Lecture overview

- ► Introduction
- Mechanism of action
- Disadvantage
- Advantages
- Extra-label use
- ► Implications for practice







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Meet Kenny





https://www.canadianveterinarians.net/documents/wcv-summer-2019

Meet Kenny





- ▶ 6 month-old intact male Australian Shepherd.
- Seen at North West Veterinary Dermatology Specialists in September 2015.
- Demodicosis lesions predominantly facial.
- Also had a severe secondary bacterial pyoderma caused by methicillinresistant Staphylococcus pseudintermedius.
- Severe pruritus. Needed to wear an Elizabethan collar 24/7!
- Considering the age, but most importantly the breed of the patient (a well know ivermetin sensitive breed), I decided it was a great opportunity to treat my first case of canine demodicosis with oral fluralaner.

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Single dose of oral fluralaner before and after pictures









Day 44

CHAPITE SECV



Introduction

- Flea and tick infestation is a major health problem in dogs and cats.
- Control presents an economic burden to pet owners.
- Recent advances in product technology have greatly expanded the available options for veterinarians and pet owners.
- Afoxolaner, fluralaner, lotilaner and sarolaner are novel synthetic members of the isoxazoline class of parasiticides showing activity against insects and acarines, including fleas and ticks.
- There are currently 8 isoxazoline containing products available in Canada.
- The wide array of available ectoparasiticides can lead to confusion.





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2 types of products currently available in Canada





- Products containing an isoxazoline alone (6)
- Currently only labelled for the treatment and prevention/control of fleas and ticks in Canada.
- ► Four oral products are commercially available for oral administration in dogs:
- 1. Afoxolaner (NexGard®, Boehringer Ingelheim Canada)
- 2. Fluralaner (Bravecto®, Merck Animal Health)
- 3. Lotilaner (Credelio™, Elanco Canada)
- 4. Sarolaner (Simparica™, Zoetis Canada)
- ► Fluralaner is also available as a spot-on (Bravecto® Topical Solution, Merck Animal Health) for dogs or cats.





CHAPITE SECV



2 types of products currently available in Canada

- Combination products (2)
- ► Labelled for the treatment and prevention/control of fleas and ticks, as well other important endo- and ectoparasites.
- 1. Oral combination of afoxolaner and milbemycin oxime (NexGard SPECTRA™, Boehringer Ingelheim Canada) covers fleas, ticks, heartworms, and intestinal worms (roundworms, hookworms, and whipworms) in dogs.
- 2. Topical combination of sarolaner and selamectin (Revolution® PLUS, Zoetis Canada) covers fleas, ticks, ear mites, heartworms, and intestinal worms (roundworms and hookworms) in cats.



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Oral products currently available in Canada













Bravecto® 2014

Nexgard[®]2014

Oral products currently available in Canada











Simparica[™] 2016

Credelio[™] 2019

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Topical products currently available in Canada









2016





2018

Bravecto[®] **Topical Solution**

Combination products currently available in Canada











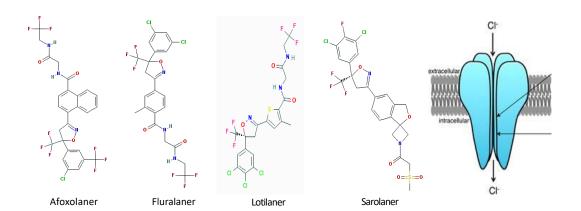


Revolution® PLUS 2019

NexGard SPECTRA™ **2019**

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Mechanism of action



Isoxazolines have a novel mode of action and specifically block arthropod ligand-gated chloride channels.

Mechanism of action





Isoxazolines are potent selective inhibitors of 2 types of ligand-gated chloride channels:

γ-aminobutyric acid-gated chloride channels (GABACls) L-glutamate-gated chloride channels (GluCls)

- By acting on these receptors, they inhibit GABA and glutamate-regulate uptake of chloride ions.
- ► This results in uncontrolled neuromuscular activity, leading to rapid parasite death.



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Disadvantage

- The only disadvantage of isoxazolines is that fleas and ticks must attach to the host and commence feeding in order to be exposed to the active substance.
- Not an issue for flea allergic dogs. In one study, a single administration of Bravecto™ alleviated or resolved clinical signs associated with FAD in all treated dogs over the recommended 12-week treatment period.
- Possibly an issue in regards to Lyme Disease (LD) transmission. In rodent models, transmission of LD spirochetes can occur in <16 hours and frequently in <24 hours. In humans and in dogs, the minimum attachment time for transmission of infection has never been established.
- Zero risk does not exist. LD infection can never be excluded after a tick bite irrespective of the estimated duration of attachment time.



