



Isoxazolines

Craig Datz, DVM, MS, DABVP, DACVN
University of Missouri

Disclosure: Dr. Datz is also affiliated with Royal Canin.

Isoxazolines kill fleas and are indicated for the treatment and prevention of flea infestations, as well as the treatment and control of various tick infestations.¹⁻⁶

OVERVIEW

- ▶ The isoxazoline drug class was launched in the United States in 2014 with afoxolaner, followed shortly by oral fluralaner, sarolaner, topical fluralaner, and lotilaner.

MECHANISM OF ACTION

- ▶ Isoxazolines are absorbed systemically; fleas and ticks must bite the animal to be killed.
 - Isoxazolines work by selective inhibition of GABA- and glutamate-gated chloride channels, leading to hyperexcitation and death of the flea or tick.⁷⁻¹⁰
 - Because GABA channels in mammals have much a lower sensitivity to isoxazolines and mammals lack anion-inhibitory glutamate channels, there is low toxicity potential.⁸
- ▶ For fleas, the onset of action for all products is reported to be 2 to 4 hours, with nearly 100% of fleas killed within 8

hours¹⁻⁶; for ticks, the onset of action for >90% tick control is 4 to 8 hours, although study protocols often assess tick control at 48 hours after administration.¹⁻⁶

CLINICAL APPLICATION

- ▶ Several studies have shown that isoxazolines can reduce the risk for tick-borne disease transmission.
 - Afoxolaner and sarolaner each prevented *Borrelia burgdorferi* infection (ie, Lyme disease) in controlled laboratory studies.^{11,12}
 - In other laboratory studies, afoxolaner, fluralaner, and lotilaner each prevented transmission of *Babesia canis*.¹³⁻¹⁶
 - *Ixodes holocyclus*, the Australian paralysis tick, was controlled by afoxolaner, fluralaner, and sarolaner.^{17,18}
 - In a comparative laboratory study, transmission of *Ehrlichia canis* was prevented by permethrin–imidacloprid and prevented in some but not all dogs by either afoxolaner or fluralaner.¹⁹

ADMINISTRATION & DOSING

- ▶ Fluralaner and lotilaner chewables should be administered with food, whereas afoxolaner and sarolaner may be given with or without food.^{1-3,6}

- ▶ Labeled ages, body weights, and dosing intervals vary (see **Isoxazolines at a Glance**).
 - Collies with the multidrug sensitivity gene (*MDR1* gene, also known as *ABCB1* gene) mutation (ivermectin-sensitive) were treated with up to 10 times the label dose of afoxolaner or 3 times the label dose of fluralaner with no adverse effects noted.^{20,21}
- ▶ Fluralaner has been shown to be well tolerated with concurrent use of milbemycin–praziquantel and deltamethrin collars in dogs and emodepsid–praziquantel in cats.²²⁻²⁴
- ▶ Extra-label use of isoxazolines for other ectoparasites has been reported.
 - In one study of generalized demodicosis in 8 adult dogs, a single dose of fluralaner resulted in elimination of *Demodex canis* mites and resolution of dermatologic signs.²⁵
 - Afoxolaner, sarolaner, and lotilaner at label doses were also shown to be effective in dogs with generalized demodicosis.²⁶⁻²⁹

- In dogs with *Sarcoptes scabiei var canis*, 2 doses of afoxolaner (on days 0 and 28) or sarolaner (on days 0 and 30) or a single dose of fluralaner eliminated mites and resulted in skin improvement within 4 weeks.³⁰⁻³³
- Dogs with ear mites (*Otodectes cynotis*) have been successfully treated with afoxolaner, fluralaner, and sarolaner; topical fluralaner is effective in cats with ear mites.^{28,34,35}

