

**READ THE LABEL**

Sarolaner is highly effective against fleas and ticks on dogs when dosed once monthly.

FOCUS ON

Sarolaner Use in Dogs

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Sarolaner is an ectoparasiticide that is effective against fleas and ticks on dogs when administered once a month. This article covers its development, mechanism of action, dosage, safety, and efficacy against 6 common species of ectoparasites. It also compares the safety and efficacy of sarolaner with those of 2 other popular ectoparasiticides in the same class: afoxolaner and fluralaner.

DEVELOPMENT

Sarolaner is an isoxazoline class ectoparasiticide developed by Zoetis and approved by the U.S. Food and Drug Administration (FDA) in 2016 (Simparica, zoetis.com).¹ Its development followed that of other isoxazoline compounds, such as afoxolaner (NexGard, boehringer-ingelheim.com) and fluralaner (Bravecto, merck-animal-health-usa.com), and preceded that of lotilaner (Credelio, elanco.us). To optimize drug potency and pharmacokinetic properties, Zoetis designed sarolaner from an azetidine-based isoxazoline lead.² During development, the S-enantiomer of sarolaner was found to have long-lasting plasma concentrations (half-life of 11 to 12 days) and greater in vitro flea and tick potency than fluralaner and afoxolaner.³ Initial clinical trials showed that it maintained an effective flea and tick kill rate and a rapid kill speed (>98% within 48 hours of infestation) for 1 month.²⁻⁴

MECHANISM OF ACTION

Isoxazoline ectoparasiticides overstimulate the arthropod nervous system, resulting in arthropod convulsions and death.⁵ Specifically, these drugs inhibit arthropod chloride-gated gamma aminobutyric acid (GABA) and glutamate channels in the neuromuscular junction.^{3,5} Unlike mammalian glutamate receptors, which are solely excitatory, invertebrate glutamate receptors can be either excitatory or inhibitory.⁵ Isoxazoline ectoparasiticides specifically target these insect-specific inhibitory receptors.⁵ Chloride-gated channels are also bound by isoxazolines with a greater affinity in arthropods than in mammals.⁵ These 2 unique features of arthropod inhibitory receptors make them an ideal target for ectoparasiticides; targeting arthropod-specific receptors greatly helps spare the mammalian patient from unwanted side effects.⁵ In addition, isoxazolines appear to bind GABA receptors at a novel site compared with other GABA-inhibiting antiparasitics (e.g., phenylpyrazoles such as fipronil).⁵ To that end, isoxazolines may be effective against arthropods resistant to older ectoparasiticides.⁵

DOSAGE

Sarolaner is designed to provide dogs with sustained protection against fleas and ticks when given orally once a month.²⁻⁴ As opposed to topical ectoparasiticides,

which may be unknowingly dosed onto the fur, licked off, or washed off, oral formulations can perform more consistently throughout the month.⁴ In addition, oral dosing greatly decreases drug exposure of humans and other animals.⁴

Initial dosing studies conducted by Zoetis evaluated the efficacy of sarolaner doses ranging from 0.625 mg/kg to 5 mg/kg.²⁻⁴ A series of 3 studies were used to evaluate the efficacy of sarolaner against fleas and several common species of tick: *Ctenocephalides felis felis* (cat flea), *Amblyomma americanum* (lone star tick), *Amblyomma maculatum* (Gulf Coast tick), *Dermacentor reticulatus* (ornate cow tick), *Dermacentor variabilis* (American dog tick), *Rhipicephalus sanguineus* (brown dog tick), and *Ixodes scapularis* (deer tick).⁴ These studies indicated that fleas were more sensitive to sarolaner than all species of ticks and that the parasites most resistant to sarolaner were *Amblyomma* spp. ticks.⁴ Using *A. maculatum* ticks to test appropriate dosing, they found that a dose of 1 mg/kg lost efficacy around day 28 of treatment, when the kill rate dropped below 90% at 48 hours after reinfestation. A higher dose of 2 mg/kg produced a superior kill rate of >93% at 48 hours after reinfestation for up to 35 days.⁴ For these reasons, the appropriate monthly dose of sarolaner for flea and tick control in dogs was determined to be a minimum of 2 mg/kg. Simparica comes as flavored, chewable tablets and is available in a variety of sizes: 5, 10, 20, 40, 80, and 120 mg.⁶