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Advantages





Several criteria are judged important for both veterinarians and pet owners:

Spectrum of activity **Duration of efficacy** Ease of use Safety Speed of kill



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Spectrum of activity and duration of efficacy





- Isoxazolines show activity against insects and acarines.
- Due to their pharmacokinetic properties, isoxazolines were the first and are currently the only orally administered drugs to provide effective and long-lasting (for a month or more) parasiticidal activity against both fleas and ticks after a single administration.



CHAPTED SECV



Ease of use

- ► The isoxazolines-containing products are easy to administer and palatable. This enhances pet owner compliance.
- Bypassing topical therapy eliminates the concern for :

Loss of efficacy following bathing and swimming ('waterproof')

Incorrect topical spot-on application

Cutaneous adverse drug reactions

Better option in dogs that are bathed or swim frequently.



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Very good safety profile







- Isoxazolines are not substrates of the P-glycoprotein.
- These products are generally quite safe for use in dogs, including those with the ABCB1-Δ1 (formerly multi-drug resistance gene, mdr-1) mutation associated with neurological adverse effects of macrocyclic lactones.
- ► The adverse effects consist most commonly of mild and transient gastrointestinal upset (vomiting, diarrhea, anorexia, flatulence), and lethargy.
- ► The frequency of these adverse events is classified as rare.



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CHAPTER SBCV



Great speed of kill

- ► Speed of kill is also an important criterion for assessing a flea control product, because the more quickly fleas are killed the less likely a pet owner is to observe them on the pet.
- ► It also influences flea egg production, and faster speed of kill therefore results in less flea egg contamination of the environment.
- ▶ Isoxazolines kill over 95% of the fleas, starting as early as 4 to 8 hours.



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Extra-label use in Canada (# of papers)





Recently, isoxazolines have received extra-label use for :

Canine flea allergy dermatitis
Canine demodicosis (14)
Feline demodicosis (2)
Canine scabies (5)
Canine otoacariasis (4)
Feline otoacariasis (1)

Canine infestation caused by sucking lice (1)



Labelled use in other countries













Canine demodicosis Canine scabies Canine otoacariasis





Canine demodicosis Canine scabies Canine otoacariasis

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Canine demodicosis - Afoxolaner





First study (2016)



OPEN @ ACCESS





Efficacy of oral afoxolaner for the treatment of canine generalised demodicosis

Frédéric Beugnet^{1,*}, Lénaïg Halos¹, Diane Larsen¹, and Christa de Vos²

8 client-owned dogs

NexGard compared with topical Advantage Multi (8 dogs)

Treated on days 0, 14, 28 and 56

Afoxolaner-treated group: 87.5% mite free at day 84

Topical combination imidacloprid/moxidectin-treated group: 7/8 dogs still infested at day 84

No adverse effects









Day	Pre-treatment
Mite count	676



Day	28	
Mite count	25	

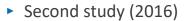


Day	56	
Mite count	0	



Day	84	
Mite count	0	

Canine demodicosis - Afoxolaner



Case Report of Afoxolaner Treatment for Canine Demodicosis in Four Dogs Naturally Infected with Demodex Canis

Fernando Chávez, DVM

4 client-owned dogs Treated on days 0, 28 and 56 100% mite free at day 56 Adverse effects not recorded









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Figure 1. Skin condition on ventral aspect of Dog #3 before treatment with afoxolaner on Day 0 (a); I week after treatment (b); 4 weeks after treatment (c); 8 weeks after treatment (d).



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Canine demodicosis - Afoxolaner



Third study (2018)





Efficacy of oral afoxolaner for the treatment of canine generalized demodicosis in Japan

N. MURAYAMA*, Y. OSHIMA*

*Dermatology Services for Dogs and Cats, Koto-ku, Tokyo, Japan

15 client-owned dogs Treated on days 0, 28 and 56 with oral afoxolaner-milbemycin oxime 100% mite free at day 84 Adverse effects not recorded



Source of funding:



Canine demodicosis - Afoxolaner





Fourth study (2018)



