LIFE FOR DOGS

Shown to have a **100% kill rate** within 12 hours for 35 days.<sup>9</sup>

In a head-to-head study, **100% of dogs were flea-free with Credelio** after 3 monthly doses vs 93.2% with NexGard.<sup>13</sup>




# TOUGH ON TICKS, INCLUDING HARD-TO-KILL SPECIES



**Credelio kills common ticks that can spread serious diseases in dogs, such as Rocky Mountain spotted fever, ehrlichiosis, babesiosis and Lyme disease.**

## STUDIES SHOW HIGH EFFICACY ALL MONTH LONG<sup>10</sup>

	American dog tick	Brown dog tick	Lone Star tick	Black-legged tick
Day	% efficacy	% efficacy	% efficacy	% efficacy
2	100	100	100	100
9	100	100	99	99
16	100	100	100	98
23	100	100	100	100
30	100	100	100	99.6



# GENTLE ON PUPPIES

Credelio is gentle enough for pups and dogs as small as 4.4 pounds and as young as 8 weeks old.



## EXTRA-PURIFIED ACTIVE INGREDIENT

An extra purification step is taken for the active ingredient mixture, leaving only the active portion in the final product. Benefits of extra-purification include:


- More efficient drug delivery in a small tablet that is easy to give<sup>1</sup>
- Less work for the dog or puppy's body to process<sup>1</sup>
- Less potential for side effects<sup>14</sup>

## LONE STAR TICKS ARE A CHALLENGE

In general, ticks are more resilient than other types of parasites. Lone Star ticks are of particular concern to dogs because they are:

- **Highly aggressive:** Have large mouthparts and actively seek out or hunt pets to feed on
- **A constant threat to dogs:** Populations maintain easily in the wild and are prone to rapid increases in numbers (tick blooms) when favorable conditions arise
- **Expanding in prevalence:** Lone Star ticks have expanded their prevalence northward and are no longer considered "southern ticks"

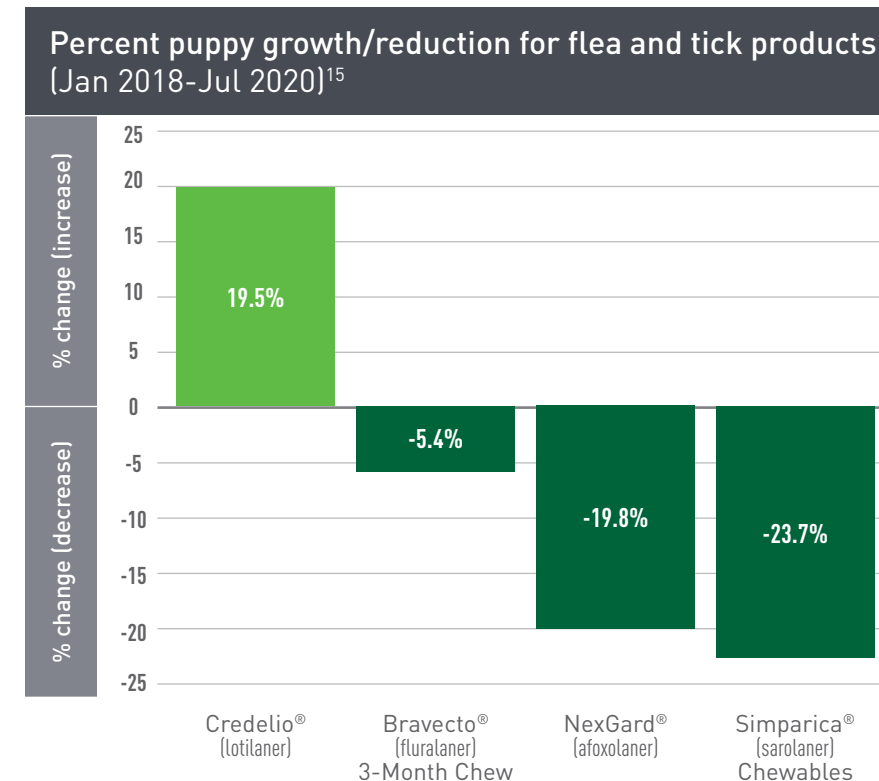

Time at which effectiveness was demonstrated (Lone Star tick)	
Credelio® (lotilaner)	<b>48 HOURS</b>
Bravecto® (fluralaner) 3-Month Chew	72 HOURS
NexGard® (afoxolaner)	72 HOURS
Simparica Trio® (sarolaner, moxidectin, and pyrantel chewable tablets)	72 HOURS