SAFETY

Several clinical trials funded by Zoetis published shortly after drug approval showed impressive results concerning safety and incidence of adverse effects in dogs.^{3,4,7-9} Most notably, a series of randomized, controlled studies conducted in the United States, Europe, and Australia evaluated 806 dogs (not including patients withdrawn from the studies) receiving a 90-day course of sarolaner, dosed at 2 to 4 mg/kg every 30 days.⁷⁻⁹ The dogs were enrolled through veterinary practices that covered a wide geographic range and included dogs of any breed but excluded pregnant or lactating dogs.⁷⁻⁹ Across all studies, no treatment-related adverse events or side effects associated with sarolaner were found, and observed clinical signs were considered consistent with allergies or sporadic conditions common in dogs.⁷⁻⁹ Serious adverse events were rare and included the following in 1 dog each: worsening of pre-existing renal disease, sudden death from dilated cardiomyopathy,⁷ death

from septicemia, death from acute peritonitis secondary to pyometra,⁸ worsening of pre-existing heart disease, severe arthritis leading to euthanasia, and congenital pulmonary arterial hypoplasia.⁹ None of these conditions were considered likely to be treatment-related, although the conflict of interest associated with all studies being funded by Zoetis is acknowledged. In addition, no adverse drug reactions were noted, despite some dogs receiving concomitant medications such as corticosteroids, antimicrobials, and other parasite preventives, although the exact number of dogs receiving these medications is not described.⁷

These initial reports contrast with recent media coverage concerning neurologic abnormalities observed in dogs receiving isoxazoline ectoparasiticides such as sarolaner, afoxolaner, fluralaner, and lotilaner.^{10,11} In September 2018, the FDA released an alert warning veterinarians and pet owners that animals receiving isoxazoline antiparasitics had been experiencing muscle tremors, ataxia, and seizures.¹⁰ During safety studies conducted during sarolaner drug approval, some 8-week-old beagles receiving 3 times and 5 times the upper end of the recommended dose (i.e., 12 mg/kg and 20 mg/kg, respectively) every 28 days for 10 doses exhibited seizures, tremors, and ataxia, which mostly resolved by the time the dogs reached 6 months of age, except for 1 dog with abnormal head coordination after dose 6, which led to the drug being approved only for dogs 6 months of age and older.¹ In a field effectiveness study of 315 dogs, 1 dog exhibited lethargy, ataxia, elevated third eyelids, and inappetence 1 day after receiving sarolaner concurrently with ivermectin/pyrantel pamoate; these signs resolved within 24 hours.¹ The prevalence of and potential risk factors for neurologic adverse effects are currently unknown, but the FDA maintains that isoxazolines are still safe for most animals.^{10,11} Additional research is needed to further characterize the nature and prevalence of these adverse neurologic events, and the FDA is asking manufacturers to revise their product labels to include potential neurologic side effects and cautioning veterinarians to use discretion when prescribing drugs in this class.^{10,11}

EFFICACY

Multiple randomized trials conducted by Zoetis have found sarolaner to be highly effective at eliminating and preventing flea and tick infestations.^{3,4,7-9,12,13}

Fleas

Sarolaner was found to kill adult *C. felis felis* fleas on dogs within 4 hours of administration and to have a 100% kill rate against pre-existing experimental infestations within 12 hours.¹² When challenged with re-infestation, sarolaner maintained a kill rate of $\geq 98\%$ within 8 hours of exposure to new fleas for 28 days.¹² In a simulated home environment already contaminated with flea eggs, sarolaner treatment reduced flea counts by $>95\%$ at 14 days and eradicated the infestation after 2 doses (2 months) because of its ability to kill fleas before they could lay eggs.¹²

Ticks

Sarolaner is also highly effective against ticks. A 2 mg/kg dose of sarolaner achieved a $>99\%$ kill rate against pre-existing infestations of *A. americanum*, *A. maculatum*, *D. variabilis*, *R. sanguineus*, and *I. scapularis* ticks after 48 hours.¹³ The same dose maintained a kill rate of $>96\%$ after 48 hours against weekly re-infestations for 35 days.¹³ This rapid kill speed is significant because these tick species are common vectors of bacterial diseases in the United States; *Rickettsia rickettsii* (Rocky Mountain spotted fever) is transmitted by *Dermacentor* ticks, *Borrelia burgdorferi* (Lyme disease) by *Ixodes* ticks, and *Ehrlichia* and *Babesia* by several tick species including those of the genera *Dermacentor*, *Amblyomma*, and *Rhipicephalus*.¹³ Typically, these diseases are transmitted after a tick has been attached to its host for 24 to 48 hours, meaning that transmission may be interrupted by rapid kill.¹³⁻¹⁶ Rapid kill of ticks is especially important, given the rising incidence and spread of tick-borne diseases in recent years.¹³⁻¹⁵ In addition, although not approved for these uses, sarolaner has been found to effectively treat mite infestations (caused by *Demodex*, *Otodectes*, and *Sarcoptes*) and to prevent transmission of *Babesia canis* from experimentally infected ticks.¹⁷⁻¹⁹

