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REVIEW ARTICLE

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Current review of isoxazoline ectoparasiticides used in veterinary medicine

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Abstract

The isoxazolines are a novel class of ectoparasiticides with potent inhibitory activity on glutamate- and gamma-aminobutyric acid-gated chloride channel located in nervous system of invertebrates. In recent years, studies have been performed to evaluate the efficacy and safety of isoxazolines against various types of ectoparasites, including fleas, ticks, and mites. As more single and combined isoxazoline products have been approved by the United States Food and Drug Administration and European Medicines Agency, a more comprehensive understanding of isoxazolines becomes essential for veterinary clinical practitioners. This article provides a complete review of isoxazolines with respect to pharmacodynamics, pharmacokinetics, ectoparasiticidal efficacy, and safety, which will provide veterinarians information to allow them to make the best choice of ectoparasiticide for their clients' specific needs.

KEYWORDS
afoxolaner, ectoparasiticide, fluralaner, isoxazoline, lotilaner, sarolaner

1 | INTRODUCTION

Ectoparasites such as fleas, ticks, and mites are the source of several important systemic and local diseases and conditions, including direct damage to the skin barrier through parasitic feeding, tissue invasion, and hypersensitivity reactions, in addition to their function as vectors and reservoirs for significant pathogenic microorganisms such as *Bartonella*, *Rickettsia*, *Borrelia*, *Anaplasma*, *Ehrlichia*, and *Babesia* (Breitschwerdt et al., 2010; Dantas-Torres et al., 2012; Durden et al., 2005).

Ectoparasites are an important concern for health status of animals, as well as prevention of zoonotic diseases. A wide array of compounds are currently on the market for treatment of ectoparasites for animals, with various modes of action that target arthropod-specific ligand-gated ion channels and G protein-coupled receptors (Hsu & Martin, 2013; Taylor, 2001). Afoxolaner, fluralaner, sarolaner, and lotilaner are members of isoxazolines, a novel class of insecticide/acaricide with potent inhibitory activity on glutamate- and gamma-aminobutyric acid (GABA)-gated chloride channels in invertebrates, and generally have a high safety margin in vertebrates (Ozoe et al., 2010). These novel ectoparasiticides are currently marketed as oral canine products with FDA-approved labels against fleas, black-legged ticks, American dog ticks, brown dog ticks, and the lone star ticks. Fluralaner is additionally available in topical spot-on form for both dogs and cats. Beyond their FDA-approved usage against common fleas and ticks, all four marketed isoxazoline products have experimentally and clinically demonstrated efficacy in the treatment of mite infestations (Becskei, De Bock, Illambas, Cherni, et al., 2016; Carithers et al., 2016; Six et al., 2016; Snyder et al., 2017; Taenzler et al., 2016).

2 | PHARMACODYNAMICS

2.1 | Mechanism of action

Gamma-aminobutyric acid is the primary inhibitory neurotransmitter within the central nervous system (CNS) of vertebrates (Gassel et al., 2014; Krnjevic, 2004; Krnjević, 2010) and in both the CNS

and peripheral nervous system of invertebrates (Lunt, 1991). GABA receptors are members of the Cys-loop superfamily linked to chloride channels (Sine & Engel, 2006). They have five transmembrane subunits, each consisting of four transmembrane helices. Current research indicates the helical subunits are the target of isoxazolines, though the precise inhibition site has not yet been identified (Weber et al., 2016). Variation in arrangement and substitution of these subunits is ultimately responsible for the different pharmacological action of the drug targeting the receptor and the degree of safety in the use of a particular isoxazoline in vertebrates. A study utilizing fly and rat models has demonstrated a significant preference of isoxazolines for invertebrate GABA receptors over vertebrates (Gassel et al., 2014). The glutamate-gated chloride channel, a ligand-gated ion channel unique to invertebrates and the target of macrocyclic lactones, is also targeted by isoxazolines to a lesser degree (Gassel et al., 2014). GABA and glutamate exert their actions by stimulating chloride influx on the postsynaptic tissue, causing hyperpolarization, preventing the generation of an action potential. Isoxazolines inhibit this modulatory action by binding to the postsynaptic tissue, preventing chloride influx leading to depolarization/hyperexcitation, paralysis, and death of the parasite (Gassel et al., 2014; Ozoe et al., 2010).

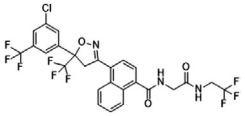
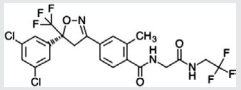
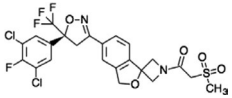
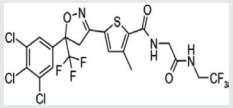
3 | APPROVED USAGE OF ISOXAZOLINES

