

Second-Generation H₁ Antihistamines

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Second-generation H₁ antihistamines can be effective tools in the treatment of canine chronic urticaria. Anecdotal reports have also found them to be useful in the control of pruritus in some dogs with atopic dermatitis (AD) and in cats with allergic skin disease.

CLINICAL APPLICATIONS

Cetirizine (active metabolite of hydroxyzine), loratadine, and fexofenadine (active metabolite of terfenadine) are the most commonly used second-generation H₁ antihistamines in veterinary medicine.¹⁻⁴

- ▶ Recommended dose protocols
 - Cetirizine
 - **Dogs:** 1 mg/kg PO once a day^{1,3,5}
 - **Cats:** 5 mg/cat PO once a day^{6,7}
 - Loratadine¹
 - **Dogs:** 1 mg/kg PO 1-2 times a day
 - **Cats:** 2.5-5 mg/cat PO once a day
 - Fexofenadine (anecdotal)
 - **Dogs:** 5-10 mg/kg PO once a day

- **Cats:** 15-30 mg/cat PO once a day
- ▶ All 3 medications are affordably priced.
 - One month of treatment costs <\$60.

In dogs, the primary indications for use of second-generation H₁ antihistamines are chronic urticaria and AD.

- ▶ Acute and severe cases of urticaria have been treated with epinephrine and glucocorticoids (PO, IM, IV).²
 - In chronic or relapsing cases, all H₁ antihistamines can be effective in preventing development of new lesions, although they appear to have limited efficacy on existing lesions.²
- ▶ Clinical efficacy of any H₁ antihistamine treatment of canine AD is controversial, primarily because of the scarce number of well-designed randomized controlled trials.⁸
 - In a single-blinded placebo-controlled study, only 18% of dogs showed satisfactory pruritus control when treated with cetirizine at 1 mg/kg PO once a day.³
 - One double-blinded placebo-controlled study could not detect efficacy of terfenadine as an antipruritic agent in atopic dogs.⁹

- However, several open studies have shown acceptable results, especially in mildly pruritic dogs without chronic skin lesions.
 - In 1 study of 30 dogs, >60% had at least partial reduction of clinical signs when treated with 1 of 6 different antihistamines (ie, hydroxyzine, trimeprazine, chlorpheniramine, clemastine, promethazine, cyproheptadine), with hydroxyzine being the most effective.¹⁰
 - In a comparative study involving 30 dogs, fexofenadine at a high dose of 18 mg/kg PO once a day demonstrated the same efficacy as did methylprednisolone at 0.5 mg/kg PO once a day.⁴
 - A retrospective study showed that 25% of clients administering oral antihistamines to their atopic dogs reported high efficacy in controlling clinical signs.¹¹

Despite varied study results, many dermatologists agree that all H₁ antihistamines have a place in the management of canine AD.^{1,8}

- ▶ Prescribing an antihistamine for a minimum of 2 weeks before evaluating its effectiveness has been recommended.¹ The beneficial effect, if any, occurs within the first 7 to 14 days of treatment.
- ▶ Drugs of this class are best used as preventives before a flare occurs and should be given on a continuous daily basis to prevent or reduce severity of AD flares.⁸
- ▶ When using any H₁ antihistamine in the treatment of canine AD, recommended strategy is based on clinical observations and patient response.¹²
 - Efficacy appears to be variable among individuals.^{1,8}
 - All H₁ antihistamines may be additive or synergistic in their effects when used with other medications (eg, supplemental essential fatty acids, corticosteroids) and are therefore considered steroid-sparing agents (ie, they may allow for steroid dose reduction).¹³
 - Sedative actions may be partly responsible for clinical benefit.⁸
 - In some patients, first-generation antihistamines (eg, diphenhydramine, hydroxyzine, chlorpheniramine, amitriptyline) may be more effective than second-generation antihistamines.⁸

Very few reports have been published on the efficacy of second-generation H₁ antihistamine treatment of allergic skin disease in cats.