Comparison With Other Products

Compared with other isoxazoline ectoparasiticides, sarolaner seems to have the greatest efficacy throughout its dosing interval.¹⁴⁻¹⁶ Note, however, that most available studies evaluating sarolaner were funded by Zoetis, so this source of potential bias must be considered when evaluating the results of many of the studies presented in this article.

Fluralaner

A 2016 study conducted by Zoetis comparing sarolaner with fluralaner (an isoxazoline-class drug labeled for oral administration every 12 weeks)¹⁴ found a similar initial kill speed against *R. sanguineus* ticks (all ticks killed within 24 hours) for both agents. However, efficacy of sarolaner given monthly for 3 months was superior to that of a single treatment with fluralaner.¹⁴ Although a single dose of fluralaner is labeled for 84 days, efficacy against re-infestation with *R. sanguineus* ticks began to decrease approximately 44 days after dosing (day 58 efficacy = 93.5%; day 74 efficacy = 47.9%).¹⁴ By comparison, monthly dosing with sarolaner maintained a kill rate of $>98\%$ at 24 hours after re-infestation for 90 days, other than at day 74 when efficacy was 83.8%.¹⁴ In a similar study design but with fleas (*C. felis*), at 8 hours after re-infestation, flea counts were significantly lower at 74 and 90 days after treatment with sarolaner than with fluralaner; however, flea counts did not differ significantly by 12 hours after re-infestation at any time point ($>98\%$ efficacy for both agents at 12 hours through day 90).²⁰

Afoxolaner

When sarolaner was compared with afoxolaner in dogs experimentally infested with *A. americanum* ticks, sarolaner kill speed was faster and effect duration was more reliable.¹⁶ Similarly, sarolaner kill speed was faster than that of afoxolaner against *C. felis* fleas throughout the dosing interval.²¹ Another study conducted in 2016, not associated with Zoetis, compared the immediate kill speed of sarolaner with that of fluralaner, afoxolaner, and imidacloprid plus permethrin (K9 Advantix, bayerdvm.com) against *R. sanguineus* (sensu lato) ticks.¹⁵ A greater than 90% efficacy threshold was achieved by sarolaner, fluralaner, and afoxolaner after 8 hours; onset of activity was 4 hours for sarolaner and fluralaner and 8 hours for afoxolaner.¹⁵ For imidacloprid plus permethrin, onset of activity was rapid (2 hours) but efficacy was significantly lower (81% kill rate at 48 hours).¹⁵

Lotilaner

We found no studies reported in the literature that directly compared the efficacy of sarolaner with that of lotilaner.

SAROLANER IN CATS

Although the focus of this article is on dogs, it is worth noting that a topical product containing selamectin and

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sarolaner (Revolution Plus, zoetisus.com) is labeled for use in cats in the United States. This product has reportedly excellent efficacy against fleas and ticks on cats^{22,23} and is generally well tolerated. Drug approval studies reported the primary adverse effects as anorexia, lethargy, skin lesions, diarrhea, pruritus, vomiting, and alopecia at the application site.²⁴

SUMMARY

Sarolaner is an isoxazoline-class ectoparasiticide that is highly effective against fleas and ticks on dogs when dosed once monthly. The oral route of administration provides consistent performance as well as decreased drug exposure for clients and other animals. Sarolaner works by causing overstimulation of the arthropod nervous system, a mechanism of action shared by other drugs in the isoxazoline class.

When sarolaner is used according to label guidelines, adverse effects noted during drug approval were minimal, but postapproval monitoring has revealed reports of dogs experiencing neurologic signs (ataxia, tremors, seizures) after receiving sarolaner and other isoxazoline compounds, causing the FDA to release a warning to veterinarians and pet owners. Additional research is needed to determine the frequency and severity of these adverse effects in dogs. **TVP**

 To see the references for this article, please visit todaysveterinarypractice.com.

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