**Within only 2 hours of lotilaner exposure, Lone Star ticks showed vast neuromuscular breakdown, leading to impaired feeding, salivary gland dysfunction and, ultimately, death.<sup>6</sup>**

Based on label indications. Times reflect each company's desire of when to evaluate effectiveness in studies used for registration.

## POPULAR WITH PUPPY OWNERS

**CREDELIO IS THE FASTEST-GROWING TICK AND FLEA BRAND IN PUPPY DOSES SOLD OVER THE LAST 2 YEARS.<sup>15</sup>**

Please see Credelio Important Safety Information on back page.

## PROVEN EASY TO ADMINISTER

### DELIVERS 100% ADMINISTRATION SUCCESS<sup>13,16</sup>

Palatability was widely tested in:

- More than 190 dogs
- More than 70 breeds
- Toy breeds (e.g., Chihuahuas, Yorkshire Terriers)
- 567 total doses

### SMALL BUT MIGHTY

- Small, tasty, monthly chewable
- Safe for puppies and dogs as small as 4.4 pounds and as young as 8 weeks old



DOSING: Must be administered with food				
Body weight of dog (pounds)	Tablet strength	Tablet to be administered	Package color	
4.4-6	56.25 mg			Yellow
6.1-12	112.5 mg			Pink
12.1-25	225 mg			Orange
25.1-50	450 mg			Green
50.1-100*	900 mg			Blue

\*For dogs over 100 pounds, prescribe the appropriate combination of tablets to achieve a minimum dose of 9 mg/lb (20 mg/kg).

### WIDELY TESTED WITH OTHER MEDICATIONS

Over 150 medications (heartworm preventives, steroids, vaccines and antibiotics, etc.) have been administered with Credelio in studies.<sup>13,17,18</sup>

## Credelio™ (lotilaner)

Chewable Tablets

For oral use in dogs

**Caution:**

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

**Description:**

CREDELIO (lotilaner) is a beef-flavored, chewable tablet for oral administration to dogs and puppies according to their weight. Each chewable tablet is formulated to provide a minimum lotilaner dosage of 9 mg/lb (20 mg/kg).

Lotilaner has the chemical composition of 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.

**Indications:**

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.

**Dosage and Administration:**

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 (see **Clinical Pharmacology**).

Treatment with CREDELIO can begin at any time of the year and can continue year-round without interruption.

**Contraindications:**

There are no known contraindications for the use of CREDELIO.

**Warnings:**

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.

**Precautions:**

Lotilaner 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.

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

**Adverse Reactions:**

In a well-controlled U.S. field study, which included 284 dogs (198 dogs treated with CREDELIO and 86 dogs treated with an oral active control), there were no serious adverse reactions. Over the 90-day study period, all observations of potential adverse reactions were recorded. Reactions that occurred at an incidence of 1% or greater are presented in the following table.

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

Adverse Reaction (AR)	CREDELIO Group: Number (and Percent) of Dogs with the AR (n=198)	Active Control Group: Number (and Percent) of Dogs with the AR (n=86)
Weight Loss	3 (1.5%)	2 (2.3%)
Elevated Blood Urea Nitrogen (BUN)	2 (1.0%)*	0 (0.0%)
Polyuria	2 (1.0%)*	0 (0.0%)
Diarrhea	2 (1.0%)	2 (2.3%)

\*Two geriatric dogs developed mildly elevated BUN (34 to 54 mg/dL; reference range: 6 to 31 mg/dL) during the study. One of these dogs also developed polyuria and a mildly elevated potassium (6.5 mEq/L; reference range: 3.6 to 5.5 mEq/L) and phosphorous (6.4 mg/dL; reference range: 2.5 to 6.0 mg/dL). The other dog also developed a mildly elevated creatinine (1.7 to 2.0 mg/dL; reference range: 0.5 to 1.6 mg/dL) and weight loss.