These isoxazoline ectoparasiticides are currently marketed under the trade names NexGard® (afoxolaner, Boehringer Ingelheim), Bravecto® (fluralaner, Merck), Simparica® (sarolaner, Zoetis), and Credelio® (lotilaner, Elanco), as well as combination drugs NexGard Spectra®(afoxolaner and milbemycin oxime, Boehringer Ingelheim), Bravecto Plus®(fluralaner and moxidectin, Merck), Simparica Trio®(sarolaner, moxidectin, and pyrantel, Zoetis), and Revolution Plus® (selamectin and sarolaner, Zoetis) (Tables 1 and 2). Among the isoxazoline products with single active pharmaceutical ingredient, most products contain drugs formulated as chewable tablets for treatment and prevention of fleas (*Ctenocephalides felis*) infestations and control of common types of ticks in dogs in various countries, including black-legged ticks (*Ixodes scapularis*), American dog ticks (*Dermacentor variabilis*), brown dog ticks (*Rhipicephalus sanguineus*), and lone star ticks (*Amblyomma americanum*) in the USA and Canada (Canada, 2014a, 2014b, 2016, 2017, 2018, 2020b; FDA, 2014, 2018a, 2018b; Six et al., 2016); ornate cow tick (*D. reticulatus*), castor bean tick (*I. ricinus*), Hedgehog tick (*I. hexagonus*), and brown dog tick in Member States of European Union (EU) (EMA, 2013, 2014, 2015a, 2017); Australian paralysis ticks (*I. holocyclus*), brown dog tick, and Asian longhorned tick (*Haemaphysalis longicornia*) in Australia (APVMA, 2014, 2015, 2016, 2018a, 2018b, 2018c); and Asian longhorned tick in New Zealand (ACVM, 2014a, 2014b, 2015a, 2016). Other than common tick species, sarolaner has shown additional efficacy against Gulf Coast ticks (*Amblyomma maculatum*) in dogs (FDA, 2016b). In addition, most isoxazolines with single active substance are approved by EMA for treatment of demodicosis, scabies, and ear mite infestations (Table 1). Fluralaner differs from the other three isoxazolines with prolonged duration up to 12 weeks, which is three times longer than afoxolaner, sarolaner, and lotilaner (FDA, 2014). Fluralaner is also available as a topical solution for both dogs and cats; in cats, it is for the treatment and prevention of fleas and control of black-legged ticks (FDA, 2016a). Lotilaner has been approved by EMA as chewable tablets for treatment of fleas and ticks (castor bean tick) in cats (EMA, 2017). As for other detailed information of approved usage, for example, minimum dose and age of animal, please refer to Tables 1 and 2.

4 | PHARMACOKINETICS

Pharmacokinetic parameters of currently available isoxazolines are summarized in Table 3. Oral isoxazolines have varied bioavailability ranging from 8.4% to 100% with an average plasma half-life of ~2 weeks (Kilp et al., 2014; Letendre et al., 2014; McTier et al., 2016), except for lotilaner that possesses the longest plasma half-life of ~30 days in both dogs and cats (Toutain et al., 2017, 2018). It is interesting to note that, although, lotilaner has the longest plasma half-life among isoxazolines, which leads to a moderate degree of accumulation (Kuntz & Kammanadiminti, 2017). Its recommended oral dosing interval is the same as afoxolaner and sarolaner of 4 weeks (Table 1). Studies of a prolonged dosing interval (for instance, 8–12 weeks) of lotilaner are suggested to explore sustained efficacy longer than one month. Feeding of the target animal plays a critical role in the pharmacokinetics of lotilaner, especially bioavailability, which is decreased from 82% to 24% when administered to fasted dogs, and 100% to 8.4% in fasted cats (Toutain et al., 2017, 2018). Thus, it is strongly recommended to provide wet or dry food with lotilaner for an effective treatment and prevention of fleas and control of ticks. On the contrary, the plasma concentration of afoxolaner does not appear to be affected by food with a high bioavailability of 74% (Letendre et al., 2014). Isoxazolines have a high degree of plasma protein binding (≤99.9%), indicating that the clearance is likely largely hepatic rather than renal (Kilp et al., 2014; Letendre et al., 2014; McTier et al., 2016; Toutain et al., 2017, 2018). The average volume of distribution (Vss) has been determined to be ~3 L/kg for afoxolaner (Letendre et al., 2014), fluralaner (Kilp et al., 2014, 2016), and sarolaner (McTier et al., 2016), whereas lotilaner has a higher Vss value of ~6 L/kg, which implies a higher distribution into adipose tissue than other isoxazolines (Toutain et al., 2017, 2018). Besides moderate to high distribution, low clearance rate (0.3% of canine daily hepatic blood flow) of isoxazolines is another factor that contributes to the prolonged plasma half-life of isoxazolines (Kilp et al., 2014, 2016; Letendre et al., 2014; McTier et al., 2016; Toutain et al., 2017, 2018). Overall, isoxazolines are highly lipid-soluble and are readily absorbed, particularly with food, and have a persistent efficacy.

TABLE 1 Approved usage of currently available isoxazoline ectoparasiticides with single active substance for dogs and cats in the USA, European Union (EU), Canada, Australia, and New Zealand (NZ)