SAFETY & ADVERSE EFFECTS

- ▶ Vomiting, diarrhea, lethargy, and decreased appetite were occasionally observed in safety studies in puppies 8 to 9 weeks old (in both treated and control groups) at 1 time, 3 times, and 5 times the maximum oral label dose and in field studies.^{1-4,6,9,36-38}
- Neurologic signs (eg, tremors, seizures) were noted in approximately 29% of young puppies treated with sarolaner at 1 to 5 times the label dose.³
- Fluralaner topical solution was similarly studied in dogs and cats; other than cosmetic changes at the application sites, no treatment-related adverse effects were observed.^{4,5}
- In the feline field study, neurologic signs were seen with topical fluralaner in 2 of 224 cats⁵; this drug should be used with caution in cats with a history of neurologic disease.⁵
- ▶ Safety in breeding, pregnant, or lactating dogs has not been evaluated for afoxolaner, sarolaner, or lotilaner.^{1,3,6}
- Oral fluralaner was studied at up to 3 times the maximum label dose at 8-week intervals in male and female beagles through breeding, pregnancy, and lactation.
 - No treatment-related effects were observed in the adult dogs or on reproductive performance.
 - In litters from 2 of 10 dams, abnormalities (eg, limb deformity, cleft palate) were noted in some puppies on gross examination.²
- ▶ In uncontrolled, open-label field studies, all drugs were effective in reducing or resolving signs of flea allergy dermatitis in dogs.³⁹⁻⁴³

TABLE

ISOXAZOLINES AT A GLANCE¹⁻⁵

Drug	Species	Product	Minimum Age	Minimum Body Weight	Dosing Interval
Afoxolaner	Dog	Chew	8 weeks	4 lb (1.8 kg)	1 month
Fluralaner	Dog	Chew	6 months	4.4 lb (2 kg)	12 weeks*
Sarolaner	Dog	Chew	6 months	2.8 lb (1.3 kg)	1 month
Lotilaner	Dog	Chew	8 weeks	4.4 lb (2 kg)	1 month
Fluralaner	Dog	Topical solution	6 months	4.4 lb (2 kg)	12 weeks*
Fluralaner	Cat	Topical solution	6 months	2.6 lb (1.2 kg)	12 weeks*

* The dosing interval is every 8 weeks for *Amblyomma americanum* (lone star) ticks.^{2,4}