In addition, one dog experienced intermittent head tremors within 1.5 hours of administration of vaccines, an ear cleaning performed by the owner, and its first dose of CREDELIO. 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 CREDELIO. The dog recovered without treatment and completed the study. In the U.S. field study, two dogs with a history of seizures received CREDELIO and experienced no seizures throughout the study.

In three well-controlled European field studies and one U.S. laboratory study, seven dogs experienced episodes of vomiting and four dogs experienced episodes of diarrhea between 6 hours and 3 days after receiving CREDELIO.

To report suspected adverse events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), 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>.

**Clinical Pharmacology:**

Following oral administration of 43 mg/kg (approximately 1X the maximum labeled dose), peak lotilaner concentrations were achieved between 6 hours and 3 days in dogs 2 months of age and between 1 and 7 days in dogs 10 months of age. Dogs 2 months of age had a shorter elimination half-life (average of 9.6 days) than at 10 months of age (average of 28.4 days). Due to reduced drug bioavailability in the fasted state, CREDELIO must be administered with a meal or within 30 minutes after feeding.

**Mode of Action:**

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.

**Effectiveness:**

In well-controlled European laboratory studies, CREDELIO began to kill fleas four hours after administration or infestation, with greater than 99% of fleas killed within eight hours after administration or infestation for 35 days. In a well-controlled U.S. laboratory study, CREDELIO demonstrated 100% effectiveness against adult fleas 12 hours after administration or infestation for 35 days.

In a 90-day well-controlled U.S. field study conducted in households with existing flea infestations of varying severity, the effectiveness of CREDELIO against fleas on Days 30, 60 and 90 compared to baseline was 99.5%, 100% and 100%, respectively. 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.

In a well-controlled laboratory study, CREDELIO 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 well-controlled laboratory studies, CREDELIO demonstrated > 97% effectiveness 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, CREDELIO started killing *Ixodes ricinus* ticks within four hours after administration.

**Palatability:** In the U.S. field study, which included 567 doses administered to 198 dogs, 80.4% of dogs voluntarily consumed CREDELIO when offered by hand or in an empty bowl, an additional 13.6% consumed CREDELIO when offered with food, and 6.0% required placement of the chewable tablet in the back of the dog's mouth.

**Animal Safety:**

In a margin of safety study, CREDELIO was administered orally to 24 (8 dogs/group) 8-week-old Beagle puppies at doses of 43 mg/kg, 129 mg/kg, and 215 mg/kg (approximately 1, 3, and 5X the maximum labeled dose, respectively) every 28 days for eight consecutive doses. The 8 dogs in the control group (OX) were untreated. There were no clinically-relevant, treatment-related effects on clinical observations, physical and neurological examinations, body weights, food consumption, electrocardiograms, clinical pathology (hematology, clinical chemistries, coagulation profiles and urinalysis), gross pathology, histopathology, or organ weights. Blood concentrations of lotilaner confirmed systemic exposure of all treated dogs, although the exposure was less than dose proportional at 5X.

In a well-controlled field study, CREDELIO was used concurrently with other medications, such as vaccines, anthelmintics, antibiotics, steroids, NSAIDs, anesthetics, and antihistamines. No adverse reactions were observed from the concomitant use of CREDELIO with other medications.

**Storage Information:**

Store at 15-25°C (59 -77°F), excursions permitted between 5 to 40°C (41 to 104°F).

**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, 3 or 6 chewable tablets.

Approved by FDA under NADA # 141-494

Manufactured for:

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Rev. date 05/2020



# DISCOVER TOUGH TICK AND FLEA CONTROL. DISCOVER CREDELIO<sup>®</sup> (LOTILANER).

TALK TO YOUR ELANCO SALES REPRESENTATIVE TODAY  
ABOUT PRESCRIBING CREDELIO IN YOUR CLINIC.