Drug (trade name, company)	Route of dose (species)	Minimum dose (frequency)	US-approved use against:	EU-approved use against:	Canada-approved use against:	Australia-approved use against:	NZ-approved use against:
Afoxolaner (NexGard®, Boehringer Ingelheim) 	Oral chewable (canine) 8 weeks of age+	2.5 mg/kg (once per month)	Flea, black-legged tick, American dog tick, brown dog tick, lone star tick prevention of *B. burgdorferi* (FDA, 2018a)	Flea, ornate cow tick, castor bean tick, Hedgehog tick (*Ixodes hexagonus*), brown dog tick *Demodex canis* *Sarcoptes scabiei* (EMA, 2013)	Flea, black-legged tick, American dog tick, lone star tick Reduction of *B. burgdorferi* (Canada, 2014a)	Flea, Australian paralysis ticks(*I. holocyclus*), brown dog tick, Asian longhorned ticks(*Haemaphysalis longicornia*) *Demodex* spp. *Sarcoptes scabiei* *Otodectes cynotis* (APVMA, 2014)	Flea, Asian longhorned ticks(*Haemaphysalis longicornia*) (ACVM, 2014a)
Fluralaner (Bravecto®, Merck) 	Oral chewable (canine) Topical (canine and feline) 8 weeks to 6 months of age+	Dogs: Oral: 25 mg/kg (12 weeks) Topical: 25 mg/kg (12 weeks) Cats: Topical: 40 mg/kg (12 weeks)	Dogs (topical and oral): flea, black-legged tick, American dog tick, brown dog tick, lone star tick[a] (FDA, 2014, 2016a) Cats (topical): Flea, black-legged tick, American dog tick[a] (FDA, 2016a)	Dogs (oral): flea, ornate cow tick, castor bean tick, American dog tick, brown dog tick[a] *Demodex canis* *Sarcoptes scabiei* Dogs (topical): flea, ornate cow tick, castor bean tick, brown dog tick *Demodex canis* *Sarcoptes scabiei* Cats (topical): Flea, castor bean tick, *Otodectes cynotis* (EMA, 2014)	Dogs (topical and oral): flea, black-legged tick, American dog tick, brown dog tick (Canada, 2014b, 2018) Cats (topical): Flea, black-legged tick[a], American dog tick[a] (Canada, 2017)	Dogs (oral): Flea, Australian paralysis ticks, brown dog tick[a], Asian longhorned ticks[a] *Demodex* spp. *Sarcoptes scabiei* *Otodectes cynotis* (APVMA, 2015) Dogs (topical): Flea, Australian paralysis ticks, brown dog tick *Demodex* spp. *Sarcoptes scabiei* *Otodectes cynotis* (APVMA, 2018a) Cats (topical): Flea, Australian paralysis ticks *Otodectes cynotis* (APVMA, 2018b)	Dogs (oral): Flea, Asian longhorned ticks *Demodex* spp. *Sarcoptes scabiei* *Otodectes cynotis* (ACVM, 2014b) Dogs (topical): Flea, Asian longhorned ticks *Sarcoptes scabiei* *Otodectes cynotis* (ACVM, 2016) Cats (topical): Flea, Asian longhorned ticks (ACVM, 2016)
Sarolaner (Simparica®, Zoetis) 	Oral chewable (canine) 8 weeks to 6 months of age+	2 mg/kg (once per month or every 5 weeks)	Flea, American dog tick, brown dog tick, lone star tick, Gulf coast tick, black-legged tick(FDA, 2016b)	Flea, ornate cow tick, castor bean tick, Hedgehog tick, brown dog tick *Demodex canis* *Sarcoptes scabiei* *Otodectes cynotis* (EMA, 2015a)	Flea, American dog tick, brown dog tick, lone star tick, Gulf coast tick, black-legged tick(Canada, 2016)	Flea, Australian paralysis ticks, brown dog tick, Asian longhorned ticks *Demodex* spp. *Sarcoptes scabiei* *Otodectes cynotis* (APVMA, 2016)	Flea, Asian longhorned ticks *Demodex* spp. *Sarcoptes scabiei* *Otodectes cynotis* (ACVM, 2015a)
Lotilaner (Credelio®, Elanco) 	Oral chewable (canine and feline) 8 weeks of age+	Dogs: 20 mg/kg Cats: 6 mg/kg (once per month)	Dogs: Flea, black-legged tick, American dog tick, brown dog tick, lone star tick(FDA, 2018b)	Dogs: Flea, ornate cow tick, castor bean tick, Hedgehog tick, brown dog tick Cats: Flea, castor bean tick(EMA, 2017)	Flea, black-legged tick, American dog tick, brown dog tick, lone star tick(Canada, 2020b)	Flea, Australian paralysis ticks, brown dog tick, Asian longhorned ticks (APVMA, 2018c)	Not approved yet

[a]Effective for 8 weeks.

TABLE 2 Approved combination products of isoxazoline ectoparasiticides in the USA, EU, Canada, Australia, and New Zealand

Combination drug (trade name, company)	Approved countries	References
Afoxolaner and milbemycin oxime (NexGard Spectra®, Boehringer Ingelheim) Chewable tablets(canine)	Member state of EU, Canada, Australia, New Zealand	EMA (2015b), Canada (2019a), APVMA (2017), ACVM (2015b)
Fluralaner and moxidectin (Bravecto Plus®, Merck) Topical solution(feline)	US, Member state of EU, Australia, New Zealand	FDA (2019a), EMA (2018), APVMA (2020a), ACVM (2017)
Sarolaner, moxidectin and pyrantel (Simparica Trio®, Zoetis) Chewable tablets(canine)	US, Member state of EU, Canada, Australia	FDA (2020), EMA (2019), Canada (2020a), APVMA (2020b)
Sarolaner and selamectin (Revolution Plus®, Zoetis) Topical solution(feline)	US, Canada, Australia, New Zealand	FDA (2018c), Canada (2019b), APVMA (2020b)

5 | ECTOPARASITICIDAL EFFECTS

5.1 | Ticks

Tick infestations have been implicated in the transmission of rickettsial diseases, babesiosis, theileriosis, anaplasmosis, Lyme disease, and ehrlichiosis, along with a number of bacterial, viral, and other pathogens (Breitschwerdt et al., 2010; Dantas-Torres et al., 2012; Durden et al., 2005; Ozoe et al., 2010; Pantchev et al., 2015). Isoxazolines have been approved by the USA and Canada against multiple tick species as indicated above and have been demonstrated to be effective against additional species experimentally (Table 4), a majority of which are also registered as ectoparasiticides for veterinary use in EU, Australia, and New Zealand.

