Azathioprine

**Stability and Storage**
Store in a tightly sealed container, protected from light, and at room temperature. The stability of compounded formulations has not been evaluated.

**Small Animal Dosage**

**Dogs**
- Dogs weighing less than 10 kg: 1 mg IM first week, 2 mg IM second week, 1 mg/kg/wk maintenance. Dogs weighing more than 10 kg: 5 mg IM first week, 10 mg IM second week, 1 mg/kg/wk maintenance.

**Cats**
- 0.5–1 mg/cat every 7 days IM.

**Large Animal Dosage**

**Horses**
- 1 mg/kg/wk IM.

**Regulatory Information**
Do not administer to animals intended for food.

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**Azathioprine**

*ay-zah-thee’oe-preen*

**Trade and other names:** Imuran and generic

**Functional classification:** Immunosuppressive

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**Pharmacology and Mechanism of Action**
Thiopurine immunosuppressive drug. Acts to inhibit T-cell lymphocyte proliferation. It is active against T cells and B cells and can block both T- and B-cell activation, thus producing immunosuppressive activity. The exact mechanism of action is not known. Azathioprine is initially spontaneously metabolized to 6-mercaptopurine (6-MP). The metabolite 6-MP is further metabolized via thiopurine methyltransferase (TPMT) to 6-methylmercaptopurine (6-MMP), which may be associated with adverse effects, such as liver injury. It is also metabolized via TPMT to other metabolites, including the 6-thioguanine nucleotide (6-TG), which may be responsible for the immunosuppressive effects because it can accumulate in cells and acts as a purine antagonist that disrupts DNA in leukocytes. The concentrations of 6-TG are correlated with therapeutic efficacy. Other cells can use salvage pathways for purine synthesis, but stimulated lymphocytes are not capable of this synthesis.

**Indications and Clinical Uses**
Azathioprine is used to treat various immune-mediated diseases in animals, including immune-mediated hemolytic anemia, pemphigus, and inflammatory bowel disease. It is often the first drug of choice, in addition to corticosteroids, for treatment of immune-mediated hemolytic anemia and pemphigus in dogs and is often used for inflammatory bowel disease. It is usually combined with prednisone or prednisolone treatment, but benefits of this combination compared with each drug administered alone have not been confirmed. It is primarily used in dogs and is not recommended in cats. There are some case reports for its successful use to treat immune-mediated disease in horses, but experience is limited. Onset of action is delayed for 4–6 weeks in some human patients. The onset of effects in animals has not been determined, but observations indicate that it occurs more quickly than in people.
Precautionary Information
Adverse Reactions and Side Effects
Bone marrow suppression is the most serious concern. Additional adverse effects in dogs include diarrhea, increased risk of secondary infections, and vomiting. Hepatotoxicosis after administration of azathioprine also has been reported. Toxicity may be related to the metabolites, particularly 6-MMP. The incidence of hepatotoxicity may occur in dogs after the first 2–4 weeks of treatment; therefore, this is the most critical time to monitor liver enzymes and bilirubin.

Individuals who have higher sensitivity to the suppressing effects of bone marrow should have the dose reduced. There has been some association with development of pancreatitis when administered with corticosteroids, but this has not been confirmed.

Susceptibility to the adverse effects, and prediction of therapeutic effects in people may be correlated with the levels of the metabolizing enzyme, TPMT. Some people are deficient and have a higher incidence of adverse effects. However, the TPMT levels in dogs are variable and have not been associated with either hepatotoxicity or myelotoxicity. Cats are deficient in TPMT and are particularly susceptible to toxicity.

Contraindications and Precautions
Ordinarily, it should not be administered to cats, but if treatment is attempted, exercise extreme caution and careful monitoring.

Drug Interactions
Administer with caution with other drugs that may suppress the bone marrow (e.g., cyclophosphamide and anticancer drugs). There is some evidence that concurrent use with corticosteroids may increase the risk of pancreatitis. Do not administer with allopurinol because antagonism of xanthine oxidase may interfere with metabolism.

Instructions for Use
Azathioprine is usually used in combination with other immunosuppressive drugs (e.g., corticosteroids) to treat immune-mediated disease. Cats are very sensitive to the bone marrow-suppressing effects of azathioprine. Doses of 2.2 mg/kg to cats have produced toxicity, but some veterinarians have used low dosages of 0.3 mg/kg/day. Alternatively, chlorambucil has been used instead of azathioprine in cats when immunosuppressive action is needed.

Patient Monitoring and Laboratory Tests
Monitor patient’s CBC periodically because some animals are sensitive to the effects of azathioprine and its metabolite, 6-MP. After 2 weeks of treatment, a CBC is essential. Because of risk of hepatotoxicity, monitor hepatic enzymes and bilirubin regularly.

Formulations
Azathioprine is available in 25-, 50-, 75-, and 100-mg tablets and 10-mg/mL for injection.

Stability and Storage
Store in a tightly sealed container at room temperature. Compounded oral suspensions are stable for 60 days.
Small Animal Dosage
Dogs
• 2 mg/kg q24h PO initially; then 0.5–1 mg/kg q48h. In dogs, dosages as high as 1.5 mg/kg q48h PO have been used with prednisolone.

Cats (use cautiously)
• Cats are sensitive to bone marrow–suppressing effects, and many clinicians avoid azathioprine in cats altogether. However, if administered to cats, one should start with 0.3 mg/kg q24h PO and adjust the dose to q48h after careful monitoring. Tablet size may be as low as 1/30th to 1/50th of a tablet, which requires careful compounding.

Large Animal Dosage
Horses
• 3 mg/kg, PO, q24h.

Regulatory Information
Do not administer to animals intended for food.

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**Azithromycin**

**Trade and other names:** Zithromax

**Functional classification:** Antibacterial

Pharmacology and Mechanism of Action
Azalide antibiotic. Similar mechanism of action as macrolides (e.g., erythromycin), which is to inhibit bacteria protein synthesis via inhibition of ribosomal activity. Spectrum of activity is primarily gram-positive cocci, including streptococci and staphylococci. It also has good activity against *Mycoplasma* spp., *Chlamydia* spp., and some intracellular pathogens. The activity against *Toxoplasma* spp. has been questionable.

Azithromycin, like other macrolides, exerts therapeutic benefits not solely explainable by antibacterial activity. Azithromycin has multiple immunomodulatory effects that likely contribute to the therapeutic response in respiratory infections and perhaps other diseases. Even with infections caused by organisms not susceptible to azithromycin in vitro, such as infections caused by *Pseudomonas aeruginosa*, azithromycin has produced benefits by decreasing the virulence properties of the organism (e.g., inhibition of quorum sensing and inhibition of biofilm). Other beneficial effects may be caused by enhanced degranulation and apoptosis of neutrophils and inhibition of inflammatory cytokine production. It also may help clear infections by enhancing macrophage functions.

