

# Veterinary Dermatology

## Dermatologie vétérinaire

### Isoxazolines for treating canine and feline otodectic mange; feline demodicosis, lynxacariasis, lice infestation, and notoedric mange (scabies); demodicosis in hamsters; and sarcoptic and psoroptic manges in rabbits

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#### Introduction

In 2014, a new class of parasiticides was introduced to the Canadian small animal health market. Isoxazoline drugs include afoxolaner, esafoxolaner (a purified enantiomer of afoxolaner), fluralaner, lotilaner, and sarolaner.

A plethora of oral and topical spot-on products are now commercially available and contain either a single isoxazoline or an isoxazoline in combination with 1 or 2 other active ingredient(s). There are geographical differences in the availability and licensure of these drugs. Therefore, one must judiciously take into account regional prescribing recommendations. Isoxazolines currently available for use in dogs and cats in Canada are listed in Table 1 and Table 2, respectively.

In a previous article, we focused on the use of isoxazolines for treating canine demodicosis, sarcoptic mange (scabies), and

lice infestation (1). This related article reviews the clinical use (both label and extra-label) of isoxazolines in Canada to treat external ear canal parasites in dogs, cats, and rabbits; and cutaneous parasites affecting cats, hamsters, and rabbits.

#### Canine and feline otodectic mange

Otodectic mange is a common, contagious, primarily aural mite infestation caused by *Otodectes cynotis*. The efficacy of isoxazolines was evaluated in 213 dogs enrolled in 5 studies, and in 245 cats enrolled in 7 studies.

#### Oral afoxolaner

The efficacy of oral afoxolaner was evaluated in 3 controlled studies. In the 1st study (2), 8 dogs were treated with a single dose. There was a 99.4% reduction in mites at Day 28. In the

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**Table 1.** Isoxazolines currently available for use in dogs in Canada.

| Product name (market year)       | Manufacturer         | Route of administration | Isoxazoline | Macrocyclic lactone | Other    | Labelled use          | Extra-label use |
|----------------------------------|----------------------|-------------------------|-------------|---------------------|----------|-----------------------|-----------------|
| Bravecto (2014)                  | Merck/Intervet       | Oral                    | Fluralaner  | N/A                 | N/A      | F, T                  | D, S, L, O      |
| Bravecto topical solution (2018) | Merck/Intervet       | Topical                 | Fluralaner  | N/A                 | N/A      | F, T                  | D, S, L, O      |
| Bravecto one (2021)              | Merck/Intervet       | Oral                    | Fluralaner  | N/A                 | N/A      | F, T                  | D, S, L, O      |
| Credelio (2019)                  | Elanco               | Oral                    | Lotilaner   | N/A                 | N/A      | F, T                  | D, S            |
| Credelio plus (2022)             | Elanco               | Oral                    | Lotilaner   | Milbemycin oxime    | N/A      | F, T, R, HT           | D, S            |
| NexGard (2014)                   | Boehringer Ingelheim | Oral                    | Afoxolaner  | N/A                 | N/A      | F, T, D               | S, O            |
| NexGard spectra (2019)           | Boehringer Ingelheim | Oral                    | Afoxolaner  | Milbemycin oxime    | N/A      | F, T, D, HK, R, W, HT | S               |
| Simparica (2016)                 | Zoetis               | Oral                    | Sarolaner   | N/A                 | N/A      | F, T                  | D, S, L, O      |
| Simparica trio (2020)            | Zoetis               | Oral                    | Sarolaner   | Moxidectin          | Pyrantel | F, T, D, S, HK, R, HT | L               |

D — Demodicosis; F — Fleas; HK — Hookworm; HT — Heartworm; L — Lice infestation; N/A — Not available; O — Otodectic mange; R — Roundworm; S — Sarcoptic mange (scabies); T — Ticks; W — Whipworm.