Several efficacy studies have been performed with a number of common tick species (Table 5), including *Dermacentor variabilis* (American dog ticks, all four products), *Ixodes scapularis* (deer ticks, all four products), *Ixodes Ricinus* (Castor bean ticks, all four products), *Amblyomma americanum* (lone star ticks, all four products), *Amblyomma maculatum* (Gulf Coast ticks, sarolaner), and *R. sanguineus* (brown dog ticks, all four products). Variations in efficacy exist among the drugs and the different genera of ticks. While the efficacy within the first 24 h is variable after treatment with the US

TABLE 3 Pharmacokinetic (PK) parameters of currently available isoxazoline ectoparasiticides for dogs and cats

Pharmacokinetics						
Drug	**Bioavailability**	**$T_{1/2}$**	**T_{max}**	**C_{max}**	**V_d**	**Clearance**
Afoxolaner: canine systemic	74%	~16 days	2–6 h	2.5 mg/kg PO: ~1.7 μg/ml	V_{ss} = 2.68L/kg (1 mg/kg IV)	4.95 ml/h/kg (1 mg/kg IV)
Fluralaner: canine oral	26% (25 mg/kg PO)	12–15 days	1 day	Fasted: 1.6 μg/ml Fed: 3.4 μg/ml (25 mg/kg PO)	V_z = 3.1L/kg (12.5 mg/kg IV)	5.8 ml/h/kg (12.5 mg/kg IV)
Fluralaner: canine topical	~25%	~19 days	25 days	Dose dependent, 25 mg/kg: 0.7 μg/ml 50 mg/kg: 1.7 μg/ml	V_z = 3.1L/kg (12.5 mg/kg IV)	5.8 ml/h/kg (12.5 mg/kg IV)
Fluralaner: feline topical	~25%	12 days	6–9 days	Dose dependent, 20 mg/kg: 0.8 μg/ml 40 mg/kg: 1.9 μg/ml	V_z = 3.5L/kg (5 mg/kg IV)	9.6 ml/h/kg (5 mg/kg IV)
Sarolaner: canine systemic	>85%	11–12 days	<24 h	Fasted: 1.1 μg/ml (~2 mg/kg PO)	V_{ss} = 2.81L/kg (2 mg/kg IV)	7.2 ml/h/kg (2 mg/kg IV)
Lotilaner: canine systemic	Fasted: 24.3% Fed: 81.7% (20 mg/kg PO)	~30 days	2–4 h	Fasted: 1.5 μg/ml Fed: 4.0 μg/ml (20 mg/kg PO)	V_{ss} = 6.45L/kg (3 mg/kg IV)	7.5 ml/h/kg (3 mg/kg IV)
Lotilaner: feline systemic	Fasted: 8.4% Fed: 100% (6 mg/kg PO)	~30 days	2–4 h	Fasted: 0.4 μg/ml Fed: 4.0 μg/ml (6 mg/kg PO)	V_{ss} = 5.37L/kg (3 mg/kg IV)	5.4 ml/h/kg (3 mg/kg IV)

Note: For afoxolaner PK: Letendre et al., 2014; Kunkle et al., 2014. For oral fluralaner PK: Kilp et al., 2014; Walther, Allan, et al., 2014a. For topical fluralaner PK: Kilp et al., 2016. For sarolaner PK: McTier et al., 2016. For canine lotilaner PK: Toutain et al., 2017. For feline lotilanver PK: Toutain et al., 2018.

Abbreviations: C_{max}: maximum plasma concentration; $T_{1/2}$: half-life; T_{max}: time to maximum plasma concentration; V_d: volume of distribution; V_{ss}: steady-state volume of distribution; V_z: apparent volume of distribution during the terminal phase.

FDA-approved recommended dose, though by 24 h, most isoxazolines have 100% efficacy against common tick species (Halos et al., 2014; Six et al., 2016; Six et al., 2016; Six et al., 2016; Wengenmayer et al., 2014). Despite a 12-week label claim for fluralaner for the action against black-legged ticks, American dog ticks, and brown dog ticks, results of studies suggest the efficacy declines in the last month of the dosing interval (Beugnet et al., 2015a; Ohmes et al., 2015; Vatta et al., 2019; Wengenmayer et al., 2014); care should be taken by veterinarians prescribing the off-label use of isoxazolines to ensure proper coverage based on different geographical areas.

5.2 | Fleas

Commonly used insecticides for the treatment of flea infestations typically possess either a rapid onset of action and/or remain effective long enough to be used as a monthly preventive. Isoxazolines are effective against fleas in 2–4 h and exhibit a prolonged duration of action with efficacy rates >95% by hour 8 following infestation (Cavalleri, Murphy, Gorbea, et al., 2017; Cavalleri et al., 2017a; Kunkle et al., 2014; Six et al., 2016; Taenzler et al., 2014) and >99% throughout the respective dosing intervals (Cavalleri, Murphy, Gorbea, et al., 2017; Cavalleri et al., 2017b; Hunter et al., 2014; McTier et al., 2016; Six et al., 2016; Six et al., 2016). Isoxazolines prevent oviposition (Dryden et al., 2015; Williams et al., 2014) and have larvicidal (Williams et al., 2014) and adulticidal activity (Cavalleri, Murphy, Gorbea, et al., 2017; Cavalleri et al., 2017b; Hunter et al., 2014; Six et al., 2016; Taenzler et al., 2014; Williams et al., 2014). However, with administration of minimum dose of isoxazolines, the primary effect is exerted by rapid onset of adulticidal activity prior to oviposition, as the study of Williams et al was conducted at subinsecticidal concentrations. Isoxazolines are effective in reducing flea infestations within a home environment, a critical aspect of breaking the parasite life cycle (Dryden et al., 2016, 2017, 2018; 2020; Six et al., 2016), and reduce skin lesions associated with flea-allergic dermatitis and pruritus (Dryden et al., 2016, 2017, 2018; 2020). There is evidence that isoxazolines outperform spinosad, an insect nicotinic receptor agonist with significantly higher portion of dogs with ≥90% reduction in fleas (Cherni et al., 2016). All four isoxazolines are 100% effective against fleas 24 h after treatment (Cavalleri et al., 2018, 2018a; Dumont et al., 2014; Six et al., 2016; Six et al., 2016; Taenzler et al., 2014). As with ticks, the killing speed of afoxolaner, fluralaner, and sarolaner decreases toward the end of the dosing interval; though within 24 h following flea reinfestation, efficacy of these three isoxazolines is near 100% (Table 6) (Bosco et al., 2019; Taenzler et al., 2014).