**Pharmacokinetics:** Pharmacokinetic data show extremely long plasma, tissue, and leukocyte half-lives in dogs, cats, and horses. It is minimally metabolized, and very little active drug is excreted in the urine. Plasma half-life is 15–18 hours in horses, 35 hours in cats, and 30 hours in dogs. The volume of distribution is also large, with values exceeding 10 L/kg. Oral absorption in dogs is 90% but less in cats (58%) and horses (40%–45%). Azithromycin, like other long-acting macrolides, is characterized by low-plasma drug concentrations, but much higher (100–200×) concentrations in leukocytes, bronchial secretions, and some tissues.
Instructions for Use
Dosing of activated charcoal has used a ratio of 10:1 (charcoal:toxin) to administer for treatment of intoxication. However, more recent evidence indicates that a ratio greater than 40:1 is more appropriate, which may require higher doses than previously thought. Activated charcoal is effective to treat intoxication if administered up to 4 hours after exposure, but after 4 hours, benefits decrease. Charcoal is available in a variety of forms and usually is used as treatment for poisoning. Many commercial preparations contain sorbitol, which acts as a flavoring agent and promotes intestinal catharsis.

Patient Monitoring and Laboratory Tests
When used as treatment for intoxication, careful monitoring of effects of toxin is necessary because charcoal will not adsorb all of the toxicant.

Formulations
- Charcoal is available in oral suspension and granules. Strengths of formulations vary from 15 g/72 mL to 50 g/240 mL. Many formulations contain sorbitol, which is a sweetener and also can produce an intestinal cathartic effect.

Stability and Storage
Store in a tightly sealed container at room temperature. Do not mix with other compounds because it will adsorb other chemicals.

Small Animal Dosage
Dogs and Cats
- 1–4 g/kg PO (granules) or 6–12 mL/kg (suspension). Administer a single dose shortly after poisoning. A common dose for dogs is a single dose of 2 g/kg as soon as possible after ingestion of a toxin.

Large Animal Dosage
- Large animal use is not reported, but it may be considered for treatment of a poisoning. Consider a dose of 1 g/kg PO (granules) or 6–10 mL/kg (suspension) PO.

Regulatory Information
No residue concerns. Withdrawal time: 0 days.

Chlorambucil
klor-am-byeo-sil
Trade and other names: Leukeran
Functional classification: Anticancer agent

Contraindications and Precautions
Used primarily as treatment for intoxication. If administered by gastric administration with a stomach tube, serious complications can occur if it is deposited in the airways.

Drug Interactions
Charcoal adsorbs most other drugs administered orally to prevent their absorption.
Chlorambucil

Pharmacology and Mechanism of Action
Chlorambucil is an immunosuppressive agent. Chlorambucil is an alkylating agent of the nitrogen mustard category. It is sometimes used as a substitute for cyclophosphamide. It has a similar action as cyclophosphamide but is one of the slowest acting of the class of nitrogen mustards. As an alkylating agent, it interferes with DNA replication and RNA transcription by alkylation and cross-linking the strands of DNA. When used in metronomic dosing protocols for cancer, it may decrease angiogenesis in tumors.

Indications and Clinical Uses
Chlorambucil is used for treatment of various tumors and immunosuppressive therapy. Although little has been published on the clinical use of chlorambucil, it may be effective in dogs and cats for immune-mediated disease. However, direct comparisons to other immunosuppressive drugs have not been reported. One of the most frequent uses has been for treatment of immune-mediated skin diseases of cats, for which it has been used to treat cats with pemphigus and eosinophilic granuloma complex (EGC). It is often administered concurrently with corticosteroids. It also has been used to treat inflammatory bowel disease (IBD) in cats and dogs and has been effective for chronic enteropathy characterized by protein losing enteropathy in dogs.

Chlorambucil also has been used as an anticancer agent in some protocols. At a dosage of 4 mg/m² PO q24h, it was well tolerated and produced partial remissions for transitional cell carcinoma.

Precautionary Information

Adverse Reactions and Side Effects
Myelosuppression is possible, although most cats tolerate chlorambucil well. Cystitis does not occur with chlorambucil as with cyclophosphamide. Diarrhea and anorexia may occur in some patients. At low doses used in metronomic protocols in dogs, it was well tolerated.

Contraindications and Precautions
Cytotoxic, potentially immunosuppressive agent. Do not use in animals with suppressed bone marrow.

Drug Interactions
Chlorambucil will potentiate other immunosuppressive drugs.

Instructions for Use
Chlorambucil may be combined with prednisolone for treatment of immune-mediated disorders, but it is not known if the combination is more effective than prednisolone alone. It also can be used in dogs as a continuous treatment (everyday dose) at low doses of 4 mg/m² every day. The cost of chlorambucil has increased dramatically, and some veterinarians have relied on compounded formulations. It is not known if compounded forms are equivalent to the FDA-approved forms.

Patient Monitoring and Laboratory Tests
Monitor CBC in animals during treatment because myelosuppression is the most serious adverse effect.

Formulations
- Chlorambucil is available in a 2-mg tablet. The tablet may be difficult to divide for small animals.
Stability and Storage
Store in a tightly sealed container, protected from light, and at room temperature. Chlorambucil undergoes rapid hydrolysis (within 10 minutes) in the presence of water. Hydrolysis occurs most readily at pH greater than 2. Therefore chlorambucil can decompose rapidly in compounded aqueous formulations, such as those that contain simple syrup and other excipients. Hydrolysis is slower if mixed in alcohol-based solutions. If mixed with alcohol and stored in the freezer, it is stable for 31 days. Exposure to light reduces the drug’s stability.

Small Animal Dosage
Dogs
- 4 mg/m² q24h PO as a starting dose; then increase the interval to q48h PO. (Equivalent dose is 0.1–0.2 mg/kg)
- Intestinal disease: Start with 4–6 mg/m² PO q24 for the first 7–21 days; then reduce dose. It may be administered with prednisolone in refractory cases.

Cats
- Immune-mediated disease: 0.1–0.2 mg/kg (approximately one-half tablet) q24h initially; then q48h PO. Often administered concurrently with corticosteroids. Cats with immune-mediated hemolytic anemia have been treated with 2 mg per cat q48h.
- IBD: 2 mg per cat (one tablet) q48–72h PO.
- Cancer treatment: 2 mg per cat PO q48h.

Large Animal Dosage
- No dose has been reported for large animals.

Regulatory Information
Withdrawal times are not established for animals that produce food. This drug should not be used in animals intended for food because it is an anticancer agent.

Chloramphenicol

Pharmacology and Mechanism of Action
Antibacterial drug. Mechanism of action is inhibition of protein synthesis via binding to 50 S ribosome subunit. It has a broad spectrum of activity that includes gram-positive cocci, gram-negative bacilli (including Enterobacteriaceae), and Rickettsia. Chloramphenicol is usually regarded as a bacteriostatic drug, and it is important to maintain drug concentrations above the MIC for as long as possible during the dosing interval. However, there is some evidence that against some bacteria, it may have bactericidal effects.