- ▶ In 1 study, cetirizine administered at 5 mg/cat PO once a day

H₁ antihistamines, best used as preventives before a flare occurs, should be given on a continuous daily basis.⁸

was effective in controlling pruritus in 13 of 32 (41% of) cats with allergic skin disease.⁷

- ▶ Because of the steroid-sparing effect of antihistamines, they are usually given to allergic cats in combination with steroids.²

PHARMACOLOGY

All H₁ antihistamines down-regulate allergic inflammation directly, acting as inverse agonists that combine with and stabilize inactive conformation of the H₁ receptor on sensory neurons and small blood vessels.^{14,15}

- ▶ They also appear to decrease histamine release from basophils and mast cells in vitro.¹⁶
- ▶ Hydroxyzine and its metabolite cetirizine have demonstrable antihistaminic action in dogs and according to some authors should be the preferred antihistamines used in that species.^{5,8}

Second-generation H₁ antihistamines were developed to avoid the sedation (considered a main side effect) of first-generation H₁ antihistamines.¹⁵

- ▶ Because of their lipid solubility, relatively high molecular weight, and affinity for the P-glycoprotein efflux pump, second-generation H₁ antihistamines penetrate poorly into the CNS.¹⁷
 - They also appear to have low potential of crossing the blood-brain barrier. P-glycoprotein further reduces the accumulation of cetirizine and fexofenadine in the CNS.¹⁷
- ▶ *Third-generation antihistamine* is occasionally used to define the newest members of this antihistamine family (ie, levocetirizine, desloratadine, fexofenadine).
 - However, the pharmacologic characteristics of both second- and third-generation antihistamines are essentially the same and, therefore, have been grouped together.¹⁴

AD = atopic dermatitis
 CNS = central nervous system
 H₁ = histamine 1 receptor

There may be some basis for the belief that second-generation H₁ antihistamines may not be as effective as their first-generation counterparts.

- ▶ However, good head-to-head comparisons of the pharmacologic actions of first- vs second-generation antihistamines are lacking.
- ▶ An advantage of second-generation H₁ antihistamines is their relatively minimal sedative effect as compared with their first-generation counterparts.¹⁵
 - Second-generation drugs are considered a good alternative for patients that respond to antihistamines but present with unwanted side effects (eg, drowsiness, behavioral changes).¹²
 - However, as noted earlier, the sedative actions of first-generation antihistamines may have clinical benefits in some patients.⁸
- ▶ Another main advantage is the longer half-life of second-generation antihistamines and once- or twice-daily administration.
 - In dogs, the terminal half-life of cetirizine is 10 to 11 hours.⁵
 - In comparison, first-generation antihistamines require more frequent administration (ie, 2-3 times a day).⁵

DRUG INTERACTIONS & ADVERSE EVENTS

No known contraindications are associated with second-generation H₁ antihistamines.

- ▶ Substances that act as inhibitors of the cytochrome P450 3A4 (CYP3A4) enzyme (eg, ketoconazole, erythromycin, cimetidine) can lead to increased plasma levels of loratadine.¹⁵
- ▶ In the author's experience, cetirizine, loratadine, and fexofenadine appear to be well tolerated in dogs and cats.
 - Vomiting, loss of appetite, or drowsiness has occasionally been reported.^{3,4}

Terfenadine, a second-generation H₁ antihistamine, has shown cardiotoxic effects (ie, arrhythmia, prolonged QT interval) in humans, especially at high doses.¹⁵

- ▶ This product has been removed from the market in the United States, Canada, and most European countries.
- ▶ Cardiotoxicity has not been detected in canine or feline patients receiving cetirizine, loratadine, or fexofenadine. ■■■

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AD = atopic dermatitis

CYP3A4 = cytochrome P450 3A4

References appear online at plumbstherapeuticsbrief.com

sentinel[®] spectrum[®]