5.3 | Mites

In our opinion, the most important future application of isoxazoline ectoparasiticides is in the treatment of mite infestations, including demodicosis and scabies. While not currently approved by the USA and Canada for use against mites, isoxazolines demonstrate high efficacy in the treatment of mites while offering greater ease of application, safety margin for the animal treated, and efficacy (Zhou et al., 2020), and are registered for treatment of mite infestations in EU, Australia, and New Zealand (Table 1).

5.3.1 | Demodex

Demodicosis is a common form of mange disease in canine patients, occasionally affecting cats. Conventional treatments including amitraz and macrocyclic lactones have been shown variable likelihood of clinical resolution, some may require prolonged treatment course with high probability of adverse effects (Arsenovic et al., 2015; Saari et al., 2009).

All four isoxazolines have shown efficacy in the treatment of generalized demodicosis (Beugnet, Halos, et al., 2016; Fourie et al., 2015; Six et al., 2016; Snyder et al., 2017), with marked reduction of mites as early as day 14 with the sarolaner treatment (Six et al., 2016). Afoxolaner, fluralaner, and sarolaner have been evaluated against weekly topical application of 2.5 mg/kg moxidectin plus 10 mg/kg imidacloprid (Advocate®), which demonstrated 99% reduction of *Demodex* in 4 weeks, compared with 90–98% efficacy with topical Advocate® treatment (Beugnet, Halos, et al., 2016; Fourie et al., 2015; Six et al., 2016). Lotilaner treatment also killed mites 99.9% with monthly applications (Snyder et al., 2017). While none of isoxazolines is currently labeled for use against demodicosis in the USA or Canada, they represent an excellent improvement in the field of veterinary dermatology (Zhou et al., 2020).

5.3.2 | Sarcoptes/Notoedres

Sarcoptic mange is caused by *Sarcoptes scabiei* var. *canis* in dogs and *Notoedres cati* in cats. This condition (scabies) is characterized by intense pruritus with or without secondary bacterial infection and pyoderma. Treatment modalities involve topical and oral medications with variable licensing based on individual country. These treatment options include lime–sulfur dips, amitraz dips, and topical dose of macrocyclic lactones (Folz et al., 1984; Malik et al., 2006; Shanks et al., 2000). As with the treatment of demodicosis, these treatment modalities can be risky and cumbersome. All isoxazolines except lotilaner have been studied extensively for the treatment of canine sarcoptic mange (Becskei, De Bock, Illambas, Cherni, et al., 2016; Beugnet, de Vos, et al., 2016; Hyun et al., 2019; Taenzler et al., 2016). Sarolaner has been demonstrated to be extremely effective within 14 days of dose against nymphs, larvae, and adults, with over 99% efficacy compared with the control groups by week 2 and 100% reduction by week 4 (Becskei, De Bock, Illambas, Cherni, et al., 2016). In a field study juxtaposing the efficacy of sarolaner and imidacloprid/moxidectin topical treatments (Advocate®), clear rates were 89% and 100% for sarolaner by days 30 and 60, respectively, and 85% and

TABLE 4 List of additional tick species with corresponding effective isoxazolines

Tick species	Effective isoxazolines	References
Dermacentor reticulatus (ornate cow ticks)	Afoxolaner Fluralaner Sarolaner Lotilaner	Becskei, De Bock, Illambas, Cherni, et al. (2016), Beugnet et al. (2014), Cavalleri, Murphy, Gorbea, et al. (2017), Geurden et al. (2016), McTier et al. (2016a), Taenzler et al. (2015), Taenzler et al. (2016)
Ixodes hexagonus (hedgehog ticks)	Sarolaner	Geurden et al. (2016)
I. ricinus (Castor bean ticks)	afoxolaner fluralaner Sarolaner Lotilaner	Cavalleri, Murphy, Gorbea, et al. (2017), Dumont et al. (2014), Geurden et al. (2016), Halos et al. (2014), Six et al. (2016), Wengenmayer et al. (2014), Williams et al. (2015)
I. holocyclus (Australian paralysis ticks)	Fluralaner Sarolaner Lotilaner	Baker et al. (2018), Fisara and Webster (2015), Packianathan et al. (2017)
Ornithodoros moubata (African hut tampans)	Fluralaner	Gassel et al. (2014)
O. turicata (relapsing fever ticks)	Sarolaner	McTier et al. (2016b)
Rhicephalus microplus (cattle ticks)	Fluralaner	Gassel et al. (2014)
Amblyomma cajennense (Cayenne ticks)	Sarolaner Lotilaner	Lasmar et al. (2018), Scott et al. (2017)
Haemaphysalis longicornia (Asian longhorned ticks)	Afoxolaner Fluralaner Sarolaner Lotilaner	Kondo et al. (2014), Oda et al. (2019), Otaki et al. (2018), Toyota et al. (2019)
Haemaphysalis elliptica (African yellow dog ticks)	Sarolaner	Fourie et al. (2019)