**Table 2.** Isoxazolines currently available for use in cats in Canada.

| Product name (market year)       | Manufacturer         | Route of administration | Isoxazoline  | Macrocyclic lactone | Other        | Labelled use       | Extra-label use |
|----------------------------------|----------------------|-------------------------|--------------|---------------------|--------------|--------------------|-----------------|
| Bravecto topical solution (2017) | Merck/Intervet       | Topical                 | Fluralaner   | N/A                 | N/A          | F, T               | D, O            |
| Credelio cat (2022)              | Elanco               | Oral                    | Lotilaner    | N/A                 | N/A          | F, T               |                 |
| NexGard combo (2022)             | Boehringer Ingelheim | Topical                 | Esafoxolaner | Eprinomectin        | Praziquantel | F, T, R, TP, HT, O | L, N            |
| Revolution plus (2019)           | Zoetis               | Topical                 | Sarolaner    | Selamectin          | N/A          | F, T, R, HK, HT, O | D               |
| Vitrecto topical solution (2020) | Merck/Intervet       | Topical                 | Fluralaner   | Moxidectin          | N/A          | F, T, R, HK, HT    |                 |

D — Demodicosis; F — Fleas; HK — Hookworm; HT — Heartworm; L — Lice infestation; N — Notoedric mange (scabies); N/A — Not available; O — Otodectic mange; R — Roundworm; T — Ticks; TP — Tapeworm.

2nd study (3), 10 dogs were treated twice, 30 d apart. All dogs were mite free at Day 42. In the 3rd study (4), 8 cats were treated with a single dose. All cats were mite free on video-otoscopic examination at Day 2. There were no adverse effects in these studies.

### Topical esafoxolaner

The efficacy of the topical combination of esafoxolaner, eprinomectin, and praziquantel in cats was evaluated in 2 placebo-controlled laboratory studies and in 1 placebo-controlled field study (5). A total of 72 cats assigned to the treated groups received a single topical spot-on dose, whereas another 79 cats received topical mineral oil once. Mite reduction varied from 97.2% (Day 28) to 97.4% (Day 30) to 99.9% (Day 32) in treated cats. There were no adverse effects in these studies.

### Oral/topical fluralaner

The efficacy of oral or topical fluralaner was evaluated in 1 controlled study (6). Eight dogs were treated with a single oral dose. Eight dogs and 8 cats were treated with a single topical spot-on dose, whereas another 8 dogs and 8 cats received a topical saline solution once. There was a 99.8% reduction in mites at Day 28 in treated dogs. All treated cats were mite free at Day 28. The efficacy of the topical combination of fluralaner-moxidectin was

evaluated in 1 controlled study (7). Eight cats were treated with a single spot-on dose, whereas another 8 cats received a topical saline solution once. All treated cats were mite free at Day 28. There were no adverse effects in these studies.

### Oral/topical sarolaner

The efficacy of oral sarolaner in dogs was evaluated in 1 placebo-controlled laboratory study and in 1 controlled field study. In the 1st study (8), 8 dogs were treated with a single dose, whereas another 8 dogs were treated twice, 30 d apart. Eight dogs received a single placebo tablet, whereas another 8 dogs received a placebo tablet twice, 30 d apart. The single dose resulted in a 98.2% reduction in mites at Day 30, whereas the 2 doses resulted in a 99.5% reduction in mites at Day 60. In the 2nd, noninferiority study (9), 163 dogs were treated orally, either with a single dose or twice, 30 d apart. At Day 60, 99.4% of dogs were mite free. Another 78 dogs were treated topically with a spot-on solution containing imidacloprid and moxidectin, either with a single dose or twice, 30 d apart. Oral sarolaner performed better than the spot-on treatment. There were no adverse effects in these studies.

In cats, the efficacy of the topical combination of sarolaner-selamectin was evaluated in 2 placebo-controlled studies and in 1 controlled field study. In the placebo-controlled studies (10),

