

FOCUS

Cyclosporine & Ketoconazole:
Combine with Caution

Cyclosporine (CsA) is licensed for the treatment of canine atopic dermatitis, the target dose for which is 5 mg/kg PO q24h, presumably for the duration of life. Although effective, the drug can be cost prohibitive, so methods to decrease cost have been attempted. One off-label protocol is to combine CsA with ketoconazole (KTZ); both drugs are metabolized by liver cytochrome P450 enzyme. Anecdotal evidence, despite a lack of studies, suggests that concurrent administration of ketoconazole can decrease CsA dose by as much as 50% while still maintaining therapeutic CsA concentrations.

Whole blood and skin concentrations of CsA were determined in 4 treatment protocols: CsA at 5 mg/kg/day (treatment 1), CsA at 2.5 mg/kg/day (treatment 2), CsA at 2.5 mg/kg/day and KTZ at 2.5 mg/kg/day (treatment 3), and CsA at 2.5 mg/kg/day and KTZ at 5 mg/kg/day (treatment 4). Six laboratory beagles were randomly assigned to a treatment protocol for 7 days, followed by a washout and assignment to a second protocol; peak and trough blood and skin samples were collected and CsA assays performed. Mean blood concentrations in the treatment 1 group were not different than those in treatment groups 2 and 4. Mean skin concentrations in treatment 1 were greater than treatment 2 concentrations, not different than those in

treatment 4, and less than those in treatment 3.

■ Commentary

Even though this study demonstrated administration of KTZ at 5 mg/kg/day and CsA at 2.5 mg/kg/day may be as effective as CsA at 5.0 mg/kg/day alone, *this is off-label use*. I do not support this drug combination for several reasons: First, it is important to know whether a dog responds to CsA; starting a drug combination that *may* be as effective is not the same as knowing it *will* be effective. Second, many dogs can be transitioned to q48h dosing of CsA, decreasing dose and cost. Third, routine laboratory monitoring of serum biochemistry profiles is necessary in dogs receiving KTZ; concurrent use may be false economy. On a final note, atopic dermatitis management is complex and requires tending to many flare factors.

—Karen A. Moriello, DVM, DACVD

■ ■ Source

The effect of ketoconazole on whole blood and skin cyclosporin concentrations in dogs. Gray LL, Hillier A, Cole LK, Rajala-Schultz PJ. *VET DERMATOL* 24:118-125, 2013

■ ■ ■ For More

To find more about cyclosporine, see **Cyclosporine: An Overview for Alternative Use** by Dr. Alexander Werner in the December 2012 issue or at cliniciansbrief.com/cyclosporine-alternative-use

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revolution®
(selamectin)

Topical Parasiticide for Dogs and Cats

BRIEF SUMMARY:

See package insert for full prescribing information.

CAUTION:

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

INDICATIONS:

Revolution is recommended for use in dogs six weeks of age or older and cats eight weeks of age and older for the following parasites and indications:

Dogs:

Revolution kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. Revolution also is indicated for the treatment and control of sarcoptic mange (*Sarcoptes scabiei*) and for the control of tick infestations due to *Dermacentor variabilis*.

Cats:

Revolution kills adult fleas and prevents flea eggs from hatching for one month and is indicated for the prevention and control of flea infestations (*Ctenocephalides felis*), prevention of heartworm disease caused by *Dirofilaria immitis*, and the treatment and control of ear mite (*Otodectes cynotis*) infestations. Revolution is also indicated for the treatment and control of roundworm (*Toxocara cati*) and intestinal hookworm (*Ancylostoma tubaeforme*) infections in cats.

WARNINGS:

Not for human use. Keep out of the reach of children.

In humans, Revolution may be irritating to skin and eyes. Reactions such as hives, itching and skin redness have been reported in humans in rare instances. Individuals with known hypersensitivity to Revolution should use the product with caution or consult a health care professional. Revolution contains isopropyl alcohol and the preservative butylated hydroxytoluene (BHT). Wash hands after use and wash off any product in contact with the skin immediately with soap and water. If contact with eyes occurs, then flush eyes copiously with water. In case of ingestion by a human, contact a physician immediately. The material safety data sheet (MSDS) provides more detailed occupational safety information. For a copy of the MSDS or to report adverse reactions attributable to exposure to this product, call 1-800-366-5288.