Pharmacokinetics: Chloramphenicol is absorbed orally in most animals, except ruminants, with a volume of distribution of 1–2 L/kg in animals. The half-life is approximately 2.4 hours in dogs with a peak concentration of approximately 20 mcg/mL. The half-life is 5 hours in cats. Oral absorption in horses is low and variable, ranging from 21% to 40%, depending on the study. The half-life in horses ranges from approximately 2.5 to 3.5 hours, with a peak concentration from oral administration of 3.5–5.25 mcg/mL, depending on the study.
**Cyclophosphamide**  
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**Formulations**  
- Cyanocobalamin is available in tablets ranging from 25 to 1000 mcg. Injection formulations range from 1000 to 5000 mcg/mL (1–5 mg/mL). Vitamin B complex solutions may contain 10–100 mcg/mL of vitamin B12.

**Stability and Storage**  
Store in a tightly sealed container, protected from light, and at room temperature. Stability of compounded formulations has not been evaluated.

**Small Animal Dosage**  
**Dogs**  
- 100–200 mcg/day PO or 250–500 mcg/day IM or SQ.

**Cats**  
- 50–100 mcg/day PO or 250 mcg IM or SQ weekly. If levels are maintained with once-weekly injections for 6 weeks, increasing the interval to 2 weeks, 4 weeks, and 6 weeks (incrementally) can be attempted.

**Large Animal Dosage**  
**Calves and Foals**  
- 500 mcg once per foal or calf twice weekly IM or SQ.

**Lambs and Pigs**  
- 500 mcg once per lamb or pig twice weekly IM or SQ.

**Cattle and Horses**  
- 1000–2000 mcg per horse or cattle once or twice weekly IM or SQ.

**Regulatory Information**  
No withdrawal times are available. Because clearance is rapid and there is little risk from residues, no withdrawal time is suggested for animals intended for food.

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**Cyclophosphamide**  
sye-kloe-foss-fah-mide

**Trade and other names:** Cytoxan, Neosar, and CTX

**Functional classification:** Anticancer agent

**Pharmacology and Mechanism of Action**  
Cyclophosphamide is a cytotoxic anticancer agent. Cyclophosphamide is one of the oldest anticancer agents and belongs to the group of nitrogen mustards. The nitrogen mustards are alkylating agents (bifunctional alkylating agents) that alkylate various macromolecules but preferentially alkylate the N-7 of the guanine base of DNA. They are cytotoxic to cancer cells and are toxic to the rapidly dividing cells of the bone marrow. Cyclophosphamide must be metabolized to active metabolites for pharmacologic effect, which requires P450 enzyme activation. The metabolites hydroxyphosphamide and aldophosphamide are cytotoxic. Aldophosphamide is converted at the tissue site to phosphoramide mustard and acrolein. Phosphoramide mustard is responsible for the antitumor effect, and acrolein is responsible for the cytotoxic action that causes toxicity (e.g., hemorrhagic cystitis). The half-life of the parent drug in dogs is 4–6.5 hours.
Cyclophosphamide

Indications and Clinical Uses
Cyclophosphamide is used primarily as an adjunct for cancer chemotherapy and as immunosuppressive therapy. Cyclophosphamide is the most potent of the nitrogen mustards. It is used in chemotherapy protocols for a variety of tumors, carcinomas, sarcomas, feline lymphoproliferative diseases, mast cell tumor, mammary carcinoma, and especially lymphoproliferative tumors (lymphoma). Cancer protocols such as cyclophosphamide, Oncovin, and prednisone (COP) and cyclophosphamide, hydroxydaunomycin, Oncovin, and prednisone (CHOP) incorporate cyclophosphamide as one of the agents.

Cyclophosphamide is also used as continuous treatment for some cancers, also known as metronomic dosing. The advantage of metronomic dosing is decreased adverse effects (lower dose), and other benefits such as decreased angiogenesis in tumors (decreased proliferation), decreased vascular endothelial growth factor (VEGF), and decreased circulating T-regulatory cells (T-reg). However, the benefits of metronomic dosing in small animals has not been established, except for some limited experience. See the dosing section for metronomic protocol.

Cyclophosphamide has been used as an immunosuppressive agent for some forms of immune-mediated disease. Although it has been used for various immune-mediated disorders in animals (immune-mediated hemolytic anemia [IMHA], pemphigus, systemic lupus erythematosus), efficacy has not been reported in controlled studies for these diseases. For treatment of IMHA (50 mg/m²), there was no benefit over prednisolone alone.

Precautionary Information
Adverse Reactions and Side Effects
Cyclophosphamide is toxic to the bone marrow in a dose-dependent manner. After a single large bolus dose, the nadir of toxicity occurs in 7–10 days, but the effect is reversible because stem cells are usually unaffected. Recovery usually occurs in 21–28 days. Vomiting and diarrhea may occur in some patients. Sterile, hemorrhagic cystitis is a serious and limiting complication to therapy in dogs. It is caused by the toxic effects of metabolites on the bladder epithelium (especially acrolein) that are concentrated and excreted in the urine. Various attempts are used to decrease the injury to the bladder epithelium. Corticosteroids are usually administered with cyclophosphamide to induce polyuria and decrease inflammation of the bladder. The drug mesna (Mesnex, mercaptoethane sulfonate) provides free active thiol groups to bind metabolites of cyclophosphamide in the urine. Furosemide (2.2 mg/kg) administered at the same time as the cyclophosphamide dose may decrease risk of sterile hemorrhagic cystitis. Cats are less susceptible to developing cystitis than dogs. Cyclophosphamide may cause hair loss when used in some chemotherapeutic protocols. Dogs most susceptible are those with continuously growing hair (e.g., poodles and Old English sheepdogs). Cats do not tend to lose hair from cyclophosphamide treatment.

Contraindications and Precautions
Bone marrow suppressive and immunosuppressive. Use cautiously in animals at risk for infection. Teratogenic and embryotoxic. Do not use in pregnancy.

Drug Interactions
Use cautiously with other drugs that may cause bone marrow suppression. Although this drug is highly metabolized to active metabolites, it is not known what effect other drugs have on enzyme activity.
Instructions for Use

Cyclophosphamide is usually administered with other drugs (other cancer drugs in cancer protocols or corticosteroids when used for immunosuppressive therapy). Consult specific anticancer protocols for specific regimens. For example, the COAP protocol (COAP is a combination of cyclophosphamide, vincristine, prednisolone, and cytosine arabinoside) uses 50 mg/m² PO q48h, with vincristine, cytosine arabinoside, and prednisone for 8 weeks, but one CHOP protocol uses 100–150 mg/m² IV on the first day of the protocol followed by other drugs such as doxorubicin, vincristine, and prednisone. In dogs, the maximum tolerated dose is 500 mg/m² IV (with autologous bone marrow support).