アフォキソラネルの犬ニキビダニ症6例に対する治療効果

Efficacy of Afoxolaner in Six Cases of Canine Demodicosis

飯島裕子 伊藤直之* 木村祐哉 北里大学

Yuko Iijima, Naoyuki Itoh*, Yuya Kimura

6 client-owned dogs Treated with 1, 2 or 3 doses 21, 28, 35 or 42 days apart 100% mite free at day 77 No adverse effects





Source of funding:



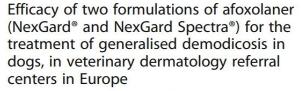
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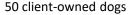
Canine demodicosis - Afoxolaner

Fifth study (2018)





Wilfried Lebon ^{1,2}, Massimo Beccati³, Patrick Bourdeau⁴, Thomas Brement⁴, Vincent Bruet⁴, Agnieszka Cekiera⁵, Odile Crosaz⁶, Céline Darmon⁶, Jacques Guillot⁶, Marion Mosca⁷, Didier Pin⁷, Jaroslaw Popiel⁵, Dorota Pomorska Handwerker⁸, Diane Larsen⁹, Eric Tielemans¹, Frédéric Beugnet² and Lénaïg Halos^{2*}



Treated on days 0, 28 and 56 with either oral afoxolaner (31 dogs) or afoxolanermilbemycin oxime (19 dogs)

98% mite reduction at day 84 No adverse effects











Source of funding:





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Canine demodicosis - Afoxolaner

Sixth study (2019)

Efficacy of Afoxolaner Plus Milbemycin Oxime in the Treatment of Canine Demodicosis

Camilo Romero-Núñez² Anahí Romerod Linda Guiliana Bautista-Gómezª Ariadna Floresª Galia Sheinbergʰ Rafael Herediaª Alberto Martín² Laura Mirandaª

68 client-owned dogs Treated once with oral afoxolaner-milbemycin oxime 82.4% mite reduction at day 28 Adverse effects not recorded









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CSTAPRICE SBCV



Source of funding:

Canine demodicosis - Fluralaner

First study (2015)

RESEARCH

Efficacy of orally administered fluralaner (BravectoTM) or topically applied imidacloprid/moxidectin (Advocate®) against generalized demodicosis in dogs

Josephus J Fourie^{1*}, Julian E Liebenberg¹, Ivan G Horak², Janina Taenzler³, Anja R Heckeroth³ and Regis Frénais⁴

8 client-owned dogs

Bravecto compared with topical Advantage Multi (8 dogs)

Fluralaner-treated group (treated once): 100% mite free at day 56

Topical combination imidacloprid/moxidectin-treated group (Day 0, 28 and 56): 95% mite

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reduction at day 84

No adverse effects

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Photographic documentation



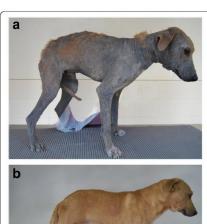




Figure 1 Example of hair re-growth in a dog suffering from generalized demodicosis pre-treatment (a) and 12 weeks after initiation of treatment (b).



Canine demodicosis - Fluralaner





Second study (2015)

Efficacy of fluralaner for the treatment of canine demodicosis

J. KARAS-TECZA* and J. DAWIDOWICZ†
*Dermatology Clinic For Dogs and Cats "Dermawet",
Warsaw, Poland
†Veterinary Clinic "Brynów", Katowice, Poland

163 client-owned dogs Dogs treated on days 0 and 90 87% mite free at day 30 100% mite free at day 84 No adverse effects



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Canine demodicosis - Fluralaner



Effectiveness of fluralaner (Bravecto® MSD) in treating generalized demodicosis in four dogs

P. T. ARIAS* and A. M. CORDERO[†]
*Clinica Dermatologica Alhaurin, Monterrey, Nuevo
Leon, Mexico; [†]VETDERM Dermatología Veterinaria
Especializada, Guadalajara, Jalisco, Mexico

4 client-owned dogs Treated on days 0 and 60 98% mite reduction at day 84 Adverse effects not recorded



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Canine demodicosis - Fluralaner

Case report (2017)

A CASE OF DEMODICOSIS (DEMODEX INJAI) TREATED WITH A NOVEL ISOXAZOLINE.