96% for imidacloprid/moxidectin combination (Becskei, De Bock, Illambas, Cherni, et al., 2016). Topical and oral fluralaner were evaluated with complete resolution of mite counts, and significant improvement in clinical signs was observed with both dose routes (Taenzler et al., 2016). Compared with sarolaner, the data of the fluralaner study suggest a more rapid resolution of canine sarcoptic mange by achieving 100% efficacy in a month, while sarolaner required 2 months to reach clinical cure with a monthly dosing interval (Taenzler et al., 2016). In addition, a study of six racoon dogs revealed 100% negative skin scraping in 7 days following a single oral dose of fluralaner; parasitological and clinical cure maintained up to 21 days (Hyun et al., 2019). Afoxolaner, given orally on days 0, 14, 28, and 56, appeared to exhibit a slower speed of killing against *Sarcoptes scabiei* in dogs, as it necessitated one more month than sarolaner to obtain 99% efficacy (Beugnet, de Vos, et al., 2016).

To our best knowledge, no research evaluating isoxazolines against the parasite of feline scabies (*Notoedres cati*) has been published.

5.3.3 | Otodectes

Otodectes cynotis, an obligate parasite of the external ear canal, is a common cause of otitis externa, particularly in kittens, with zoonotic potential (Van de Heyning & Thienpont, 1977). Current treatment methods involve topicals, both on- and off-label, and off-label oral moxidectin (0.2 mg/kg oral, twice a day for 10 days) (Six et al., 2016). Oral sarolaner at the recommended dose of 2 mg/kg yields a 98.2% mite reduction by day 28, followed by a 99.5% reduction by day 60 following a second monthly dose (Six et al., 2016). Afoxolaner has similar efficacy with >98% mite reduction by day 28 following a single 2.5 mg/kg oral dose (Carithers et al., 2016). Fluralaner is 100% effective against *O. cynotis* in both dogs and cats by day 28 after treatment in dogs; both oral and topical applications are effective (Taenzler et al., 2017).

5.3.4 | Miscellaneous ectoparasites

In addition to common mites affecting cats and dogs, fluralaner was investigated against *Psoroptes cuniculi* in naturally infested rabbits. *P. cuniculi* is a common ear mite in rabbits, causing otitis externa. Rabbits were treated with a one-time 25 mg/kg oral dose of fluralaner, significant mite reduction was seen by day 4; by day 8, mites were present in only one of the 30 treated rabbits and a marked reduction in ear exudate was also observed (Sheinberg et al., 2017). Fluralaner was evaluated for the efficacy compared with moxidectin/imidacloprid treatment for infestations of *Lynxacarus radovskyi*, feline fur mites that are common in Malaysia. Both treatments demonstrated significant efficacy in mite reduction by day 14 of the treatment period, with 100% elimination in both groups by day 28. Based on the bias present in group selection and inconsistencies in data presentation, the main implication taken from this study is the

TABLE 5 Efficacy of four common tick species after treatment with an isoxazoline

Tick species	Medication	0–24 h	Day 2–4	Day 28–30	Other	Note	References
Dermacentor variabilis	Afoxolaner: canine oral		100%(2.5 mg/kg PO single dose)	≥97% (2.5 mg/kg PO single dose)		Tick counts 2 days postinfestations	Mitchell et al. (2014)
	Fluralaner: canine oral		98% (25.1 – 49.4 mg/kg PO single dose)	97% (25.1 – 49.4 mg/kg PO single dose)	Day 56: 83% Day 84: 9% (25.1 – 49.4 mg/kg PO single dose)	Tick counts 12 hrs. postinfestations	Ohmes et al. (2015)
	Fluralaner: feline oral			100% (35.21 – 43.16 mg/kg PO single dose)	Day 56: 100% Day 84: 90% Day 90: 78% (35.21 – 43.16 mg/kg PO single dose)	Tick counts 2 days postinfestations	Vatta et al. (2019)
	Sarolaner: canine oral		100% (2 mg/kg PO single dose)	>99% (2 mg/kg PO single dose)	Day 35: >99% (2 mg/kg PO single dose)	Tick counts 2 days postinfestations	Six et al. (2016)
	Lotilaner: canine oral		100% (20 mg/kg PO single dose)	99% (20 mg/kg PO single dose)	Day 37: 98%(20 mg/kg PO single dose)	Tick counts 2 days postinfestations	Murphy et al. (2017)
Ixodes scapularis	Afoxolaner: canine oral		98% (2.5 mg/kg PO single dose)	94% (2.5 mg/kg PO single dose)		Tick counts 2 days postinfestations	Mitchell et al. (2014)
	Fluralaner: feline topical			100% (35.21–43.16 mg/kg PO single dose)	Day 56:100% Day 84:90% Day 90: 78% (35.21–43.16 mg/kg PO single dose)	Tick counts 2 days postinfestations	Vatta et al. (2019)
	Sarolaner: canine oral	4 h: 0% 8 h: 57% 12 h: 99% 24 h: 100% (2 mg/kg PO single dose)		4 h: 10% 8 h: 10% 12 h: 62% 24 h: 97% (2 mg/kg PO single dose)	Day 35: 75% (2 mg/kg PO single dose)	Tick counts 24 hrs. postinfestation if not specified.	Six et al. (2016)
	Lotilaner: canine oral		100% (20 mg/kg PO single dose)	100% (20 mg/kg PO single dose)	Day 37: 99% (20 mg/kg PO single dose)	Tick counts 2 days postinfestations	Murphy et al. (2017)
Ixodes ricinus	Afoxolaner: canine oral	12 h: 93% 24 h: 100% (2.5 mg/kg PO single dose)		91% (2.5 mg/kg PO single dose)		Tick counts 24 hrs. postinfestations, if not specified.	Halos et al. (2014)
	Fluralaner: canine oral	4 h: 90% 8 h: 98% 12 h: 100%24 h: 100% (25 mg/kg PO single dose)		4 h:33% 8 h:97% 12 h:100%24 h: 100% (25 mg/kg PO single dose)	Day 56: 100% Day 84: 98.1% (25 mg/kg PO single dose)	Tick counts 24 hrs. postinfestation if not specified	Wengenmayer et al. (2014)