Patient Monitoring and Laboratory Tests


Formulations

- Cyclophosphamide is available in 25-mg/mL injection and 25- and 50-mg tablets.

Stability and Storage

Store in a tightly sealed container, protected from light, and at room temperature. Tablets are coated and should not be split to retain stability. Do not let temperatures exceed 30°C. Subject to hydrolysis in aqueous solutions. Use reconstituted solutions within 24 hours at room temperature and within 6 days if refrigerated, although some refrigerated solutions have been stable for 60 days.

Small Animal Dosage

Dogs

- Anticancer dosage: 50 mg/m² (≈2.2 mg/kg) q48h or once daily 4 days/wk PO. Alternatively, some protocols use 150–300 mg/m² IV and repeat in 21 days.
- Metronomic dosage (continuous administration to suppress T cells): 10–15 mg/m² q24h PO (approximately 0.3 mg/kg).
- Immunosuppressive therapy: Dogs: 50 mg/m² q48h PO or 2.2 mg/kg once daily for 4 days/wk.
- Pulse therapy: 200–250 mg/m² (10 mg/kg) once every 3 weeks. Dividing the 250-mg/m² dose into three treatments over 3 days may reduce risk of sterile hemorrhagic cystitis.

Cats

- 6.25–12.5 mg/cat once daily 4 days/wk, PO. In some protocols, the dosage has been increased to 25 mg per cat twice per week PO. Alternatively, doses of 200 mg/m² have been used.

Large Animal Dosage

- No dose has been reported for large animals.

Regulatory Information

Withdrawal times are not established for animals that produce food. This drug should not be used in animals intended for food because it is an anticancer agent.

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**Cyclosporine, Cyclosporin A**

*siklo-spör-een*

**Trade and other names:** Atopica (veterinary preparation), Neoral (human preparation), Sandimmune, Optimmune (ophthalmic), Gengraf, and generic brands. In the United States, it is called cyclosporine; the international name is ciclosporin.

**Functional classification:** Immunosuppressive drug

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These proofs may contain color figures. Those figures may print black and white in the final printed book if a color print product has not been planned. The color figures will appear in color in all electronic versions of this book.
Instructions for Use
Cyclophosphamide is usually administered with other drugs (other cancer drugs in cancer protocols or corticosteroids when used for immunosuppressive therapy). Consult specific anticancer protocols for specific regimens. For example, the COAP protocol (COAP is a combination of cyclophosphamide, vincristine, prednisolone, and cytosine arabinoside) uses 50 mg/m² PO q48h, with vincristine, cytosine arabinoside, and prednisone for 8 weeks, but one CHOP protocol uses 100–150 mg/m² IV on the first day of the protocol followed by other drugs such as doxorubicin, vincristine, and prednisone. In dogs, the maximum tolerated dose is 500 mg/m² IV (with autologous bone marrow support).

Patient Monitoring and Laboratory Tests

Formulations
- Cyclophosphamide is available in 25-mg/mL injection and 25- and 50-mg tablets.

Stability and Storage
Store in a tightly sealed container, protected from light, and at room temperature. Tablets are coated and should not be split to retain stability. Do not let temperatures exceed 30°C. Subject to hydrolysis in aqueous solutions. Use reconstituted solutions within 24 hours at room temperature and within 6 days if refrigerated, although some refrigerated solutions have been stable for 60 days.

Small Animal Dosage
- Dogs
  - Anticancer dosage: 50 mg/m² (=2.2 mg/kg) q48h or once daily 4 days/wk PO. Alternatively, some protocols use 150–300 mg/m² IV and repeat in 21 days.
  - Metronomic dosage (continuous administration to suppress T cells): 10–15 mg/m² q24h PO (approximately 0.3 mg/kg).
  - Immunosuppressive therapy: Dogs: 50 mg/m² q48h PO or 2.2 mg/kg once daily for 4 days/wk.
  - Pulse therapy: 200–250 mg/m² (10 mg/kg) once every 3 weeks. Dividing the 250-mg/m² dose into three treatments over 3 days may reduce risk of sterile hemorrhagic cystitis.
- Cats
  - 6.25–12.5 mg/cat once daily 4 days/wk, PO. In some protocols, the dosage has been increased to 25 mg per cat twice per week PO. Alternatively, doses of 200 mg/m² have been used.

Large Animal Dosage
- No dose has been reported for large animals.

Regulatory Information
Withdrawal times are not established for animals that produce food. This drug should not be used in animals intended for food because it is an anticancer agent.
Cyclosporine, Cyclosporin A

Pharmacology and Mechanism of Action
Cyclosporine is a commonly used immunosuppressive drug. Cyclosporine binds to a specific cellular receptor on calcineurin and inhibits the T-cell receptor–activated signal transduction pathway. Particularly important are its effects to suppress interleukin-2 (IL-2) and other cytokines (e.g., IL-4 and tumor necrosis factor-alpha) and block proliferation of activated T lymphocytes. The action of cyclosporine is more specific for T cells compared with B cells and affects both helper T cells and cytotoxic T cells. Production of autoantibodies by B cells may be suppressed because this process requires the help of activated T cells. Therefore, calcineurin inhibitors such as cyclosporine may decrease humoral immune response by interfering with T-helper cells instead of interfering directly.

Cyclosporine also inhibits the mitochondrial permeability-transition pores that may attenuate myocardial injury during reperfusion.

Pharmacokinetics: The half-lives of cyclosporine are 8–9 hours (average) in dogs and 8–10 hours (average) in cats. However, there is high variability on both species. Oral absorption is low (20%–30%) and may be affected by food and drug interactions. Peak concentration after oral administration occurs at 1–2 hours. The average peak concentration (with high variability) in dogs is approximately 900 ng/mL (600–1200 ng/mL) at 5 mg/kg.

Indications and Clinical Uses
Systemic uses (usually oral) for cyclosporine include IMHA, atopic dermatitis in dogs, and perianal fistulas. Other diseases have been treated with cyclosporine, such as sebaceous adenitis, idiopathic sterile nodular panniculitis, vesicular cutaneous lupus erythematosus, IMHA, immune-mediated thrombocytopenia, IBD, immune-mediated polyarthritis, myasthenia gravis, idiopathic chronic hepatitis, and aplastic anemia. It has also been used for treatment of granulomatous meningoencephalitis (3–6 mg/kg q12h). For many of these indications, efficacy has not been established through well-controlled clinical studies, and the use is based on anecdotal experience and recommendations from clinical experts.

In dogs, there is strong evidence for effective treatment of atopic dermatitis, for which there is similar efficacy as prednisolone. Treatment response may be delayed for 2 weeks and for as long as 4 weeks in some dogs. During this induction time, it is acceptable to administer other medications (e.g., corticosteroids or oclacitinib) to control pruritus in dogs with atopic dermatitis. There is minimal effectiveness for immune-mediated pemphigus foliaceus (PF) in dogs, but it may have benefits for treating PF in cats. In dogs, some dermatologists have reported improved efficacy when combined with azathioprine for immune-mediated diseases (e.g., PF). Cyclosporine use for keratoconjunctivitis sicca is limited to topical administration.