Flammable—Keep away from heat, sparks, open flames or other sources of ignition.

Do not use in sick, debilitated or underweight animals. (see SAFETY)

PRECAUTIONS:

Prior to administration of Revolution, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. Revolution is not effective against adult *D. immitis* and, while the number of circulating microfilariae may decrease following treatment, Revolution is not effective for microfilariae clearance.

Hypersensitivity reactions have not been observed in dogs with patent heartworm infections administered three times the recommended dose of Revolution. Higher doses were not tested.

ADVERSE REACTIONS:

Pre-approval clinical trials:

Following treatment with Revolution, transient localized alopecia with or without inflammation at or near the site of application was observed in approximately 1% of 691 treated cats. Other signs occurred rarely (≤0.5% of 1743 treated cats and dogs) included vomiting, loose stool or diarrhea with or without blood, anorexia, lethargy, salivation, tachypnea, and muscle tremors.

Post-approval experience:

In addition to the aforementioned clinical signs that were reported in pre-approval clinical trials, there have been reports of pruritus, urticaria, erythema, ataxia, fever and rare reports of death. There have also been rare reports of seizures in dogs. (see WARNINGS)

SAFETY:

Revolution has been tested safe in over 100 different pure and mixed breeds of healthy dogs and over 15 different pure and mixed breeds of healthy cats, including pregnant and lactating females, breeding males and females, puppies six weeks of age and older, kittens eight weeks of age and older, and avermectin-sensitive collies. A kitten, estimated to be 5–6 weeks old (0.3 kg), died 8–12 hours after receiving a single treatment of Revolution at the recommended dosage. The kitten displayed clinical signs which included muscle spasms, salivation and neurological signs. The kitten was a stray with an unknown history and was malnourished and underweight (see WARNINGS).

DOGS: In safety studies, Revolution was administered at 1, 3, 5, and 10 times the recommended dose to six-week-old puppies, and no adverse reactions were observed. The safety of Revolution administered orally also was tested in case of accidental oral ingestion. Oral administration of Revolution at the recommended topical dose in 5- to 8-month-old beagles did not cause any adverse reactions. In a pre-clinical study selamectin was dosed orally to ivermectin-sensitive collies. Oral administration of 2.5, 10, and 15 mg/kg in this dose escalating study did not cause any adverse reactions; however, eight hours after receiving 5 mg/kg orally, one avermectin-sensitive collie became ataxic for several hours, but did not show any other adverse reactions after receiving subsequent doses of 10 and 15 mg/kg orally. In a topical safety study conducted with avermectin-sensitive collies at 1, 3 and 5 times the recommended dose of Revolution, salivation was observed in all treatment groups, including the vehicle control. Revolution also was administered at 3 times the recommended dose to heartworm infected dogs, and no adverse effects were observed.

CATS: In safety studies, Revolution was applied at 1, 3, 5, and 10 times the recommended dose to six-week-old kittens. No adverse reactions were observed. The safety of Revolution administered orally also was tested in case of accidental oral ingestion. Oral administration of the recommended topical dose of Revolution to cats caused salivation and intermittent vomiting. Revolution also was applied at 4 times the recommended dose to patent heartworm infected cats, and no adverse reactions were observed.

In well-controlled clinical studies, Revolution was used safely in animals receiving other frequently used veterinary products such as vaccines, anthelmintics, antiparasitics, antibiotics, steroids, collars, shampoos and dips.

STORAGE CONDITIONS: Store below 30°C (86°F).

HOW SUPPLIED: Available in eight separate dose strengths for dogs and cats of different weights. Revolution for puppies and kittens is available in cartons containing 3 single dose tubes. Revolution for cats and dogs is available in cartons containing 3 or 6 single dose tubes.

NADA 141-152, Approved by FDA.

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 Pfizer Animal Health

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