Myriam Martín Benito¹, Natalia Sastre¹, Iván Ravera¹ ¹ Universidad Católica de Valencia



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1 client-owned dog Treated once 100% mite free at day 49 Adverse effects not recorded

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Canine demodicosis - Fluralaner

Fourth study (2018)

Vet Dermatol 2018

DOI: 10.1111/vde.12524

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A field trial in Thailand of the efficacy of oral fluralaner for the treatment of dogs with generalized demodicosis

Lerpen Duangkaew* (D, Lawan Larsuprom*, Pojnicha Anukkul*, Chalermpol Lekcharoensuk* and Charles Chen†



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115 client-owned dogs initially (49 lost to follow-up)

21 juvenile-onset

45 adult-onset

Treated 1 to 3 times q84d

Followed up to one year

100% mite free at day 84

No adverse effects

Figure and table





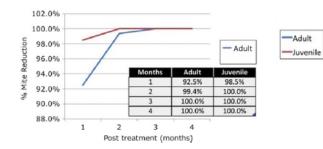


Figure 1. Mean percentage reduction in demodex mite numbers for adult and juvenile dog groups before and during fluralaner therapy for demodicosis.

Table 1. Treatment of canine demodicosis: follow-up period after reaching parasitological cure and number of fluralaner doses given to 46 dogs with adult-onset generalized demodicosis and 21 dogs with juvenile-onset generalized demodicosis.

45 adult cases*	One dose	Two doses	Three doses	Every three months	Tota
Follow up 10-12 months	16	4	2	6	28
Follow up 6-9 months	10	2	1		13
Follow up 2–5 months	2	1	1		4
21 juvenile cases	One dose	Two doses	Three doses	Every three months	Total
Follow up 10-12 months	8	3	2		13
Follow up 6-9 months	3				3
Follow up 2-5 months	2	3			5

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Canine demodicosis - Lotilaner





First study (2017)

RESEARCH

Open Access

Efficacy of lotilaner (Credelio™), a novel oral isoxazoline against naturally occurring mange mite infestations in dogs caused by *Demodex* spp.



Source of funding:

ELANCO

Daniel E. Snyder^{1*}, Scott Wiseman² and Julian E. Liebenberg³

10 stray dogs Treated on days 0, 28 and 56 90% mite free at day 28 100% mite free at day 70 No adverse effects



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Canine demodicosis - Sarolaner





First study (2016)

Efficacy of sarolaner, a novel oral isoxazoline, against two common mite infestations in dogs: *Demodex* spp. and *Otodectes cynotis*

Robert H. Six ^{a,*}, Csilla Becskei ^b, Mark M. Mazaleski ^a, Josephus J. Fourie ^c, Sean P. Mahabir ^a, Melanie R. Myers ^a, Nathalie Slootmans ^b





Source of funding:

8 client-owned dogs

Simparica compared with topical Advantage Multi (8 dogs)
Sarolaner-treated group (day 0, 30 and 60): 100% mite free at day 42

Topical combination imidacloprid/moxidectin-treated group (treated q7d): 100% mite free at 10.5 weeks

No adverse effects

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Canine demodicosis - Sarolaner

Second study (2018)

Efficacy and safety of sarolaner against generalized demodicosis in dogs in European countries: a non-inferiority study

Simparica

(samlanen rhewahle tablets

Source of funding:

Csilla Becskei* 🌔, Otto Cuppens* and Sean P. Mahabir†

53 client-owned dogs

Simparica compared with topical Advantage Multi (28 dogs)

Followed up to 6 months

Sarolaner-treated group (treated 2 to 6 times q30d): 100% mite free at day 150

Topical combination imidacloprid/moxidectin-treated group (treated q7-30d): 1/3 dogs still infested at 6 months

No adverse effects

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Feline demodicosis - Fluralaner

Case report (2017)



The use of oral fluralaner for the treatment of feline generalised demodicosis: a case report

I. Matricoti*.¹ and E. Maina†

*Servizi Dermatologici Veterinari, Bologna, 40125, Italy

*Servizi Dermatologici Veterinari, Lovere, 24065, Italy

1 client-owned cat (*Demodex cati*)
Treated once (112.5 mg per cat PO)
Negative skin scrapings at 1 and 2 months
No adverse effects



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FIG 1. Alopecia, marked erythema and papules on the dorsal nasal region and periocular skin of a cat affected with generalised demodicosis due to



FIG 2. Two months after treatment with a single dose of 28 mg/kg

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Feline demodicosis - Fluralaner





Case report (2018)

Letter to the Editor

Lerpen Duangkaew† (D) and Heather Hoffman* †Dermatology Clinic, Veterinary Teaching Hospital, Kasetsart University, 50 Ngamwongwan Road, Chatuchak, Bangkok, 10900, Thailand