In cats, cyclosporine has shown beneficial effects for treatment of EGC, IBD, atopic dermatitis (60% effective), oral stomatitis, and airway disease (feline asthma). Cyclosporine (Atopica for cats) is approved for control of feline allergic dermatitis. Higher doses are needed in cats compared with dogs because the oral absorption is more variable. In horses, it is effective as a localized treatment of anterior uveitis.

Precautionary Information
Adverse Reactions and Side Effects
The most common adverse effects in dogs and cats are GI problems (vomiting, diarrhea, anorexia, and weight loss). Vomiting is often observed only during...
initial treatment and may be transient. Hypersalivation has been observed in cats. Cyclosporine may induce shedding of hair and stimulate new hair growth in dogs of a different consistency. Neurotoxicity from high doses has been seen in dogs, which can be seen as tremors. However, this is uncommon from recommended doses. Although kidney injury has been reported with older formulations, it has not been reported from use of current formulations of cyclosporine. Less commonly, cyclosporine can produce gingival proliferation (gingival hyperplasia) in animals, which is caused by a growth factor-mediated proliferation of gingival tissues. There are some reports that administration of azithromycin has been successful to resolve gingival hyperplasia. Occasionally, gingivitis and periodontitis may occur, which can be reversed after discontinuing the drug. There is no confirmed evidence that cyclosporine is a risk factor for neoplasia in dogs or cats.

Calcineurin inhibitors can inhibit pancreatic beta cells and increase risk of diabetes in people. It may increase tissue insulin resistance and impair insulin production or secretion to increase glycemia. However, diabetes has not been reported in pets from clinical use of cyclosporine.

Papillomas have been observed in dogs with chronic use. Unlike other immunosuppressive drugs, it does not cause myelosuppression. Cyclosporine may increase thromboxane TXA₂ in platelets and increase platelet activation, but increased risk of thromboembolism has not been associated with cyclosporine treatment in dogs or cats. Aspirin can block this response. **Effect on vaccination:** At three times the clinical dose, it did not affect the immune response to killed rabies vaccine in dogs, but it failed to increase antibody titers from live parvovirus vaccine. Cats treated with cyclosporine, even at high doses, are capable of mounting a memory humoral immune response to booster vaccination (feline calcivirus, parvovirus, feline leukemia virus [FeLV], feline herpesvirus type 1 [FHV-1], and rabies) that is adequate for protection. However, at high doses, a primary humoral response was not observed within 4 weeks of exposure to a novel antigen (feline immunodeficiency virus [FIV]). Therefore, naïve cats vaccinated before cyclosporine treatment should be able to mount an adequate primary immune response, and subsequent cyclosporine treatment should not affect immune response from booster vaccinations.

**Effect on infections in cats:** Administration to cats at 7.5 mg/kg did not increase the severity of infection by *Toxoplasma gondii* in cats that were previously exposed (seropositive). However, administration of cyclosporine to cats that are naïve (seronegative) may increase the severity of *T. gondii* infection. Naïve cats may have a greater risk of developing clinical toxoplasmosis if they become infected while receiving cyclosporine treatment. Do not administer to cats infected with FeLV or FIV. In cats infected with FHV-1, administration of cyclosporine activated the infection, but the disease was mild and self-limited in most cats.

**Contraindications and Precautions**

At high doses, cyclosporine has produced embryotoxic and fetotoxic effects in laboratory animals. It is not recommended to administer to pregnant animals, but there are no specific reports on adverse effects on pregnancy in dogs or cats. It is excreted in milk of lactating animals. Warn animal owners to keep out of reach of children. If used with other drugs, consult the Drug Interactions section for possible interference. A withdrawal time prior to allergen-specific allergy testing in dogs is not necessary.
Drug Interactions
Cimetidine, erythromycin, diltiazem, itraconazole, fluconazole, clarithromycin, or ketoconazole may increase cyclosporine concentrations when used concurrently. Dosages of ketoconazole of 2.5–10 mg/kg/day in dogs have been shown to substantially decrease the clearance of cyclosporine and reduce the required dose by one half or more. Grapefruit juice also inhibits clearance and reduces the required dose, although high doses are needed. For example, 10 g of powdered whole grapefruit is needed in dogs to substantially affect exposure (such a large dose of 42 capsules is impractical). Food decreases oral absorption by 15%–22%. Metoclopramide and rifampin (and possibly other drugs that induce enzymes) will lower cyclosporine blood concentrations. There is no evidence that cyclosporine enhances or inhibits allergen-specific immunotherapy (ASIT) treatment.

Instructions for Use
Atopica (veterinary) and Neoral (human) are identical formulations except the sizes of capsules vary. After animals have been treated with initial doses (see the dosing section) and are stable, doses may be adjusted by increasing the interval to once every other day or every third day rather than lowering the daily dose. Individual doses may be adjusted by monitoring blood concentrations, but monitoring is not necessary for routine use. Most of the experience is with the approved dose to treat atopic dermatitis and allergic dermatitis with doses of 5 mg/kg in dogs and 7 mg/kg in cats. When used to treat animals for immune-mediated disease and organ transplantation, the doses are generally higher, often administered twice daily, and the blood concentrations maintained at a higher level.

Atopica and Neoral oral products are absorbed more predictably than Sandimmune, which is no longer recommended. Atopica and Neoral may produce 50% higher blood concentrations in some patients or reduce the variability in absorption that was associated with the Sandimmune formulations. The injectable formulation has been used infrequently in dogs and cats. It may produce some injection-site reactions such as hair loss, crusts, or injection-site swelling.

There are more than 20 human generic formulations, but none has been tested for bioequivalence in dogs or cats. There is one generic formulation approved for dogs, which is bioequivalent to the proprietary brand. Feeding may reduce oral absorption in dogs but does not decrease efficacy. For cats, it is recommended to administer with food if it does not affect their appetite. If necessary, the oral solution can be diluted to make it more palatable.

To reduce the dose or increase blood concentrations, some veterinarians have administered ketoconazole or other enzyme-inhibiting compounds concurrently.