**Table 3.** Feline demodicosis: Fluralaner and sarolaner studies.

| Reference (year) | Treatment protocol and outcome   |
|------------------|--|
| 13 (2017)        | Case report: 1 cat with generalized demodicosis caused by <i>Demodex cati</i><br>Single oral dose of fluralaner<br>100% mite free at Day 30<br>No adverse effects  |
| 14 (2018)        | Case report: 2 shelter cats (a queen and her kitten) with demodicosis caused by <i>Demodex gatoi</i><br>Single oral dose of fluralaner<br>100% mite free at Day 30<br>Adverse effects not recorded   |
| 15 (2019)        | Case series: 7 cats with generalized demodicosis caused by <i>Demodex cati</i><br>Single topical spot-on dose of fluralaner<br>100% mite free at Day 14<br>No adverse effects  |
| 16 (2021)        | Case report: 1 cat with generalized demodicosis caused by <i>Demodex cati</i><br>Single topical spot-on dose of fluralaner<br>100% mite free at Day 7<br>No adverse effects  |
| 17 (2022)        | Case report: 1 cat with localized demodicosis and bilateral otodemodicosis caused by <i>Demodex cati</i><br>Single topical spot-on dose of fluralaner<br>100% mite free at Day 42<br>Adverse effects not recorded  |
| 18 (2019)        | Case report: 2 sibling cats with demodicosis caused by <i>Demodex gatoi</i><br>Monthly topical spot-on doses of sarolaner-selamectin combination<br>Skin scrapings not repeated (personal communication)<br>Almost complete hair regrowth 15 wk after onset of treatment<br>Adverse effects not recorded |
| 19 (2020)        | Case report: 1 cat with generalized demodicosis caused by <i>Demodex</i> spp.<br>Single oral dose of sarolaner<br>100% mite free at Day 21<br>Adverse effects not recorded   |
| 20 (2021)        | Case report: 1 cat with unilateral otodemodicosis caused by <i>Demodex cati</i><br>4 topical spot-on doses of sarolaner-selamectin combination, 30 d apart<br>100% mite free at Day 120<br>No adverse effects  |

15 cats were treated with a single spot-on dose, whereas another 15 cats received only the topical excipients once. There was a 99.2 to 99.3% reduction in mites at Day 30. In 1 cat, alopecia was noted at the topical administration site starting 3 d after treatment. In the 2nd study (11), 124 cats were treated with a single spot-on dose, whereas another 63 cats were treated once, topically, with a combination of imidacloprid-moxidectin. In that study, 94.4% of cats were mite free at Day 30. The sarolaner-selamectin spot-on treatment performed better than

**Table 4.** Numbers of recommended doses of isoxazolines (use either a single isoxazoline product or a combination product).

| Disease                          | Number of doses  |
|----------------------------------|--|
| Canine otodectic mange           | 2 monthly oral doses of afoxolaner<br>1 oral or topical dose of fluralaner<br>2 monthly oral doses of sarolaner  |
| Feline otodectic mange           | 1 oral dose of afoxolaner<br>1 topical dose of esafoxolaner or fluralaner<br>1 oral or topical dose of sarolaner |
| Feline demodicosis               | 1 oral or topical dose of fluralaner or sarolaner  |
| Feline lynxacariasis             | 1 oral dose of fluralaner or sarolaner   |
| Feline lice infestation          | 1 topical dose of esafoxolaner   |
| Feline notoedric mange (scabies) | 1 topical dose of esafoxolaner   |
| Demodicosis in hamsters          | 1 oral dose of fluralaner  |
| Sarcoptic mange in rabbits       | 1 oral or topical dose of fluralaner   |
| Psoroptic mange in rabbits       | 1 oral dose of afoxolaner or fluralaner  |

the imidacloprid-moxidectin spot-on. Vomiting was noted in 3.2% of cats in the sarolaner-selamectin-treated group. However, this occurred 9 to 28 d after treatment and was not considered likely to be due to the topical administration. The efficacy of oral sarolaner was evaluated in 1 controlled study (12). Ten cats were treated with a single dose. All cats were mite free on video-otoscopic examination at Day 2. There were no adverse effects.

## Feline demodicosis

Feline demodicosis is a rare skin disease caused by proliferation of *Demodex* mites. To the authors' knowledge, the efficacy of isoxazolines for the treatment of feline demodicosis has not been evaluated in controlled studies. There is a paucity of data in the veterinary literature, as the use of isoxazolines was reported in only 16 cats in 8 case reports. Details are summarized in Table 3.

### Oral/topical fluralaner

The efficacy of oral or topical fluralaner was reported in 12 cats in 5 case reports (13–17).

### Oral/topical sarolaner

The efficacy of oral or topical sarolaner was reported in 4 cats in 3 case reports (18–20).

## Feline lynxacariasis

Feline lynxacariasis is an infestation caused by the fur mite *Lynxacarus radovskyi*, typically seen in tropical climates. The efficacy of isoxazolines was evaluated in 17 cats enrolled in 2 studies.