References

1. Nexgard [package insert]. Duluth, GA: Merial; 2015.
2. Bravecto [package insert]. Madison, NJ: Merck Animal Health; 2014.
3. Simparica [package insert]. Kalamazoo, MI: Zoetis; 2016.
4. Bravecto (fluralaner topical solution) for Dogs [package insert]. Madison, NJ: Merck Animal Health; 2016.
5. Bravecto (fluralaner topical solution) for Cats [package insert]. Madison, NJ: Merck Animal Health; 2016.
6. Credelio [package insert]. Greenfield, IN: Elanco Animal Health; 2018.
7. Shoop WL, Hartline EF, Gould BR, et al. Discovery and mode of action of afoxolaner, a new isoxazoline parasiticide for dogs. *Vet Parasitol*. 2014;201(3-4):179-189.
8. Gassel M, Wolf C, Noack S, Williams H, Ilg T. The novel isoxazoline ectoparasiticide fluralaner: selective inhibition of arthropod γ -aminobutyric acid- and L-glutamate-gated chloride channels and insecticidal/acaricidal activity. *Insect Biochem Mol Biol*. 2014;45:111-124.
9. McTier TL, Chubb N, Curtis MP, et al. Discovery of sarolaner: a novel, orally administered, broad-spectrum, isoxazoline ectoparasiticide for dogs. *Vet Parasitol*. 2016;222:3-11.
10. Rufener L, Danelli V, Bertrand D, Sager H. The novel isoxazoline ectoparasiticide lotilaner (Credelio): a non-competitive antagonist specific to invertebrates γ -aminobutyric acid-gated chloride channels (GABA_{Cl}s). *Parasit Vectors*. 2017;10(1):530.
11. Baker CF, McCall JW, McCall SD, et al. Ability of an oral formulation of afoxolaner to protect dogs from *Borrelia burgdorferi* infection transmitted by wild *Ixodes scapularis* ticks. *Comp Immunol Microbiol Infect Dis*. 2016;49:65-69.
12. Honsberger NA, Six RH, Heinz TJ, et al. Efficacy of sarolaner in the prevention of *Borrelia burgdorferi* and *Anaplasma phagocytophilum* transmission from infected *Ixodes scapularis* to dogs. *Vet Parasitol*. 2016;222:67-72.
13. Beugnet F, Halos L, Larsen D, Labuschagné M, Erasmus H, Fourie J. The ability of an oral formulation of afoxolaner to block the transmission of *Babesia canis* by *Dermacentor reticulatus* ticks to dogs. *Parasit Vectors*. 2014;7:283.
14. Taenzler J, Liebenberg J, Roepke RK, Heckerth AR. Prevention of transmission of *Babesia canis* by *Dermacentor reticulatus* ticks to dogs treated orally with fluralaner chewable tablets (Bravecto). *Parasit Vectors*. 2015;8:305.
15. Taenzler J, Liebenberg J, Roepke RKA, Heckerth AR. Prevention of transmission of *Babesia canis* by *Dermacentor reticulatus* ticks to dogs after topical administration of fluralaner spot-on solution. *Parasit Vectors*. 2016;9:234.
16. Cavalleri D, Murphy M, Seewald W, Drake J, Nanchen S. Two randomized, controlled studies to assess the efficacy and safety of lotilaner (Credelio) in preventing *Dermacentor reticulatus* transmission of *Babesia canis* to dogs. *Parasit Vectors*. 2017;10:520.
17. Packianathan R, Hodge A, Bruellke N, Davis K, Maeder S. Comparative speed of kill of sarolaner (Simparica) and afoxolaner (NexGard) against induced infestations of *Ixodes holocyclus* on dogs. *Parasit Vectors*. 2017;10:98.
18. Fisara P, Webster M. A randomized controlled trial of the efficacy of orally administered fluralaner (Bravecto) against induced *Ixodes holocyclus* (Australian paralysis tick) infestations on dogs. *Parasit Vectors*. 2015;8:257.
19. Jongejan F, Crafford D, Erasmus H, Fourie JJ, Schunack B. Comparative efficacy of oral administered afoxolaner (NexGard) and fluralaner (Bravecto) with topically applied permethrin/imidacloprid (Advantix) against transmission of *Ehrlichia canis* by infected *Rhipicephalus sanguineus* ticks to dogs. *Parasit Vectors*. 2016;9(1):348.
20. Walther FM, Paul AJ, Allan MJ, Roepke RK, Nuernberger MC. Safety of fluralaner, a novel systemic antiparasitic drug, in MDR1(-/-) collies after oral administration. *Parasit Vectors*. 2014;7:86.
21. European Medicines Agency Committee for Medicinal Products for Veterinary Use. CVMP assessment report for NexGard (EMA/V/C/ 002729/0000). http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/veterinary/002729/WC500164068.pdf. Published December 12, 2013. Accessed March 1, 2018.
22. Walther FM, Fisara P, Allan MJ, Roepke RK, Nuernberger MC. Safety of concurrent treatment of dogs with fluralaner (Bravecto) and milbemycin oxime-praziquantel. *Parasit Vectors*. 2014;7:481.