Patient Monitoring and Laboratory Tests
Although routine blood concentration monitoring is not necessary, it may be helpful to identify drug interactions, poor absorption, adverse reactions, or poor compliance. However, there has been no correlations established between blood concentrations in dogs and cats and clinical response. When monitoring, collect whole blood in ethylenediaminetetraacetic acid (EDTA; purple top) tube for submission to laboratory. Suggested trough blood concentration range (whole blood assay) is 300–400 ng/mL, although in some studies, levels as low as 200 ng/mL have been effective. Peak concentrations (collected at approximately 2 hours after oral administration of 5 mg/kg) should be in the range of 600–1200 ng/mL. Consult the laboratory to determine if the laboratory result is specific or if it also measures inactive metabolites and requires a conversion. Cyclosporine does not interfere with intradermal skin testing.
Formulations

- Cyclosporine is available in 10-, 25-, 50-, and 100-mg capsules (Atopica) and 25- and 100-mg microemulsion capsules.
- There is one FDA-approved generic formulation of cyclosporine for dogs, which has shown to be bioequivalent with the proprietary form (original brand). It is approved in the same size capsules as the original formulation.
- Atopica for cats is available as a 100-mg/mL oral solution as a microemulsion. This may be mixed with the cat’s food if it does not affect their appetite.
- Human forms are also available as a 100-mg/mL oral solution (Neoral, for microemulsion); 100-mg/mL oral solution and 25- and 100-mg capsules (Sandimmune); and 0.2% ophthalmic ointment (Optimmune). Generic human capsules are available (e.g., Gengraf). The human generic formulations are therapeutically equivalent in people but have not been compared in dogs or cats to Atopica.

Stability and Storage

Store in a tightly sealed container, protected from light, and at room temperature. It does not require refrigeration but store below 30°C. Freezing capsules at −20°C for 28 days did not affect stability or oral absorption. Compounded ophthalmic products are stable at room temperature for 60 days, but do not refrigerate.

Small Animal Dosage

Dogs

- 3–7 mg/kg/day PO. The typical starting dosage is 5 mg/kg/day PO. After the induction period, some dogs with atopic dermatitis have been controlled with dosages as low as 5 mg/kg every other day to every third day.
- For perianal fistulas and immune-mediated diseases (e.g., IMHA), higher doses and more frequent administration have been used (5–8 mg/kg q12h). When a response is observed, the dose and frequency can be reduced.
- For immune suppression associated with organ transplantation, doses should be higher (e.g., 7–10 mg/kg q12h PO).
- IBD: 5 mg/kg PO q12h; then reduce the frequency to q24h after a response is observed.
- Idiopathic chronic hepatitis: 5–8 mg/kg/day, PO.

Cats

- 7.5 mg/kg per day PO. Some cats can be controlled with administration of this dose every other day or twice weekly. Administer on a small amount of food or at the time of feeding, but if mixed with food, some cats may refuse to eat.
- For immune suppression associated with organ transplantation, doses should be higher (e.g., 3–5 mg/kg q12h PO).

Large Animal Dosage

- Only local administration has been used in horses (ocular). No other dose has been reported for large animals.

Regulatory Information

Withdrawal times are not established for animals that produce food. This drug should not be used in animals intended for food because it may have mutagenic potential.
Precautionary Information

Adverse Reactions and Side Effects
Excessive use may cause fluid and electrolyte loss.

Contraindications and Precautions
Use lactulose with caution in animals with diabetes because it contains lactose and galactose.

Drug Interactions
No drug interactions are reported for animals. It potentially could change the oral absorption of some drugs by changing the intestinal pH.

Instructions for Use
In veterinary medicine, clinical studies to establish efficacy are not available. In addition to doses cited, 20–30 mL/kg of 30% solution retention enema has been used in cats.

Patient Monitoring and Laboratory Tests
When used for treating hepatic encephalopathy, monitor the patient’s hepatic status.

Formulations
- Lactulose is available in 10 g/15 mL liquid solution (3.3 g per 5 mL).

Stability and Storage
Store in a tightly sealed container, protected from light, and at room temperature. It is soluble in water. Darkening of the solution may occur without affecting stability. Avoid freezing.

Small Animal Dosage
Dogs
- Constipation: 1 mL/4.5 kg q8h (to effect) PO.
- Hepatic encephalopathy: 0.5 mL/kg q8h PO.

Cats
- Constipation: 1 mL/4.5 kg q8h (to effect) PO.
- Hepatic encephalopathy: 2.5–5 mL/cat q8h PO.

Large Animal Dosage
Horses and Cattle
- 0.25–0.5 mL/kg/day PO.

Regulatory Information
There is little risk of residues in animals intended for food. No withdrawal times are necessary.

Leflunomide
le-flo‘noe-mide or leh-flew’nah-mide
Trade and other names: Arava and generic
Functional classification: Immunosuppressive drug
Leflunomide is an isoxazole immunosuppressive drug. Leflunomide is not active as the parent drug, but it is converted to an active metabolite A77 1726 (also known as M1 and teriflunomide), which inhibits T-cell and B-cell proliferation and is responsible for clinical immunosuppressive effects. It inhibits the synthesis of pyrimidine via inhibition of the enzyme dihydroorotate dehydrogenase. This enzyme is important for the de novo pyrimidine synthesis, which is critical for function of activated and stimulated lymphocytes. It also may produce anti-inflammatory effects by inhibiting proinflammatory cytokines.

**Pharmacokinetics:** After oral absorption, the plasma levels of leflunomide are low or undetectable. Therapeutic effects are produced from the metabolite A77 1726 (M1) for the immunosuppressive action. If monitoring is performed, the measurement should focus on the metabolite concentrations. In people, the metabolite M1 has a very long half-life of approximately 2 weeks. But in studies performed in experimental dogs, the half-life was only 21–25 hours, and the peak concentrations were much lower than in people. In people, the long half-life requires several days to accumulate to steady-state levels and to decline from a peak level. Loading doses are often administered in people. However, because of the shorter half-life, loading doses are not needed in dogs, and steady-state concentrations are attained in approximately 5 days. In cats, the half-life is 60 hours with complete oral absorption.

**Indications and Clinical Uses**

This drug is used in people primarily for rheumatoid arthritis. In dogs, it has been used for a variety of immune-mediated diseases as a substitute for other drugs such as azathioprine or mycophenolate. These diseases include myasthenia gravis, Evan syndrome, immune-mediated hemolytic anemia and thrombocytopenia, and polymyositis/polymyositis. Efficacy has not been studied in controlled clinical studies. Dosing recommendations have been reported in small observational studies or from uncontrolled retrospective studies. In most reports, it was administered with corticosteroids. In one case report, there was a positive response in most dogs with immune-mediated polyarthritis treated at 3–4 mg/kg once daily.

**Precautionary Information**

**Adverse Reactions and Side Effects**

The most common adverse effects in dogs have been decreased appetite, lethargy, and diarrhea. Liver enzymes were elevated in some animals. Adverse gastrointestinal (GI) effects are more common with higher doses. Because of the GI effects, many clinicians start with a low dose and gradually titrate up to higher doses. Mild anemia and lethargy also have been observed. Although rare, leukopenia, anemia, and anorexia are possible with doses greater than 4 mg/kg. Periodic complete blood count (CBC) is recommended to monitor patients during treatment. In cats, the most common adverse effects have been intermittent vomiting, which is mild and transient.

**Contraindications and Precautions**

Do not administer to pregnant animals. This drug can be toxic to a developing fetus.

