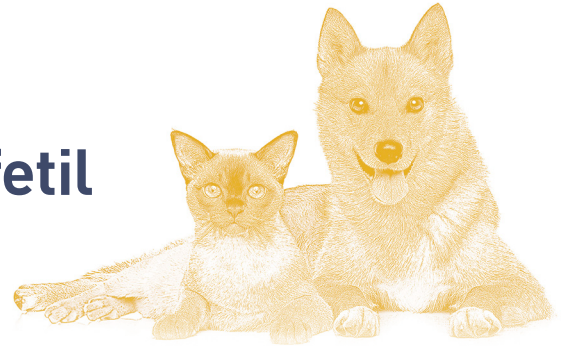




Mycophenolate Mofetil



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In recent years, the indications and reported frequency of use of mycophenolate mofetil (MMF) in veterinary patients has rapidly expanded.

Clinical Applications



Clinically, MMF is used to suppress the immune system.

- Often used in conjunction with other immunosuppressive medications (eg, glucocorticoids) for the treatment of immune-mediated disease or prevention of tissue rejection following organ transplantation
- Veterinary conditions in which MMF therapy has been investigated include immune-mediated hemolytic anemia, aplastic anemia, immune-mediated thrombocytopenia, glomerulonephritis, myasthenia gravis, inflammatory neurologic disease, and autoimmune dermatologic disease.¹⁻⁷
- Prospective clinical trials are warranted to confirm efficacy and better guide MMF use in veterinary patients.
—To date, efficacy has primarily been reported retrospectively.



MMF exerts its effect primarily through inhibition of T- and B-lymphocyte proliferation and subsequent reduction in antibody production.

- MMF is the bioavailable prodrug of mycophenolic acid, an inhibitor of the inosine-5'-monophosphate dehydrogenase enzyme necessary for lymphocyte purine production.⁸

Protocol



Commonly, 10 mg/kg PO or IV administered twice a day is used in dogs.

- Reported dose regimens have ranged from 10 mg/kg 2 to 3 times a day to up to 20 mg/kg twice a day, with higher doses often resulting in unacceptable GI toxicity.⁹
—Dosages at or exceeding 15 mg/kg twice a day generally are not recommended by the authors.



No pharmacokinetic studies have evaluated MMF use in cats.

- A single report has described clinical MMF use at 10 mg/kg PO twice a day with apparent tolerance in 2 cats with immune-mediated hemolytic anemia.¹⁰



Availability of both oral and parenteral formulations allows MMF to be used in both the intensive and chronic stages of therapy.

- Commercial products include 250-mg capsules, 500-mg tablets, a 200-mg/mL oral suspension, and a powder for IV injection (diluted with 5% dextrose to a final concentration of 6 mg/mL before administration).¹¹
- IV administration of MMF is labeled as incompatible with other infusions¹¹; the total dose should be administered slowly over a minimum of 2 hours to achieve peak plasma concentrations, similar to oral administration.¹²



MMF can be compounded into an oral liquid without loss of efficacy over time if mixed correctly and handled appropriately.^{13,14}

- Storage at room (25°C) or refrigerated (5°C) temperature results in a shelf life of 28 or 210 days, respectively.
- Most solutions should be mixed by gently shaking before withdrawing each dose.^{13,14}
- Caution is recommended to ensure compounded products do not contain artificial sweeteners (eg, xylitol) that are unsafe for use in animals.

Pharmacokinetics



Following oral administration, MMF is rapidly absorbed and subsequently undergoes primarily hepatic metabolism with renal excretion.^{9,15-17}

- Lesser degrees of renal and intestinal metabolism of administered MMF, as well as biliary excretion of metabolites, have been documented in humans and experimental animal models.^{16,18}
- Maximum immunosuppressive effects are typically noted 2 to 4 hours after oral administration.⁸
- Appropriate dose strategy in patients with renal or hepatic insufficiency is unknown, although neither nephrotoxicity nor hepatotoxicity has been reported.

Prospective clinical trials are warranted to confirm efficacy and better guide use of mycophenolate mofetil in veterinary patients, as to date efficacy has primarily been reported retrospectively.