Efficacy of oral fluralaner for the treatment of Demodex gatoi in two shelter cats

* Brookville Animal Hospital, 764S Weber Road,



Self-funded

Bolingbrook, IL 60490, USA

2 shelter cats (one DSH queen and her 6 month old kitten) Treated once (112.5 mg per cat PO) Negative skin scrapings at 1, 2 and 3 months Adverse effects not recorded

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CHAPTE SBCV



Canine scabies - Afoxolaner

First study (2016)

RESEARCH ARTICLE

OPEN 3 ACCESS



aturally (a

Source of funding:



Efficacy of afoxolaner in a clinical field study in dogs naturally infested with *Sarcoptes scabiei*

Frédéric Beugnet 1,* , Christa de Vos², Julian Liebenberg², Lénaïg Halos¹, Diane Larsen¹, and Josephus Fourie²

10 client-owned dogs

NexGard compared with an untreated group (10 dogs)

Treated on days 0 and 28

Afoxolaner-treated group: 100% mite free at day 28

No adverse effects

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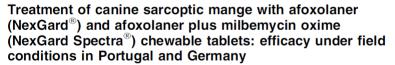
Canine scabies - Afoxolaner

Second study (2018)



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Verena Hampel¹, Martin Knaus², Jürgen Schäfer¹, Frederic Beugnet³, and Steffen Rehbein^{2,*}

65 client-owned dogs

Treated on days 0 and 30 with either oral afoxolaner (38 dogs) or afoxolaner-milbemycin oxime (27 dogs)

Afoxolaner-treated group: 99.7% mite free at day 60

Afoxolaner-milbemycin oxime treated group: 100% mite free at day 60

No adverse effects

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Source of funding:







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Canine scabies - Fluralaner

Second study (2016)

RESEARCH

Open Access



Efficacy of fluralaner administered either orally or topically for the treatment of naturally acquired Sarcoptes scabiei var. canis infestation in dogs

Janina Taenzler^{1*}, Julian Liebenberg², Rainer K. A. Roepke¹, Régis Frénais³ and Anja R. Heckeroth¹

20 client-owned dogs

Bravecto compared with placebo (9 dogs)

Treated once

Oral fluralaner-treated group (9 dogs): 100% mite free at day 28 Topical fluralaner-treated group (11 dogs): 100% mite free at day 28

No adverse effects









Source of funding:





Canine scabies - Fluralaner



Third study (2016)

Vet Dermatol 2016; 27: 353-e88

Efficacy of fluralaner in 17 dogs with sarcoptic mange

Camilo Romero*, Rafael Heredia†, Jocelyn Pineda*, Jonathan A. Serrano‡, Germán D. Mendoza§, Porfirio Trápala¶ and Alberto M. Cordero**



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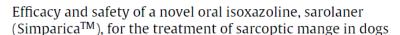
17 client-owned dogs Treated once 100% mite free at day 14 Adverse effects not recorded

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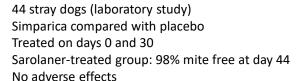
49

Canine scabies - Sarolaner

Fourth study (2016)



Csilla Becskei a,*, Filip De Bock a, Joanna Illambas a, Judith A. Cherni b, Josephus J. Fourie c, Melanie Lane b, Sean P. Mahabir b, Robert H. Six b





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Source of funding:

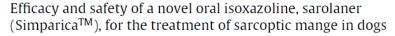






Canine scabies - Sarolaner

Fifth study (2016)



Csilla Becskei ^{a,*}, Filip De Bock ^a, Joanna Illambas ^a, Judith A. Cherni ^b, Josephus J. Fourie ^c, Melanie Lane ^b, Sean P. Mahabir ^b, Robert H. Six ^b



Source of funding:

79 client-owned dogs (field study)

Simparica compared with topical Advantage Multi (45 dogs)

Treated on days 0 and 30

Sarolaner-treated group: 100% mite free at day 60

Topical combination imidacloprid/moxidectin-treated group: 96% mite free at day 60

No adverse effects



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Canine otoacariasis - Afoxolaner

First study (2016)





RESEARCH

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Assessment of afoxolaner efficacy against Otodectes cynotis infestations of dogs

Doug Carithers^{1*}, Jordan Crawford¹, Christa de Vos², Alta Lotriet² and Josephus Fourie²

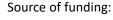


NexGard compared with an untreated group (8 dogs)

