Rapid action of lotilaner on lone star tick feeding and survival

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Derived from: "Pumping the brakes on tick feeding: Early effects of lotilaner on lone star ticks," presented at VMX 2021.

Practice implication: Novel research has revealed insights about the early effects of lotilaner on the tough-to-kill lone star tick.

The lone star tick is considered the hardest tick to kill for the isoxazoline class of drugs. This is a concern due the fast transmitting nature of diseases that lone star ticks carry, including ehrlichia and Rocky Mountain spotted fever. Additionally, their highly aggressive nature, which includes directly seeking out pets, and their large mouthparts and propensity to appear in clusters make them an additional challenge for pet owners and veterinarians. With the lone star tick spreading from its historical habitat of the Southeastern USA to other parts of the country, having a product that can effectively and quickly kill this troublesome tick will be imperative.[1,2]

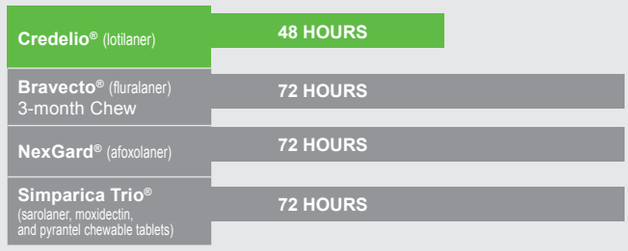
The mechanisms of tick feeding

Unlike fleas and mosquitoes that feed directly from capillaries under the skin, ticks are pool feeders. They use piercing mouthparts to cut through capillaries in order to create a continuous pool of blood to feed from. Because the pool does not have the pressure that a capillary has, ticks have developed a highly sophisticated feeding apparatus that relies on muscles and nerves to generate the sucking power (pump) needed to pull blood and tissues fluid in as well as the spitting power needed push saliva and pathogens into the host.[3]

Filling a knowledge gap with the highly potent, newest isoxazoline, lotilaner

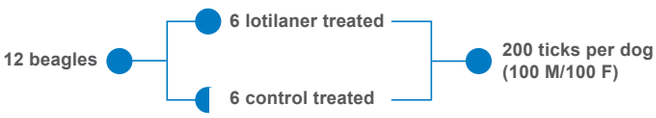
While the current standard for tick product evaluation revolves around efficacy achieved by a specific time point (typically 48 or 72 hours), it does not offer insight to veterinarians about how the drug is affecting the tick during this period, such as its ability feed and transmit diseases. These studies also offer no information about at what time point a tick was exposed to enough drug to be lethal, which is a measure of potency.

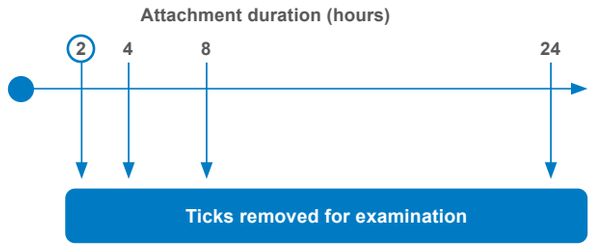
Time at which effectiveness was demostrated (lone star tick)



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

Novel research into how soon lotilaner affects tick feeding and survival[4]





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

Weight loss	Lotilaner-treated ticks lost weight, indicating dehydration as a result of impaired feeding and ability to take in fluids.
Paralysis and loss of coordination	Loss of ability to orient or move toward a positive stimulus. Unable to self-right (ability to flip over) due to neuromuscular impairment.
100% lethality	After only 2 hours of exposure, lotilaner-treated ticks were dead when evaluated 24 hours later.

Key takeaway: The Anti-Feeding Study revealed that lotilaner killed 100% of lone star ticks in treated dogs after 2 hours by paralyzing the feeding machinery needed to sustain life and transmit diseases. This was accomplished using the most difficult tick to kill for the isoxazoline class. An unexpected finding was that fewer ticks attached to lotilaner-treated dogs than control dogs. More research is warranted to investigate why this occurred.

Credelio 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.

Credelio Important Safety Information

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 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 complete safety information, please see Credelio product label or ask your veterinarian.

References: 1. Ticks and tick-borne diseases. University of Missouri Extension. Available at: https://extension.missouri.edu/publications/ipm1032. Accessed March 4, 2021. **2.** Springer YP, et al. *J Med Entomol* 2014;51(2):342–351. **3.** Vancova M, et al. *Scientifi c Reports* 2020;10:165. **4.** Data on file. Elanco. 2020.

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.

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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/pyodermatitis 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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