



Cyclosporine

Cyclosporine, a calcineurin inhibitor, is increasingly used to treat dermatologic and systemic inflammatory and immune-mediated diseases in dogs and cats.¹

Todd M. Archer, DVM, MS, DACVIM

Claire L. Fellman, DVM

Mississippi State University

Overview

- ⚠️ As an immunosuppressive agent affecting primarily T-cells, cyclosporine was originally used for organ transplantation in human and veterinary medicine.¹
- ⚠️ A veterinary ophthalmic topical cyclosporine preparation is also available.
- ⚠️ Caution should be used when administering this potent agent.

Formulations

- ⚠️ The only veterinary-approved formulation is ultramicronized modified cyclosporine¹ (Atopica).
 - Absorbed more consistently and can lower risks associated with over- or underdosing
- ⚠️ Vegetable oil-based formulation (Sandimmune) is not approved for use in dogs and cats.¹
 - Because of variability in oral bioavailability, marked intraindividual and interindividual variation in blood concentrations can be seen.¹
 - Atopica and Sandimmune are not bioequivalent.²

Gastrointestinal Upset & Solutions

- ⚠️ Most commonly cited side effect associated with administration of cyclosporine to dogs and cats is GI upset,¹⁻⁵ notably
 - Vomiting
 - Diarrhea
 - Inappetence

Administration Options

- ⚠️ Various options for administering oral cyclosporine can help alleviate GI side effects.
 - Administer concurrent anti-emetic⁵ (eg, metoclopramide, maropitant)
 - Administer frozen capsules^{1,5}
 - In dogs, may decrease blood concentrations and jeopardize treatment efficacy
 - Administer capsules with small amount of food^{1,5}
 - In dogs, may decrease blood concentrations and jeopardize treatment efficacy
 - Start at a lower dose (1–2 mg/kg q24h) and gradually increase to final dose⁵
 - Not appropriate for life-threatening immune-

mediated diseases, such as immune-mediated hemolytic anemia

- Decrease dose^{1,5}

Cyclosporine-Induced Gingival Hyperplasia

- ⚠️ Monitoring
 - Gingival hyperplasia is a known side effect of cyclosporine in dogs and cats, so patients on cyclosporine should be monitored for the condition.¹⁻⁵
 - Risk appears dose-dependent, but significant interindividual differences exist in incidence and severity⁵
- ⚠️ Managing
 - Generally mild and of limited clinical significance⁵
 - If problematic, hyperplasia often improves with cyclosporine dose reduction.⁵
 - Significant hyperplasia may require drug discontinuation.⁵
 - Azithromycin toothpaste and systemic azithromycin have improved the severity of gingival hyperplasia in some dogs.⁵

Check any medication administered concurrently with cyclosporine for possible drug interactions.

Less Common Disorders & Adverse Effects

⚠️ Less common adverse effects include^{3,4}

- **Cats only**
 - Behavior disorders (eg, hiding, hyperactivity, aggression)
 - Hypersalivation
 - Ocular discharge
 - Sneezing/rhinitis
- **Dogs only**
 - Cutaneous papillomatosis

- Lymphadenopathy
- Persistent otitis externa
- **Dogs & cats**
 - Secondary infection
 - Lethargy

Drug Interactions & Patient Assessment

- ⚠️ Cyclosporine is metabolized by the cytochrome P450 enzyme CYP3A; some drugs can impact CYP3A activity.¹
- Check any medication

administered concurrently with cyclosporine for possible drug interactions.

- Interactions can increase or decrease cyclosporine blood concentrations and potentially cause drug toxicity or failure.^{1,2}
- Ketoconazole is the most common drug co-administered to purposefully decrease cyclosporine dosages and still achieve adequate cyclosporine blood concentrations.

Potential for Drug Toxicity or Failure

⚠️ Drugs that can increase cyclosporine blood concentrations²

A acetazolamide, allopurinol, amiodarone, amlodipine, azithromycin, azole antifungals	F fluvoxamine
B bromocriptine	G glipizide, grapefruit juice or powder
C calcium channel blockers, carvedilol, chloramphenicol, ciprofloxacin, cisapride, colchicine, corticosteroids	I imipenem
D danazol, digoxin	L Losartan
E enrofloxacin, estrogens	M macrolide antibiotics, medroxyprogesterone, metronidazole
	O omeprazole
	S sertraline
	T tinidazole
	V valsartan

⚠️ Drugs that can decrease cyclosporine blood concentrations²

A azathioprine	R rifampin
C carbamazepine, clindamycin, cyclophosphamide	S St. John's wort, sulfadiazine, sulfamethoxazole, sulfasalazine
F famotidine	G griseofulvin
N nafcillin	O octreotide
P phenobarbital, phenytoin	T terbinafine, trimethoprim
	W warfarin



Because individual patient responses can vary, it may be beneficial to measure blood concentrations from samples obtained at trough and 2 hours after dosing or, in the case of dogs only, to assess pharmacodynamics.