(milbemycin oxime-lufenuron-praziquantel)

Caution

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

Indications

SENTINEL[®] SPECTRUM[®] (milbemycin oxime/lufenuron/praziquantel) is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*; for the prevention and control of flea populations (*Ctenocephalides felis*); and for the treatment and control of adult roundworm (*Toxocara canis*, *Toxascaris leonina*), adult hookworm (*Ancylostoma caninum*), adult whipworm (*Trichuris vulpis*), and adult tapeworm (*Taenia pisiformis*, *Echinococcus multilocularis* and *Echinococcus granulosus*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

Dosage and Administration

SENTINEL SPECTRUM should be administered orally, once every month, at the minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime, 4.55 mg/lb (10 mg/kg) lufenuron, and 2.28 mg/lb (5 mg/kg) praziquantel. For heartworm prevention, give once monthly for at least 6 months after exposure to mosquitoes.

Dosage Schedule				
Body Weight	Milbemycin Oxime per chewable	Lufenuron per chewable	Praziquantel per chewable	Number of chewables
2 to 8 lbs.	2.3 mg	46 mg	22.8 mg	One
8.1 to 25 lbs.	5.75 mg	115 mg	57 mg	One
25.1 to 50 lbs.	11.5 mg	230 mg	114 mg	One
50.1 to 100 lbs.	23.0 mg	460 mg	228 mg	One
Over 100 lbs.	Administer the appropriate combination of chewables			

To ensure adequate absorption, always administer SENTINEL SPECTRUM to dogs immediately after or in conjunction with a normal meal.

SENTINEL SPECTRUM may be offered to the dog by hand or added to a small amount of dog food. The chewables should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole. Care should be taken that the dog consumes the complete dose, and treated animals should be observed a few minutes after administration to ensure that no part of the dose is lost or rejected. If it is suspected that any of the dose has been lost, redosing is recommended.

Contraindications

There are no known contraindications to the use of SENTINEL SPECTRUM.

Warnings

Not for use in humans. Keep this and all drugs out of the reach of children.

Precautions

Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention.

Prior to administration of SENTINEL SPECTRUM, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. SENTINEL SPECTRUM is not effective against adult *D. immitis*.

Mild, transient hypersensitivity reactions, such as labored breathing, vomiting, hypersalivation, and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Do not use in puppies less than six weeks of age.

Do not use in dogs or puppies less than two pounds of body weight.

The safety of SENTINEL SPECTRUM has not been evaluated in dogs used for breeding or in lactating females. Studies have been performed with milbemycin oxime and lufenuron alone.

Adverse Reactions

The following adverse reactions have been reported in dogs after administration of milbemycin oxime, lufenuron, or praziquantel: vomiting, depression/lethargy, pruritus, urticaria, diarrhea, anorexia, skin congestion, ataxia, convulsions, salivation, and weakness.

To report suspected adverse drug events, contact Virbac at 1-800-338-3659 or the FDA at 1-888-FDA-VETS.

Information for Owner or Person Treating Animal

Echinococcus multilocularis and *Echinococcus granulosus* are tapeworms found in wild canids and domestic dogs. *E. multilocularis* and *E. granulosus* can infect humans and cause serious disease (alveolar hydatid disease and hydatid disease, respectively). Owners of dogs living in areas where *E. multilocularis* or *E. granulosus* are endemic should be instructed on how to minimize their risk of exposure to these parasites, as well as their dog's risk of exposure. Although SENTINEL SPECTRUM was 100% effective in laboratory studies in dogs against *E. multilocularis* and *E. granulosus*, no studies have been conducted to show that the use of this product will decrease the incidence of alveolar hydatid disease or hydatid disease in humans. Because the prepatent period for *E. multilocularis* may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfect and shed eggs between treatments.

Manufactured for: Virbac AH, Inc.
P.O. Box 162059, Ft. Worth, TX 76161

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