## INDICATIONS

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## IMPORTANT SAFETY INFORMATION

Lotilaner is a member of the isoxazoline class of drugs. This class has been associated with neurologic adverse reactions including tremors, ataxia, and seizures. Seizures have been reported in dogs receiving this class of drugs, even in dogs without a history of seizures. Use with caution in dogs with a history of seizures or neurologic disorders. The safe use of Credelio in breeding, pregnant, or lactating dogs has not been evaluated. The most frequently reported adverse reactions are weight loss, elevated blood urea nitrogen, polyuria, and diarrhea. For full prescribing information see Credelio package insert.

## REFERENCES

<sup>1</sup>Toutain C, Seewald W, Jung M. The intravenous and oral pharmacokinetics of lotilaner in dogs. *Parasite Vector*. 2017;10:522.

<sup>2</sup>Rufener L, Danelli V, Bertrand D, et al. The novel isoxazoline ectoparasiticide lotilaner (Credelio<sup>™</sup>): a non-competitive antagonist specific to invertebrates  $\gamma$ -aminobutyric acid-gated chloride channels (GABACl<sub>s</sub>). *Parasite Vector*. 2017;10:530.

<sup>3</sup>Bravecto prescribing information.

<sup>4</sup>Drag M, Saik J, Harriman J, et al. Safety evaluation of orally administered afoxolaner and milbemycin oxime in eight week old dogs. *J Vet Pharmacol Therap*. 2016;40:447-453.

<sup>5</sup>Simparica Trio prescribing information.

<sup>6</sup>Elanco Animal Health. Data on file.

<sup>7</sup>Cavalleri D, Murphy M, Seewald W, et al. Assessment of the onset of lotilaner (Credelio<sup>™</sup>) speed of kill of fleas on dogs. *Parasite Vector*. 2017;10:521.

<sup>8</sup>Murphy M, Cavalleri D, Seewald W, et al. Laboratory evaluation of the speed of kill of lotilaner (Credelio<sup>™</sup>) against *Ixodes ricinus* ticks on dogs. *Parasite Vector*. 2017;10:541.

<sup>9</sup>Cavalleri D, Murphy M, Seewald W, et al. Assessment of the speed of flea kill of lotilaner (Credelio<sup>™</sup>) throughout the month following oral administration to dogs. *Parasite Vector*. 2017;10:529.

<sup>10</sup>Murphy M, Garcia R, Karadzovska D, et al. Laboratory evaluations of the immediate and sustained efficacy of lotilaner (Credelio<sup>™</sup>) against four common species of ticks affecting dogs in North America. *Parasite Vector*. 2017;10:523.

<sup>11</sup>Young L, Karadzovska D, Wiseman S, et al. Efficacy of lotilaner (Credelio<sup>®</sup>) against the adult cat flea, *Ctenocephalides felis* and flea eggs following oral administration to dogs. *Parasite Vector*. 2020;13:25

<sup>12</sup>Dryden M, Canfield M, Herrin D, et al. In-home assessment of flea control and dermatologic lesions in dogs provided by lotilaner (Credelio<sup>®</sup>) and spinosad (Comfortis<sup>®</sup>) in west central Florida. *Vet Parasitol*. 2019;1:100009.

<sup>13</sup>Karadzovska D, Chappell K, Coble S, et al. A randomized, controlled field study to assess the efficacy and safety of lotilaner flavored chewable tablets (Credelio<sup>™</sup>) in eliminating fleas in client-owned dogs in the USA. *Parasite Vector*. 2017;10:528.

<sup>14</sup>Food and Drug Administration. Development of new stereoisomeric drugs. Available at: <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm122883.htm>. Accessed March 11, 2019.

<sup>15</sup>Elanco Animal Health. Data on file.

<sup>16</sup>Elanco Animal Health. Data on file.

<sup>17</sup>Cavalleri D, Murphy M, Seewald W, et al. A randomized, controlled study to assess the efficacy and safety of lotilaner (Credelio<sup>™</sup>) in controlling ticks in client-owned dogs in Europe. *Parasite Vector*. 2017;10:531.

<sup>18</sup>Cavalleri D, Murphy M, Seewald W, et al. A randomised, blinded, controlled field study to assess the efficacy and safety of lotilaner tablets (Credelio<sup>™</sup>) in controlling fleas in client owned dogs in European countries. *Parasite Vector*. 2017;10:526.