23. Walther FM, Fisara P, Allan MJ, Roepke RK, Nuernberger MC. Safety of the concurrent treatment of dogs with Bravecto (fluralaner) and Scalibor protector-band (deltamethrin). *Parasit Vectors*. 2014;7:105.
24. Walther FM, Allan MJ, Roepke RK. Safety of concurrent treatment of cats with fluralaner and emodepsid-praziquantel. *Parasit Vectors*. 2016;9:322.
25. Fourie JJ, Liebenberg JE, Horak IG, Taenzler J, Heckerth AR, Frénais R. Efficacy of orally administered fluralaner (Bravecto) or topically applied imidacloprid/moxidectin (Advocate) against generalized demodicosis in dogs. *Parasit Vectors*. 2015;8:187.
26. Beugnet F, Halos L, Larsen D, de Vos C. Efficacy of oral afoxolaner for the treatment of canine generalized demodicosis. *Parasite*. 2016;23:14.
27. Chavez F. Case report of afoxolaner treatment for canine demodicosis in four dogs naturally infected with *Demodex canis*. *J Appl Res Vet Med*. 2016;14(2):123-127.
28. Six RH, Becskei C, Mazaleski MM, et al. Efficacy of sarolaner, a novel oral isoxazoline, against two common mite infestations in dogs: *Demodex* spp and *Otodectes cynotis*. *Vet Parasitol*. 2016;222:62-66.
29. Snyder DE, Wiseman S, Liebenberg JE. Efficacy of lotilaner (Credelio), a novel oral isoxazoline against naturally occurring mange mite infestations in dogs caused by *Demodex* spp. *Parasit Vectors*. 2017;10:532.
30. Beugnet F, de Vos C, Liebenberg J, Halos L, Larsen D, Fourie J. Efficacy of afoxolaner in a clinical field study in dogs naturally infested with *Sarcoptes scabiei*. *Parasite*. 2016;23:26.
31. Becskei C, De Bock F, Illambas J, et al. Efficacy and safety of a novel oral isoxazoline, sarolaner (Simparica), for the treatment of sarcoptic mange in dogs. *Vet Parasitol*. 2016;222:56-61.
32. Taenzler J, Liebenberg J, Roepke RKA, Frénais R, Heckerth AR. Efficacy of fluralaner administered either orally or topically for the treatment of naturally acquired *Sarcoptes scabiei* var *canis* infestation in dogs. *Parasit Vectors*. 2016;9:392.
33. Romero C, Heredia R, Pineda J, et al. Efficacy of fluralaner in 17 dogs with sarcoptic mange. *Vet Dermatol*. 2016;27(5):353-e88.
34. Carithers D, Crawford J, de Vos C, Lotriet A, Fourie J. Assessment of afoxolaner efficacy against *Otodectes cynotis* infestations of dogs. *Parasit Vectors*. 2016;9:365.
35. Taenzler J, de Vos C, Roepke RKA, Frénais R, Heckerth AR. Efficacy of fluralaner against *Otodectes cynotis* infestations in dogs and cats. *Parasit Vectors*. 2017;10:30.
36. Drag M, Saik J, Harriman J, Larsen D. Safety evaluation of orally administered afoxolaner in 8-week-old dogs. *Vet Parasitol*. 2014;201(3-4):198-203.
37. Walther FM, Allan MJ, Roepke RKA, Nuernberger MC. Safety of fluralaner chewable tablets (Bravecto), a novel systemic antiparasitic drug, in dogs after oral administration. *Parasit Vectors*. 2014;7:87.
38. Kuntz EA, Kammanadiminti S. Safety evaluation of lotilaner in dogs after oral administration as flavoured chewable tablets (Credelio). *Parasit Vectors*. 2017;10(1):538.
39. Becskei C, De Bock F, Illambas J, Mahabir SP, Farkas R, Six RH. Efficacy and safety of a novel oral isoxazoline, sarolaner (Simparica) in the treatment of naturally occurring flea and tick infestations in dogs presented as veterinary patients in Europe. *Vet Parasitol*. 2016;222:49-55.
40. Dryden MW, Canfield MS, Kalosy K, et al. Evaluation of fluralaner and afoxolaner treatments to control flea populations, reduce pruritus and minimize dermatologic lesions in naturally infested dogs in private residences in west central Florida USA. *Parasit Vectors*. 2016;9:365.
41. Fisara P, Shipstone M, von Berkly A, von Berkly J. A small-scale open-label study of the treatment of canine flea allergy dermatitis with fluralaner. *Vet Dermatol*. 2015;26(6):417-420.
42. Crosaz O, Chapelle E, Cochet-Faivre N, Ka D, Hubinois C, Guillot J. Open field study on the efficacy of oral fluralaner for long-term control of flea allergy dermatitis in client-owned dogs in Ile-de-France region. *Parasit Vectors*. 2016;9:174.
43. Karadzovska D, Chappell K, Coble S, et al. A randomized, controlled field study to assess the efficacy and safety of lotilaner flavoured chewable tablets (Credelio) in eliminating fleas in client-owned dogs in the USA. *Parasit Vectors*. 2017;10:528.