(Continues)

TABLE 5 (Continued)

Tick species	Medication	0–24 h	Day 2–4	Day 28–30	Other	Note	References
	Sarolaner: canine oral	8 h: 77% 12 h: 90% 24 h: 100% (2.5 mg/kg PO single dose)		8 h: 23% 12 h: 95% 24 h: 99% (2.5 mg/kg PO single dose)	Day 35: 95% (2 mg/kg PO single dose)	Tick counts 24 hrs. postinfestation if not specified	Six et al. (2016)
	Lotilaner: feline oral		100% (6 mg/kg PO single dose)	100% (6 mg/kg PO single dose)	Day 37: >99% (6 mg/kg PO single dose)	Tick counts 2 days postinfestations	Cavalleri, Murphy, Seewald, Drake, et al. (2018)
Amblyomma americanum	Afoxolaner: canine oral		32% (3.1 – 6.2 mg/kg PO single dose)	40% (3.1 – 6.2 mg/kg PO single dose)		Tick counts 12 hrs. postinfestations	Ohmes et al. (2015)
	Fluralaner: canine oral		97% (25.1 – 49.4 mg/kg PO)	83% (25.1 – 49.4 mg/kg PO)		Tick counts 12 hrs. postinfestations	Ohmes et al. (2015)
	Sarolaner: canine oral		100% (2 mg/kg PO single dose)	100% (2 mg/kg PO single dose)	Day 36% (2 mg/kg PO single dose)	Tick counts 2 days postinfestations	Six et al. (2016)
	Lotilaner: canine oral		100% (20 mg/kg PO single dose)	100% (20 mg/kg PO single dose)		Tick counts 2 days postinfestations	Murphy et al. (2017)
Amblyomma maculatum	Sarolaner: canine oral	8 h: 90% 12 h: 99% 24 h: 100%(2 mg/kg PO single dose)	100% (2 mg/kg PO single dose)	100% (2 mg/kg PO single dose)	Day 35: >99% (2 mg/kg PO single dose)	Tick counts 2 days postinfestations	Six et al. (2016)
R. sanguineus	Afoxolaner: canine oral				Day 56: 98% Day 84: 86% (2.5 mg/kg PO monthly)	Tick counts 24 hrs. postinfestations	Beugnet et al. (2015a)
	Fluralaner: canine topical		91–100% (25 mg/kg topical single dose)	100% (25 mg/kg topical single dose)	Day 58: 99–100% Day 86: 97–100% (25 mg/kg topical single dose)	Tick counts 2 days postinfestations	J. Taenzler et al. (2016)
	Fluralaner: canine oral			100% (25 mg/kg PO single dose)	Day 56: 92% Day 84: 72% (25 mg/kg PO single dose)	Tick counts 24 hrs. postinfestations	Beugnet et al. (2015a)
	Sarolaner: canine oral	8 h: 94% 12 h: 100% 24 h: 100% (2–4 mg/kg PO single dose)		8 h: 20% 12 h: 29% 24 h:98% (2–4 mg/kg PO single dose)	Day 35: 92% (2–4 mg/kg PO single dose)	Tick counts 24 hrs. postinfestation if not specified.	Six et al. (2016)
	Lotilaner: canine oral		100% (20 mg/kg PO single dose)	Day 30:100% (20 mg/kg PO single dose)	Day 37: 100% (20 mg/kg PO single dose)	Tick counts 2 days postinfestations	Murphy et al. (2017)

TABLE 6 Efficacy of 2 flea species after treatment with an isoxazoline

Flea species	Medication	0–24 h	28–30 Days	35+ days	Other	References
C. felis	Afoxolaner: canine oral		6 h: 63%[43] 12 h: 94%[43] 24 h:100% (2.5 mg/kg PO monthly)			Beugnet et al. (2015)
	Fluralaner: canine oral	2 h: 37% 4 h: 81% 8 h:100% 24: 100% (25 mg/kg PO single dose)	4 h:97% 8 h: 100% 12 h: 100% 24 h: 100% (25 mg/kg PO single dose)	Day 84 4 h:33% 8 h:98% 12 h:99% 24 h:100% (25 mg/kg PO single dose)	Flea counts 24 hrs. postinfestations if not specified	Taenzler et al. (2014)
	Fluralaner: feline topical		100%(40 mg/kg topical single dose)	Day 84: 100% (40 mg/kg PO topical dose)		Bosco et al. (2019)
	Sarolaner: canine oral	2 h: 0% 4 h: 86% 8 h: 100% 12 h: 100% (2 mg/kg topical single dose)	2 h: 8% 4 h: 8% 8 h: 90% 12 h: 100% (2 mg/kg topical single dose)	Day 35: 100% (2 mg/kg topical single dose)	Flea counts 12 hrs. postinfestations if not specified	Six et al. (2016)
	Lotilaner: feline oral	100% (6 mg/kg PO single dose)	100% (6 mg/kg PO single dose)	Day 35: 100% (6 mg/kg PO single dose) (Cavalleri, Murphy, Seewald, Drake, et al., 2018; Cavalleri et al., 2018a)	Flea counts 24 hrs. postinfestations if not specified	Cavalleri et al., 2018a
C canis	Afoxolaner: canine oral	12 h: 100% 24 h: 100% (2.5 mg/kg PO single dose)	12 h: 69% 24 h: 100% (2.5 mg/kg PO single dose)	Day 35: 99% (2.5 mg/kg PO single dose)	Flea counts 24 hrs. postinfestations if not specified	Dumont et al. (2014)
	Sarolaner: canine oral	24 h: 100% (2 mg/kg PO single dose)	100% (2 mg/kg PO single dose)	Day 35: 100% (2 mg/kg PO single dose)	Flea counts 24 hrs. postinfestations if not specified	Six et al. (2016)