**Drug Interactions**

No interactions are reported.
Instructions for Use

Leflunomide is used most often in dogs for immunosuppressive treatment when other drugs have failed or when the patient has become refractory to other drugs and a substitute is considered. The dosing protocols used currently are derived from extrapolation and some anecdotal reports. Most veterinarians start with 4 mg/kg per day and then lower the dose as the patient responds. Pharmacokinetic studies in dogs suggest that the dosage of 4 mg/kg per day may not produce drug levels that are considered therapeutic. Therefore, in patients that have not responded, there should be consideration for higher doses if it is tolerated by the patient.

Patient Monitoring and Laboratory Tests

Monitor CBC and platelet counts in treated animals. Anemia has been reported as a consequence of treatment. If blood monitoring is pursued, plasma samples may be collected and measured for A77 1726 (the active metabolite). This metabolite is stable in serum for up to 5 months under refrigerated conditions. Drug concentrations at 12 hours (trough) are considered effective if greater than 20 mcg/mL.

Formulations

• Available in 5-, 10-, and 20-mg tablets.

Stability and Storage

Store in a tightly sealed container, protected from light, and at room temperature.

Small Animal Dosage

Dogs

• Start with 2 mg/kg per day to avoid adverse effects. It this dosage is well tolerated, increase to 4 mg/kg per day, usually in divided doses of 2 mg/kg q12h; then taper the dosage to 2 mg/kg q24h PO. After an initial induction period, the dose may be decreased by 25% increments until the patient is stabilized or until the disease resolves. Some patients may require higher starting doses.

Cats

• 2 mg/kg per day for 2 days PO; then 2 mg/kg q48h PO.

Large Animal Dosage

• No large animal doses are available.

Regulatory Information

Withdrawal times are not established for animals that produce food. This drug should be avoided in food-producing animals.

Leucovorin Calcium

leu-koe-vor-in kal-se-um

Trade and other names: Wellcovorin and generic brands

Functional classification: Antidote

Pharmacology and Mechanism of Action

Leucovorin is a reduced form of folic acid that is converted to active folic acid derivatives for purine and thymidine synthesis. The only use in veterinary medicine is as an antidote.
**Instructions for Use**

The doses listed are based on pharmacokinetics in animals and plasma concentrations needed to achieve sufficient plasma concentration above the MIC value. Efficacy studies have not been performed in dogs or cats.

**Patient Monitoring and Laboratory Tests**

Susceptibility testing: CLSI breakpoints for sensitive organisms are ≤1.0 mcg/mL using the human breakpoint. Most sensitive gram-negative bacteria of the Enterobacteriaceae have MIC values ≤0.1 mcg/mL.

**Formulations**

- Moxifloxacin is available in 400-mg tablets and 1.6-mg/mL IV solution.

**Stability and Storage**

Store in a tightly sealed container, protected from light, and at room temperature. Do not mix with products that contain ions (iron, aluminum, magnesium, and calcium).

**Small Animal Dosage**

**Dogs and Cats**

- 10 mg/kg q24h PO.

**Large Animal Dosage**

**Horses**

- 5.8 mg/kg q24h for 3 days, but it causes diarrhea in some horses. Therefore there may be risks with long-term use.

**Regulatory Information**

There are no withdrawal times established because this drug should not be administered to animals that produce food.

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**Mycophenolate Mofetil**

mye-koe-fen’oh-late

**Trade and other names:** CellCept

**Functional classification:** Immunosuppressant

**Pharmacology and Mechanism of Action**

Mycophenolate is an ester prodrug metabolized to mycophenolic acid (MPA) through presystemic de-esterification in the liver. It is used to suppress immunity for transplantation and for treatment of immune-mediated diseases. Mycophenolate, when metabolized to MPA, inhibits inosine monophosphate dehydrogenase, which is an important enzyme for the de novo synthesis of purines in immune cells, especially stimulated lymphocytes. T and B lymphocytes are critically dependent on de novo synthesis of purine nucleotides. Therefore it effectively suppresses T- and B-cell lymphocyte proliferation and decreases antibody synthesis by B cells. It has little effect on T-cell cytokine expression in dogs. In people, it is used as a replacement for people who cannot tolerate azathioprine and has been primarily used for immune suppression in patients undergoing liver or kidney transplants. Other uses in people are based on only retrospective observational studies.
**Pharmacokinetics:** Mycophenolate oral absorption is variable in dogs and has been reported from 54%–87%, with highly variable plasma drug concentrations, depending on the study. It is metabolized to mycophenolic acid, which is the active component and is cleared by the kidneys. The half-life in dogs is only 45 minutes, but it is longer for the metabolite, with a half-life of 2.2–4.6 hours and as long as 8 hours for the metabolite in some dogs. The peak effect occurs in about 2–4 hours after administration. The pharmacokinetic studies with mycophenolate in dogs indicate that frequent dosing is needed to maintain effective concentrations of the active metabolites. The concentrations needed in dogs for immunosuppressive activity is higher than in people (20–30 mcg/mL in people vs. 200 mcg/mL in dogs). At a dose of 13 mg/kg to dogs, it failed to reach concentrations that are considered in the effective range. The pharmacokinetics also have been studied in cats. They have adequate conversion of mycophenolate to the active metabolite mycophenolic acid, but the pharmacokinetics are variable among cats.

**Indications and Clinical Uses**

Mycophenolate is used to treat immune-mediated diseases in animals. It is usually used in veterinary medicine (primarily dogs and cats) when other agents such as azathioprine, cyclosporine, chlorambucil, or glucocorticoids alone fail to achieve remission of an immune-mediated disease. It is usually administered in combination with glucocorticoids, cyclosporine, or both. In dogs, mycophenolate has been used on a limited basis to treat some immune-mediated diseases such as aplastic anemia, immune-mediated hemolytic anemia, meningencephalitis, and autoimmune skin disease. The use in these diseases is supported by anecdotal accounts and small retrospective observational studies. Responses in dogs have been variable, and it is difficult to determine if mycophenolate was responsible for clinical effects or if improvement was caused by co-administered corticosteroids. There has been no difference in response shown between corticosteroids administered with mycophenolate compared with corticosteroids administered with other agents. There was no benefit in dogs when it was added to treatment for immune-mediated hemolytic anemia. In dogs, the active metabolite (MPA) is produced inconsistently, which may explain the variable results observed in dogs. It has been used by neurologists for treatment of myasthenia gravis, but one clinical report indicated that it was not effective. For treatment of pemphigus foliaceus, it was given at a dosage of 22–39 mg/kg/day divided into three treatments. It was well tolerated, but only three of eight dogs completed the study and were improved. For other immune-mediated skin diseases in dogs, it was effective at an average dosage of 14.7 mg/kg twice daily but was administered with corticosteroids in most dogs.

In cats, the use is limited and based only on small case studies or anecdotal reports. In pharmacokinetic studies in cats in which investigators examined immune suppression, it did not effectively suppress immune cells in cats at doses that did not cause GI problems. There are no published data at this time on the use of mycophenolate in horses.