MORE ►

GI = gastrointestinal,
MMF = mycophenolate mofetil



Veterinary staff and pet owners should wear gloves and wash their hands after being exposed to either the drug itself or the patient's urine.



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 reinfected and shed eggs between treatments.

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

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Adverse Effects & Cautions

GI toxicity is the most commonly reported and anecdotally encountered adverse effect of MMF use in dogs.^{1,3,5,6,9}

- Adverse effects include diarrhea, anorexia, vomiting, weight loss, and possible intestinal hemorrhage; mild allergic reactions have been suspected following parenteral use only.^{1,3,5,6,9,19,20}
- Dose reduction often resolves adverse effects; however, drug discontinuation may be required.

There is limited experience for safety and efficacy in cats.²¹

Certain drug interactions have been reported in humans^{11,22,23}; if possible, these drug combinations should be avoided until they have been evaluated in veterinary patients.

- Fluoroquinolones, metronidazole, and amoxicillin-clavulanic acid may reduce MMF efficacy when administered concurrently, though anecdotally such interactions have not been observed clinically in veterinary patients.^{22,23}
- Concurrent use with azathioprine is not recommended based on the similar mechanism of action and therefore likely increased risk for inducing bone marrow suppression.²¹

Efforts should be made to minimize direct human exposure to MMF and prevent possible toxicity.

- Veterinary staff and pet owners should wear gloves when handling MMF and wash their hands following exposure to the drug or a treated patient's urine.
- MMF should be avoided in patients whose owner may be pregnant or nursing, as the drug has shown predisposition to pregnancy loss and birth defects.^{11,24}
- To prevent aerosolization of MMF, opening capsules or splitting pills should be avoided.

GI = gastrointestinal, MMF = mycophenolate mofetil

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THERAPEUTICS SNAPSHOT

PEER REVIEWED

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ANDREW BUGBEE, DVM, DACVIM, is a clinical assistant professor of small animal internal medicine at University of Georgia, where he completed his rotating internship and internal medicine residency. His research and clinical interests include the monitoring of diabetes mellitus, methods to improve experiences for owners of pets with endocrine disorders, and immune-mediated disease management. Dr. Bugbee earned his DVM from Texas A&M University.

