

SECRETS OF TICK FEEDING REVEALED

New tick study sheds light on how ticks feed and how lotilaner works quickly to disrupt the feeding process.¹



HOW TICKS FEED²

ONE CANAL TO FEED AND SPIT

Share a common feeding canal to suck fluids in and spit saliva out

POOL FEEDERS

Feed from low pressure pools of blood, unlike mosquitoes and fleas which feed directly from high pressure capillaries

POWERFUL SUCTION

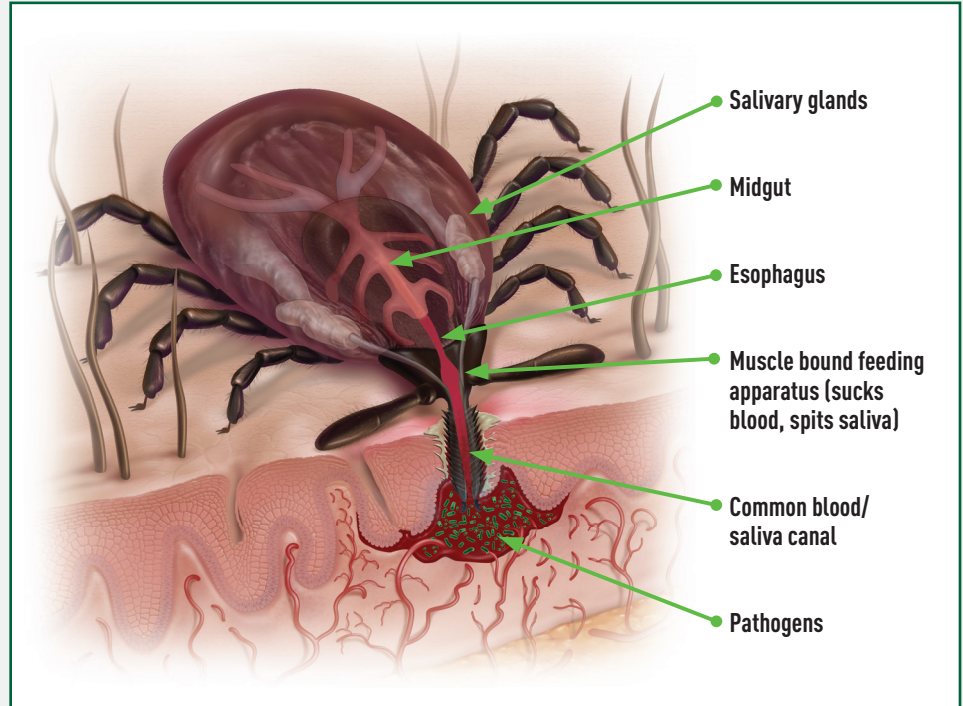
Must generate the necessary suction to pull in blood and tissue fluid

FORCEFUL SALIVATION

Must be able to spit saliva back into the host

NEUROMUSCULAR PUMPING

Create the forces needed to suck and spit by relaxing and contracting muscles within their highly innervated feeding apparatus



Tick feeding (blood sucking), salivation and disease transmission are highly complex processes that require intricate coordination between muscles and nerves.

SPEED OF TICK DISEASE TRANSMISSION

Tick Disease	Minimum Time to Infection ³⁻⁷
EHRlichiosis	3 hrs
ROCKY MOUNTAIN SPOTTED FEVER	5 hrs
ANAPLASMOSIS	6 hrs
BABESIOSIS	8 hrs
LYME DISEASE	24 hrs



UNDERSTANDING HOW TICKS FEED CAN HELP YOU WITH PRODUCT SELECTION.