potential for additional application of isoxazolines in the treatment of many different ectoparasites (Han et al., 2016). Other ectoparasites that are susceptible to isoxazolines include *Dermanyssus gallinae* (poultry red mites) (Thomas et al., 2017), *Tetranychus urticae* Koch (two-spotted spider mites) (Leviticus et al., 2020), *Phlebotomus perniciosus* (sand flies) (Bongiorno et al., 2020; Perier et al., 2019), *Triatoma infestans* nymphs (kissing bugs) (Laino et al., 2019), canine myiasis (maggots) (Han et al., 2018), and *Caparinia tripilis* (one of the common mites infesting African pygmy hedgehogs) (Romero et al., 2017).

6 | SAFETY

As mentioned earlier, isoxazolines block glutamate-gated chloride channels, which exist in invertebrates, but not vertebrates (Gassel et al., 2014). In addition, isoxazolines selectively block invertebrate GABA-gated chloride channels. These modes of action of isoxazolines account for their high margin of safety for use in veterinary species (Gassel et al., 2014). Safety studies have been performed for all four isoxazoline compounds at a minimum of five times the recommended doses with no apparent adverse effects, except neurological effects observed (Drag et al., 2014; Kuntz & Kammanadiminti, 2017, 2018; McTier et al., 2016; Walther, Allan, et al., 2014b). Prescription of isoxazolines should be determined in combination with patient medical histories on individual basis (FDA, 2019). A recent survey conducted in the USA revealed high occurrence of neurological adverse effects on dogs using isoxazolines (13.7% seizures, 15.9% ataxia, and 16.7% shaking as overall rates for afoxolaner, fluralaner, and sarolaner) (Palmieri et al., 2020). However, this survey might be non-representative and biased due to potential disadvantages of online electronic questionnaire and owner-observed reactions that may or may not be associated with isoxazoline use, caution should be taken when considering this article as a reference for isoxazoline safety. Limited safety studies

TABLE 7 Safety of isoxazolines in young animals

Drug (trade name, company)	Young animal	References
Afoxolaner (NexGard®, Boehringer Ingelheim)	safe in 8-week-old Beagle dogs (1, 3, or 5X the maximum label dose of 6.3 mg/kg, PO)	FDA (2018a)
Fluralaner (Bravecto®, Merck)	Oral chewable Dog: safe in weaned puppies, with potential drug-related effects include diarrhea and vomiting (1,3, or 5X the maximum label dose of 56 mg/kg, PO) Topical solution Dog: safe in weaned puppies (1, 3, or 5X the maximum label dose of 56 mg/kg, topical) Cat: safe in weaned kittens, with potential drug-related renal tubular degeneration/regeneration (1,3, or 5X the maximum label dose of 93 mg/kg, topical)	FDA (2014, 2016a)
Sarolaner (Simparica®, Zoetis)	Dog: Not safe in 8-week-old puppies, with drug-related neurological signs including seizures at 3X and 5X doses (1,3, or 5X the maximum label dose of 4 mg/kg, PO)	FDA (2016b)
Lotilaner (Credelio®, Elanco)	labeled doses: safe; 5x maximum labeled dose (215 mg/kg): potential drug-related corneal opacities in 8-week-old dog	FDA (2018b)

have shown that isoxazolines are safe in cats (Cavalleri, Murphy, Seewald, Drake, et al., 2018; Cavalleri et al., 2018b; Kuntz & Kammanadiminti, 2018) and MDR1-/- collies (Walther et al., 2014). Safety in puppies or kittens on afoxolaner, fluralaner, and lotilaner was confirmed with oral or topical dose at 1, 3, or 5X the maximum FDA-approved dose, while mild and self-limiting ataxia and tremors with seizures were observed in 8-week-old puppies treated at elevated doses (3X and 5X the maximum FDA-approved dose) (Table 7; FDA, 2014, 2016a, 2016b, 2018a, 2018b). Limited theriogenological data revealed that isoxazoline treatments have no notable impact on reproductive status or semen analysis, but may lead to limb deformity, enlarged heart and spleen, and cleft palate of new-born puppies (FDA, 2014). It is our opinion that veterinarians should be cautious when prescribing isoxazolines in pregnant and lactating bitches until further safety studies have been conducted.

7 | CONCLUSIONS

Isoxazolines are a novel class of ectoparasiticide that has unique characteristics of rapid absorption, prolonged duration, and broad spectrum activity against fleas/insects, ticks, and mites. The advent of isoxazolines may replace the conventional treatment of demodicosis and sarcoptic mange, due to their high efficacy with rapid resolution and few adverse effects. However, caution should be taken for animals with seizures or other neurological disorders (cerebellar ataxia, central vestibular signs, etc.) before prescribing an isoxazoline ectoparasiticide, as it might enhance the occurrence of neurological disturbances.

ANIMAL WELFARE STATEMENTS

No animals were used in this investigation.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

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