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REFERENCES

1. Wang A, Smith JR, Creevy KE. Treatment of canine idiopathic immune-mediated haemolytic anaemia with mycophenolate mofetil and glucocorticoids: 30 cases (2007 to 2011). *J Small Anim Pract*. 2013; 54(8):399-404.
2. Yuki M, Sugimoto N, Otsuka H, et al. Recovery of a dog from aplastic anaemia after treatment with mycophenolate mofetil. *Aust Vet J*. 2007;85(12):495-497.
3. Yau VK, Bianco D. Treatment of five haemodynamically stable dogs with immune-mediated thrombocytopenia using mycophenolate mofetil as single agent. *J Small Anim Pract*. 2014;55(6): 330-333.
4. Segev G, Cowgill LD, Heiene R, Labato MA, Polzin DJ. Consensus recommendations for immunosuppressive treatment of dogs with glomerular disease based on established pathology. *JVIM*. 2013;27 Suppl 1:S44-S54.
5. Dewey CW, Cerda-Gonzalez S, Fletcher DJ, et al. Mycophenolate mofetil treatment in dogs with serologically diagnosed acquired myasthenia gravis: 27 cases (1999-2008). *JAVMA*. 2010; 236(6):664-668.
6. Woolcock AD, Wang A, Haley A, et al. Treatment of canine meningoencephalomyelitis of unknown etiology with mycophenolate mofetil: 25 cases (2007-2012) [abstract]. *JVIM*. 2014;28(3):976.
7. Ginel PJ, Blanco B, Lucena R, Jiménez CR, Peinado-Guitart C, Mozos E. Steroid-sparing effect of mycophenolate mofetil in the treatment of a subepidermal blistering autoimmune disease in a dog. *J S Afr Vet Assoc*. 2010;81(4):253-257.
8. Langman LJ, Shapiro AM, Lakey JR, LeGatt DF, Kneteman NM, Yatscoff RW. Pharmacodynamic assessment of mycophenolic acid-induced immunosuppression by measurement of inosine monophosphate dehydrogenase activity in a canine model. *Transplantation*. 1996;61(1):87-92.
9. Lange S, Mueller SC, Altmann S, et al. Pharmacokinetics of oral mycophenolate mofetil in combination with CsA in dogs after nonmyeloablative allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;41(7):667-674.
10. Bacek LM, Macintire DK. Treatment of primary immune-mediated hemolytic anemia with mycophenolate mofetil in two cats. *J Vet Emerg Crit Care (San Antonio)*. 2011;21(1):45-49.
11. CellCept [mycophenolate mofetil] [package insert]. South San Francisco, CA: Genentech USA; 2012.
12. Pescovitz MD, Conti D, Dunn J, et al. Intravenous mycophenolate mofetil: safety, tolerability, and pharmacokinetics. *Clin Transplantation*. 2000;14(3):179-188.
13. Ensom MHH, Decarie D. Stability of mycophenolate mofetil in a 1:1 mixture of ora-sweet and ora-plus. *Canadian J Hosp Pharmacy*. 2002;55(1):63-65.
14. Venkataramanan R, McCombs JR, Zuckerman S, McGhee B, Pisuapati J, Dice JE. Stability of mycophenolate mofetil as an extemporaneous suspension. *Ann Pharmacother*. 1998;32(7-8):755-757.
15. Lupu M, McCune JS, Kuhr CS, Gooley T, Storb R. Pharmacokinetics of oral mycophenolate mofetil in dog: bioavailability studies and the impact of antibiotic therapy. *Biol Blood Marrow Transplant*. 2006;12(12):1352-1354.
16. Picard N, Ratanasavanh D, Prémaud A, Le Meur Y, Marquet P. Identification of the UDP-glucuronosyltransferase isoforms involved in mycophenolic acid phase II metabolism. *Drug Metab Dispos*. 2005;33(1):139-146.
17. Wolff NA, Burckhardt BC, Burckhardt G, Oellerich M, Armstrong VW. Mycophenolic acid (MPA) and its glucuronide metabolites interact with transport systems responsible for excretion of organic anions in the basolateral membrane of the human kidney. *Nephrol Dial Transplant*. 2007;22(9):2497-2503.
18. Hesselink DA, van Hest RM, Mathot RA, et al. Cyclosporine interacts with mycophenolic acid by inhibiting the multidrug resistance-associated protein 2. *Am J Transplant*. 2005;5(5):987-994.
19. Chanda SM, Sellin JH, Torres CM, Yee JP. Comparative gastrointestinal effects of mycophenolate mofetil capsules and enteric-coated tablets of sodium-mycophenolic acid in beagle dogs. *Transplant Proc*. 2002;34(8):3387-3392.
20. Dewey CW, Boothe DM, Wilkie WS. Pharmacokinetics of single-dose oral and intravenous mycophenolate mofetil administration in normal dogs [abstract]. *JVIM*. 2001;15(3):304.
21. Plumb DC. Mycophenolate mofetil. In: Plumb DC, ed. *Plumb's Veterinary Drug Handbook*. 8th ed. Ames, IA: Wiley-Blackwell; 2015:1024-1027.
22. Naderer OJ, Dupuis RE, Heinzen EL, Wiwattanawongsa K, Johnson MW, Smith PC. The influence of norfloxacin and metronidazole on the disposition of mycophenolate mofetil. *J Clin Pharmacol*. 2005;45(2):219-226.
23. Borrows R, Chusney G, Loucaidou M, et al. The magnitude and time course of changes in mycophenolic acid 12-hour predose levels during antibiotic therapy in mycophenolate mofetil-based renal transplantation. *Ther Drug Monit*. 2007; 29(1):122-126.
24. Anderka MT, Lin AE, Abuelo DN, Mitchell AA, Rasmussen SA. Reviewing the evidence for mycophenolate as a new teratogen: case report and review of the literature. *Am J Med Genet A*. 2009; 149A(6):1241-1248.