IN JUST 2 HOURS, TICK STUDY SHOWS RESULTS

Lotilaner starts killing tough Lone Star ticks in only 2 hours.¹

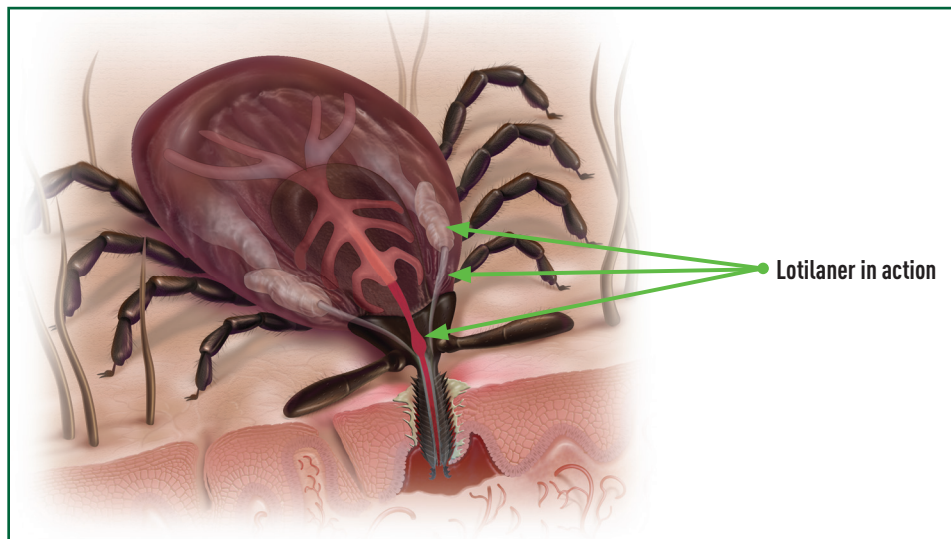
Credelio[®]
(lotilaner)

THE STUDY

Measured early effects of lotilaner on tick feeding and survival at 2, 4, 8 and 24 hours¹

Attached ticks removed at each time point for analysis:

- Ticks' ability to gain weight
- Time for ticks to reach lethal amount of lotilaner ingestion



Within only 2 hours of lotilaner exposure, Lone Star ticks showed vast **neuromuscular breakdown**, leading to impaired feeding, salivary gland dysfunction and, ultimately, **death**.¹

KEY STUDY FINDINGS¹

Achieved with Lone Star ticks, toughest tick species to kill

TICKS LOST WEIGHT

Why? Couldn't replenish water, dysfunction of muscles and nerves needed to suck in blood/tissue fluid

TICKS INGESTED LETHAL DOSE IN JUST 2 HOURS

Why? Highly potent nature of lotilaner; effects irreversible, lethal

TICKS DIED OF DEHYDRATION

Why? Disruption of salivary glands, key organs ticks need to maintain water balance, pass disease

FEWER TICKS ATTACHED TO TREATED DOGS VS. CONTROLS

Why? Potential disruption of attachment

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.

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

¹Wenger MJ, Kollasch TM, Locklear C, et al. Early onset of pre-lethal effects of lotilaner (Credelio[®]) on *Amblyomma americanum* ticks on experimentally infested dogs. *Parasite Vector*. 2021;14:322.

²Vancova M, Bily T, Simo L, et al. Three-dimensional reconstruction of the feeding apparatus of the tick *Ixodes ricinus* (Acari: Ixodidae): a new insight into the mechanism of blood-feeding. *Nature: Scientific Reports*. 2020;10:165.

³Fourie JJ, Stanneck D, Luus H, et al. Transmission of *Ehrlichia canis* by *Rhipicephalus sanguineus* ticks feeding on dogs and on artificial membranes. *Vet Parasitol*. 2013;197:595.

⁴Companion Animal Parasite Council (CAPC) Guidelines: Rocky Mountain Spotted Fever. Available from <https://capcvet.org/guidelines/rocky-mountain-spotted-fever/>. Accessed March 28, 2021.

⁵Fourie JJ, Evans A, Labuschagne M, et al. Transmission of *Anaplasma phagocytophilum* (Foggie, 1949) by *Ixodes ricinus* (Linnaeus, 1758) ticks feeding on dogs and artificial membranes. *Parasite Vector*. 2019;12:136.

⁶Varloud M, Liebenberg J and Fourie J. Early *Babesia canis* transmission in dogs with 24 h and 8 h of infestation with infected pre-activated male *Dermacentor reticulatus* ticks. *Parasite Vector*. 2018;11:41.

⁷Companion Animal Parasite Council (CAPC) Guidelines: Lyme Disease. Available from <https://capcvet.org/guidelines/lyme-disease/>. Accessed January 5, 2021.



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 (0X) 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:

Elanco US Inc
Greenfield, IN 46140 USA
Credelio.com

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