Treated once

Afoxolaner-treated group: 98.5% mite reduction at day 28

No adverse effects









Canine and feline otoacariasis - Fluralaner

Second study (2017)

RESEARCH **Open Access**

Efficacy of fluralaner against Otodectes cynotis infestations in dogs and cats

Janina Taenzler^{1*}, Christa de Vos², Rainer K. A. Roepke¹, Régis Frénais³ and Anja R. Heckeroth¹

8 experimentally infested dogs and 8 experimentally infested cats NexGard compared with placebo (8 dogs and 8 cats) Treated orally (dogs) or topically (cats) once

Fluralaner-treated group (dogs): 100% mite reduction at day 28 Fluralaner-treated group (cats): 99.8% mite reduction at day 28

No adverse effects







Source of funding:



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Canine otoacariasis - Sarolaner

Third study (2016)

Efficacy of sarolaner, a novel oral isoxazoline, against two common mite infestations in dogs: Demodex spp. and Otodectes cynotis

Robert H. Six^{a,*}, Csilla Becskei^b, Mark M. Mazaleski^a, Josephus J. Fourie^c, Sean P. Mahabira, Melanie R. Myersa, Nathalie Slootmansb



Source of funding:

Simparica



16 client-owned dogs Simparica compared with placebo (16 dogs) Treated once (8 dogs) or twice at day 0 and 30 (8 dogs) Sarolaner-treated group (1 dose): 98.2% mite reduction at day 30 Sarolaner-treated group (2 doses): 99.5% mite reduction at day 60 No adverse effects





Canine otoacariasis - Sarolaner

Fourth study (2018)

Vet Dermatol 2018

Efficacy and safety of sarolaner in the treatment of canine ear mite infestation caused by Otodectes cynotis: a non-inferiority study

Simparica

Source of funding:

Csilla Becskei* (6), Otto Cuppens* and Sean P. Mahabir†

163 client-owned dogs

Simparica compared with topical Advantage Multi (78 dogs)

Treated once or twice at day 0 and 30

Sarolaner-treated group: 93.3% mite reduction at day 60

Topical combination imidacloprid/moxidectin-treated group: 66.7% mite reduction at day 60

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No adverse effects

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Canine sucking lice - Fluralaner

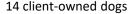
First study (2017)



CrossMark Efficacy of fluralaner (Bravecto™ chewable tablets) for the treatment of naturally acquired *Linognathus setosus* infestations

on dogs

Heike Kohler-Aanesen¹, Seppo Saari², Rob Armstrong³, Karine Péré⁴, Janina Taenzler^{5*}, Eva Zschiesche⁵



Bravecto compared with topical permethrin (10 dogs)

Treated once

Fluralaner-treated group: 100% lice free at day 28

Topical permethrin-treated group: 99.1% mite reduction at day 28

No adverse effects







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Source of funding:





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CHAPTE



Implications for practice

- Newly available
- Novel mode of action
- Easy to use
- Formulated as topical or flavored palatable chewable tablet
- Potent and effective against fleas and ticks
- Long-lasting (a month or more)
- Rapid parasite kill
- Safe



- 👑 -

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Implications for practice





- ► The results of recently published extra-label use studies are encouraging.
- ▶ This new treatment modality offers the potential to provide effective and safe control of many parasitic skin and ear diseases of companion animals, with low frequency of administration, while helping prevent and control fleas and ticks.



REDIBLE IN EVERY DETAIL



Implications for practice

Parasitic disease (Parasite species)	NexGard [®]	Bravecto®	Credelio™	Simparica™
Canine sucking lice infestation (Linognathus setosus)	N/A	Single dose	N/A	N/A
Feline ear mite infestation (Otodectes Cynotis)	N/A	Single dose	N/A	N/A
Canine ear mite infestation (Otodectes Cynotis)	A minimum of 2 doses	Single dose	N/A	A minimum of 2 doses
Canine scabies (Sarcoptes scabiei)	A minimum of 2 doses	Single dose	N/A	A minimum of 2 doses

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Implications for practice

Parasitic disease (Parasite species)	NexGard [®]	Bravecto [®]	Credelio™	Simparica™
Feline demodicosis (Demodex gatoi)	N/A	Single dose	N/A	N/A
Feline demodicosis (Demodex cati)	N/A	Single dose	N/A	N/A
Canine demodicosis (Demodex injai)	N/A	Single dose	N/A	N/A
Canine demodicosis (Demodex canis)	Three doses	Single dose	Three doses	Three doses