Do Not Use

- ⚠ In breeding, pregnant, or lactating dogs or cats^{3,4}
- ⚠ In cats with FeLV or FIV infection⁴
- ⚠ In cats that are hypersensitive to cyclosporine⁴
- ⚠ In dogs or cats with neoplasia or a history of neoplasia^{3,4}

—Reduces hepatic metabolism of cyclosporine, allowing decrease of oral cyclosporine doses by as much as 75%¹

- Although much less commonly used in clinical patients, powdered whole grapefruit can also increase blood concentrations in dogs.¹

- ⚠ Because individual patient responses can vary, measuring blood concentrations and/or assessing pharmacodynamics can be beneficial.
 - When measuring blood concentrations, obtaining samples at peak (2 hours after dosing) and trough is recommended.¹
 - Laboratory and analysis method for monitoring samples should be consistent for each patient.
 - Some laboratories measure cyclosporine metabolites and the parent drug.¹
 - *Dogs only:* To measure patient immune response by pharmacodynamic assessment, blood samples can be sent to Mississippi State University College of Veterinary Medicine (cvm.msstate.edu).
 - Obtaining test results regarding patient's immune response can help guide dose decisions (based on authors' research, samples received from private practitioners, and ongoing clinical trials at MSU).

Precautions & Potentially Fatal Outcomes

- ⚠ *Dogs only:* Food can decrease oral absorption of the ultramicrocrystallized formulation of cyclosporine in dogs, so they should receive cyclosporine on an empty stomach.³
 - Because this effect was not seen in cats, they should receive cyclosporine with a meal.⁴
- ⚠ Because safety studies have not been conducted, exercise caution when administering cyclosporine to
 - Dogs or cats younger than 6 months of age^{3,4}
 - Dogs weighing less than 4 pounds³
 - Cats weighing less than 3 pounds⁴
- ⚠ Because cyclosporine suppresses the immune system, monitor patients for development of secondary fungal or protozoal infection.
 - Even the label dose used for treating atopic dermatitis may cause significant immune effects with potential risk for increased systemic infection.^{1,6}
- ⚠ *Cats only:* Cyclosporine has been associated with potentially fatal toxoplasmosis from acute infection or secondary to reactivation of latent infection.^{7,8}
 - Monitor closely for clinical signs associated with *Toxoplasma gondii* infection.^{7,8}

TODD M. ARCHER, DVM, MS, DACVIM, is an assistant professor of small animal internal medicine at Mississippi State University, where he earned his DVM and Master's degrees as well as completed an internship and residency. Dr. Archer is part of a team that has investigated the effects of cyclosporine on the canine immune system, has published this work, and is conducting ongoing clinical trials in dogs receiving cyclosporine therapy. His clinical interests include hematology, immunology, and endocrinology.

CLAIRE L. FELLMAN, DVM, is a small animal internal medicine and veterinary clinical pharmacology resident at Mississippi State University. Her PhD research involves pharmacodynamic assessment of the effects of cyclosporine in dogs. After completion of her training, Dr. Fellman will pursue an academic appointment to continue clinical research and teaching.

REFERENCES

1. **Oral cyclosporine treatment in dogs: A review of the literature.** Archer TM, Boothe DM, Langston VC, et al. *JVIM* 28(1):1-20, 2014.
2. **Plumb's Veterinary Drug Handbook**, 7th ed. Plumb DC (ed)—Ames, IA: Wiley-Blackwell, 2011, pp 352-357.
3. Novartis Animal Health (2008). Atopica for Dogs (product label). Greensboro, NC.
4. Novartis Animal Health (2011). Atopica for Cats (product label). Greensboro, NC.
5. **Life-long diseases need life-long treatment: Long-term safety of ciclosporin in canine atopic dermatitis.** Nuttall T, Reece D, Roberts E. *Vet Rec* 174(suppl 2):3-12, 2014.
6. **Pharmacodynamic monitoring of canine T-cell cytokine response to oral cyclosporine.** Archer TM, Fellman CL, Stokes JV, et al. *JVIM* 25(6):1391-1397, 2011.
7. **A case of fatal systemic toxoplasmosis in a cat being treated with cyclosporin A for feline atopy.** Last RD, Suzuki Y, Manning T, et al. *Vet Dermatol* 15(3):194-198, 2004.
8. **Antemortem diagnosis and treatment of toxoplasmosis in two cats on cyclosporin therapy.** Barrs VR, Martin P, Beatty JA. *Aust Vet J* 84(1-2):30-35, 2006.



Trusted in the Trenches

#1

FOR 8
CONSECUTIVE YEARS

FOR DIAGNOSTIC AND TREATMENT INFORMATION¹

MOST ESSENTIAL PROFESSIONAL READING CHOICE¹

PUBLICATION VETERINARY PROFESSIONALS WOULD READ FIRST¹

Subscribe to *Clinician's Brief* for free² at
cliniciansbrief.com/subscribe or call 855-229-4956.

clinician's brief
THE OFFICIAL PUBLICATION OF THE NAVC

¹2007-2014 Essential Media Study

²For qualified recipients