### Oral fluralaner

The efficacy of oral fluralaner was evaluated in 1 controlled study (21). Ten cats were treated with a single dose, whereas another 10 cats were treated twice, topically, 2 wk apart, with a combination of imidacloprid-moxidectin. Oral fluralaner and the

imidacloprid-moxidectin spot-on treatment performed equally. All cats were mite free at Day 28. There were no adverse effects.

### Oral sarolaner

The efficacy of oral sarolaner was evaluated in 1 controlled study (22). Seven cats were treated with a single dose. There was a 96.6% reduction in mites at Day 30. There were no adverse effects.

### Feline lice infestation

The efficacy of the topical combination of esafloxolaner, eprinomectin, and praziquantel was evaluated in 1 controlled study (23). Fourteen cats with a biting (chewing) lice infestation caused by *Felicola subrostratus* were treated with a single dose. Another 17 cats were treated once with a spot-on solution containing a combination of fipronil and (S)-methoprene. All cats were lice free at Day 30. There were no adverse effects.

### Feline notoedric mange (scabies)

Feline notoedric mange (scabies) is a pruritic and contagious skin disease caused by the mite *Notoedres cati*. The efficacy of the topical combination of esafloxolaner, eprinomectin, and praziquantel was evaluated in 1 placebo-controlled laboratory study (24). Seven cats were treated with a single spot-on dose, whereas another 7 cats received topical mineral oil once. All treated cats were mite free at Day 14. There were no adverse effects.

### Demodicosis in hamsters

Demodicosis in hamsters is a skin disease caused by proliferation of *Demodex* mites. In 1 case report, a golden (Syrian) hamster with a mixed demodicosis caused by both *Demodex criceti* and *Demodex aurati* was treated with a single oral dose of oral fluralaner (25). The hamster was 100% mite free at Day 30. There were no adverse effects.

### Sarcoptic mange in rabbits

Sarcoptic mange in rabbits is a contagious skin disease caused by the mite *Sarcoptes scabiei* var. *cuniculi*. The efficacy of isoxazolines was evaluated in 30 rabbits enrolled in 3 studies.

The efficacy of oral fluralaner was evaluated in 2 case series. In the 1st study (26), 12 rabbits were treated with a single dose. All rabbits were mite free at Day 14. In the 2nd study (27), 8 rabbits were treated with a single dose. All rabbits were mite free at Day 45. There were no adverse effects in these studies.

The efficacy of the topical combination of fluralaner-moxidectin was evaluated in 1 case series (28). Ten rabbits were treated with a single spot-on dose. All rabbits were mite free at Day 21. In 1 rabbit, pruritus and erythema were noted at the topical administration site starting 2 h after treatment, but these resolved within 24 h.

### Psoroptic mange in rabbits

Psoroptic mange in rabbits is a common, contagious, primarily aural mite infestation caused by *Psoroptes cuniculi*. The efficacy of isoxazolines was evaluated in 34 rabbits enrolled in 2 studies.

Efficacy of the oral combination of afoxolaner-milbemycin oxime was evaluated in 1 controlled study (29). Nineteen rabbits were treated with a single dose. All rabbits were mite free at Day 14. The efficacy of oral fluralaner was evaluated in 1 case series (30). Fifteen rabbits were treated with a single dose. All rabbits were mite free at Day 12. There were no adverse effects in these studies.

### What are the recommended dosage and number of doses of isoxazolines?

The numbers of recommended doses, based on a review of the available scientific literature, are summarized in Table 4. It is recommended to use the labelled dosage for flea and tick prevention/control/treatment, and to conform to minimum age and body weight requirements.

### What are potential side effects of isoxazolines?

Isoxazolines have potential side effects, including vomiting, diarrhea, anorexia, lethargy, and seizures. They should only be used in suitable patients (*i.e.*, use with caution in dogs with a history of seizures or neurological disorders) and under veterinary supervision.

### Conclusion

The recent introduction of isoxazolines in veterinary medicine has resulted in effective and safe treatment of canine and feline otodectic mange; feline demodicosis, lynxacariasis, lice infestation and notoedric mange (scabies); demodicosis in hamsters; and sarcoptic and psoroptic manges in rabbits, with a low frequency of administration.

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