Lecture overview

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

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 methicillin-resistant *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 known ivermectin sensitive breed), I decided it was a great opportunity to treat my first case of canine demodicosis with oral fluralaner.

Single dose of oral fluralaner before and after pictures
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.

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.
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.

Oral products currently available in Canada

- Bravecto® 2014
- Nexgard® 2014

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
Oral products currently available in Canada

Simparica™ 2016

Credelio™ 2019

Topical products currently available in Canada

2016 2018

Bravecto® Topical Solution
Combination products currently available in Canada

Revolution® PLUS 2019

NexGard SPECTRA™ 2019

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.

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.
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

Spectrum of activity and duration of efficacy

- Isoxazolines show activity against insects and acarines.

- Due to their pharmacokinetic properties, isoazolines 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.
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.

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.
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.

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

Canine demodicosis - Afoxolaner

- First study (2016)

Efficacy of oral afoxolaner for the treatment of canine generalised demodicosis

Frédéric Beugnet1,*, 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

Source of funding:

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
Photographic documentation

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Canine demodicosis - Afoxolaner

Second study (2016)

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

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
Photographic documentation

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

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:

Boehringer Ingelheim

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
Canine demodicosis - Afoxolaner

Fourth study (2018)

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

Canine demodicosis - Afoxolaner

Fifth study (2018)

50 client-owned dogs
Treated on days 0, 28 and 56 with either oral afoxolaner (31 dogs) or afoxolaner-milbemycin oxime (19 dogs)
98% mite reduction at day 84
No adverse effects

Source of funding:
Boehringer Ingelheim
Canine demodicosis - Afoxolaner

▶ Sixth study (2019)

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

Camilo Romero-Núñez*, Linda Guillerma Bautista-Gómez*, Galia Sheinberg*, Alberto Martín*

Anahí Romero*, Ariadna Flores*, Rafael Heredia*, Laura Miranda*

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

First study (2015)

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

Josephus J Fourie1, Julian E Liebenberg1, Ivan G Horak1, Janina Taende2, Anja R Heckerth3 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 reduction at day 84
No adverse effects

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

第二研究（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 “Brynow”, Katowice, Poland

163 客户拥有的狗
狗在第0天和第90天接受治疗
87％的螨虫在第30天清除
100％的螨虫在第84天清除
没有副作用

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第三研究（2016）

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

P. T. ARIAS* and A. M. CORDERO†

* Clínica Dermatológica Alhaurín, Monterrey, Nuevo Leon, Mexico; † VETDERM Dermatología Veterinaria Especializada, Guadalajara, Jalisco, Mexico

4 客户拥有的狗
接受治疗的天数为0和60
98％的螨虫在第84天减少
没有副作用记录
Canine demodicosis - Fluralaner

- Case report (2017)

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

Myriam Martín Benito\textsuperscript{1}, Natalia Sastre\textsuperscript{1}, Iván Ravera\textsuperscript{1}
\textsuperscript{1}Universidad Católica de Valencia

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

Canine demodicosis - Fluralaner

- Fourth study (2018)

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

Lerpen Duangkaew\textsuperscript{1}, Lawan Larsuprom\textsuperscript{1}, Pojicha Anukkul\textsuperscript{1}, Chalermpol Lekcharoensuk\textsuperscript{1} and Charles Chen\textsuperscript{1}

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
Canine demodicosis - Lotilaner

First study (2017)

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

Daniel F. Snyder¹, Scott Wixman² 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
**Photographic documentation**

### 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, Csilla Becskei, Mark M. Mazaleski, Josephus J. Fourie, Sean P. Mahabir, Melanie R. Myers, Nathalie Slootmans

  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

Source of funding: zoetis
**Canine demodicosis - Sarolaner**

- Second study (2018)

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

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

**Feline demodicosis - Fluralaner**

- Case report (2017)

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

I. Matriotti* and E. Maina†

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
Photographic documentation

![Photographic documentation](image)

Feline demodicosis - Fluralaner

- Case report (2018)

**Letter to the Editor**

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

Lerpen Duangkaew† and Heather Hoffman*

†Dermatology Clinic, Veterinary Teaching Hospital, Kasetsart University, 50 Ngamwongwan Road, Chatuchak, Bangkok, 10900, Thailand

*Brookville Animal Hospital, 7645 Weber Road, Bolingbrook, IL 60440, 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

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
Canine scabies - Afoxolaner

First study (2016)

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

Frédéric Beugnet, Christa de Vos, Julian Liebenberg, Lénaïg Halos, Diane Larsen, and Josephus Fourie

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

Second study (2018)

**Treatment of canine sarcoptic mange with afoxolaner (NexGard®) and afoxolaner plus milbemycin oxime (NexGard Spectra®) chewable tablets: efficacy under field conditions in Portugal and Germany**

Verena Hampel, Martin Knauß, Rügén Schäfer, Frédéric Beugnet, and Steffen Rebbein

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
Photographic documentation

Canine scabies - Fluralaner

- Second study (2016)

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

Janka Taendera, Julian Liebenberg, Rainer K. A. Roepke, Régis Frénais and Anja R. Heckeroth

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)

  *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**

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

Canine scabies - Sarolaner

- Fourth study (2016)

  *Efficacy and safety of a novel oral isoxazoline, sarolaner (Simparica®), for the treatment of sarcoptic mange in dogs*

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

  44 stray dogs (laboratory study)
  Simparica compared with placebo
  Treated on days 0 and 30
  Sarolaner-treated group: 98% mite free at day 44
  No adverse effects
Canine scabies - Sarolaner

- Fifth study (2016)

Efficacy and safety of a novel oral isoxazole, sarolaner (Simparica™), for the treatment of sarcoptic mange in dogs

Csilla Becskei, Filip De Bock, Joanna Illamas, Judith A. Cherni, Josephus J. Fourie, Melanie Lane, Sean P. Mahabir, Robert H. Six

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

Canine otoacariosis - Afoxolaner

- First study (2016)

Assessment of afoxolaner efficacy against Otodectes cynotis infestations of dogs

Doug Carithers, Jordan Crawford, Christa de Vos, Alta Lotriet, and Josephus Fourie

8 colony dogs
NexGard compared with an untreated group (8 dogs)
Treated once
Afoxolaner-treated group: 98.5% mite reduction at day 28
No adverse effects

Dr. Vincent Defalque
Diplomate of the American College of Veterinary Dermatology
North West Veterinary Dermatology Services
Canine and feline otoacarasis - Fluralaner

- Second study (2017)

**Efficacy of fluralaner against *Otodectes cynotis* infestations in dogs and cats**

Janina Taenzler¹, Christa de Vos², Rainer K. A. Roepke¹, Regis Frénais¹ and Anja R. Heckerth¹

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

Canine otoacarasis - 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. Six³⁴, Csilla Becskei⁵, Mark M. Mazaleski², Josephus J. Fourie⁶, Sean P. Mahabir⁷, Melanie R. Myers⁴, Nathalie Slootmans⁴

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 otoacariosis - Sarolaner

- Fourth study (2018)

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

Csilla Becskai*, 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
No adverse effects

Canine sucking lice - Fluralaner

- First study (2017)

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

Helie Kohler-Aanesen1, Seppo Sari†, Rob Armstrong2, Kaline Péré3, Janina Taender3, Eva Zschiesche7 and Anja R. Heekersch**

14 client-owned dogs
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
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

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.
Implications for practice

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