**Precautionary Information**

**Adverse Reactions and Side Effects**

In dogs, GI problems (diarrhea, weight loss, anorexia, and vomiting) have been the most common effects reported, which may be caused by a direct effect on intestinal mucosa. The adverse GI effects may be delayed in some dogs. At the low dose of 10 mg/kg, it is well tolerated, but it may not be effective at this dose. As the dose is increased up to 20 and 30 mg/kg, adverse GI effects are more common (nausea, diarrhea, weight loss). In cats at 10 mg/kg PO q12h, it was well tolerated, but this dose did not suppress immune cells. At higher doses, it consistently produces adverse GI effects in cats.
Contraindications and Precautions
Mycophenolate is an immunosuppressive drug. Therefore, patients may be more prone to infection when receiving mycophenolate. When combined with other immunosuppressive drugs, there may exacerbated adverse effects.

Drug Interactions
Some drug interactions that affect oral bioavailability in humans have been reported (e.g., antibiotics, cyclosporine, antacid drugs), but these drug interactions have not been reported in animals. Mycophenolate requires acid for oral absorption; therefore, interference from acid-suppressing drugs is possible. Do not administer with azathioprine because it may increase the risk of adverse effects. However, it often administered with corticosteroids without any apparent adverse effects.

Instructions for Use
Mycophenolate is used in some patients that cannot tolerate other immunosuppressive drugs, such as azathioprine or cyclophosphamide. It has been used in combination with corticosteroids and cyclosporine. The clinical effects in dogs and cats are not well established but are based on small observational studies and anecdotal experiences.

Patient Monitoring and Laboratory Tests
Monitor for signs of infection in patients. Monitor CBC periodically when administering immunosuppressive agents.

Formulations
- Mycophenolate is available in 250- and 500-mg capsules, 500-mg tablets; 200 mg/mL oral suspension (fruit flavor).
- For IV use, reconstitute the vial of mycophenolate powder with 5% dextrose in water to a concentration of 6 mg/mL. Administer over 2 hours slowly.
- Compounded formulation: A 50-mg/mL oral suspension may be made with mycophenolate mofetil capsules mixed with Ora-Plus and cherry syrup. Mix six 250 mg capsules with 7.5 mL of Ora-Plus and stir to a uniform paste. Add 15 mL of cherry syrup in incremental proportions and transfer to a bottle for dispensing. There should be sufficient cherry syrup added to make a total volume of 30 mL. Shake well before using. It is stable during storage for 210 days at 5°C, for 28 days at 25°C–37°C, and for 11 days at 45°C.

Stability and Storage
Store in a tightly sealed container, protected from light, and at room temperature. It is slightly soluble in water. It is more stable at low pH values (less than 4). It may be prepared in a syrup suspension for flavoring and remains stable for 121 days. The oral liquid suspension has been stored at 25°C (room temperature) or in the refrigerator (5°C); it has a shelf-life of 28 days and 210 days, respectively. Shake the suspension before administration.

Small Animal Dosage
Dogs
- 10 mg/kg q8h PO or 20 mg/kg q8–12h PO. (Higher doses may be needed for clinical effects, but as the dose is increased, adverse effects are more common.)
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Cats
• No effective dose has been defined. A common dosage is 10 mg/kg q12h PO ≤15 mg/kg q8h, but it did not produce effects on immune cells at this dosage. At dosages less than 15 mg/kg q12h, it has been tolerated in cats, but at higher doses, GI problems are more common.

Large Animal Dosage
• No large animal dose has been reported.

Regulatory Information
There are no withdrawal times established because this drug should not be administered to animals that produce food.
Formulations
Prazosin is available in 1-, 2-, and 5-mg capsules.

Stability and Storage
Store in a tightly sealed container, protected from light, and at room temperature.

Small Animal Dosage
Dogs
- 0.5–2 mg per dog q8–24h (as needed).
Cats
- 0.25–1 mg per cat (0.07 mg/kg or approximately 1 mg per 15 kg) q8–12h PO.
- Cats with urethral obstruction: 0.5 mg per cat PO q8h initially; then 0.25–0.5 mg per cat once daily.

Large Animal Dosage
- No doses have been reported for large animals.

Regulatory Information
Withdrawal times are not established for animals that produce food. For extralabel use withdrawal interval estimates, contact FARAD at www.FARAD.org.
RCI Classification: 3

Prednisolone, Prednisolone Acetate

Trade and other names: Delta-Cortef, PrednisTab, and generic brands

Functional classification: Corticosteroid

Pharmacology and Mechanism of Action
Prednisolone is one of the most widely used glucocorticoids. Prednisolone is the active form of prednisone. Prednisolone, like other glucocorticoids, produces anti-inflammatory and immunosuppressive effects. Anti-inflammatory effects are complex, but via binding to cellular glucocorticoid receptors, prednisolone acts to inhibit inflammatory cells and suppresses expression of inflammatory mediators. Prednisolone is approximately four times more potent than cortisol but only one seventh as potent as dexamethasone. Prednisolone is available as the base (usually as a tablet) or as an injectable acetate form, which can be administered intramuscularly or intraarticularly.

Indications and Clinical Uses
Prednisolone, like other corticosteroids, is used to treat a variety of inflammatory and immune-mediated disease. The accompanying dosing section lists a range of doses for replacement therapy, anti-inflammatory therapy, and immunosuppressive therapy. Large animal uses include treatment of inflammatory conditions, especially musculoskeletal disorders. In horses, prednisolone is used for treatment of equine asthma syndrome when recurrent airway obstruction (RAO) occurs. In cattle, corticosteroids have been used in the treatment of ketosis. The prednisolone and trimeprazine formulation (Temaril-P) has been effective for treating pruritus in dogs. (See Trimeprazine for further details.)
Precautionary Information

Adverse Reactions and Side Effects
There are many side effects from corticosteroids, which include polyphagia, polydipsia and polyuria, behavior changes, and hypothalamic–pituitary–adrenal (HPA) axis suppression. Adverse effects include GI ulceration, steroid hepatopathy, diabetes, hyperlipidemia, decreased thyroid hormone, decreased protein synthesis, delayed wound healing, increased risk of diabetes, and immunosuppression. Secondary infections can occur as a result of immunosuppression and include demodicosis, toxoplasmosis, fungal infections, and UTIs.

In cats, there is a concern that corticosteroids such as prednisolone can exacerbate CHF through volume expansion secondary to steroid-induced hyperglycemia. This has occurred in susceptible cats after injections of methylprednisolone acetate. This has not been a clinical problem in otherwise healthy cats. In dogs, there was not an expansion of plasma volume, but short-term use can increase vascular resistance, systolic blood pressure, and increase cardiac afterload. This could potentially exacerbate CHF in some dogs. The mechanism is through increased sensitivity of the alpha receptors and angiotensin II. Thus, in both cats and dogs with heart disease, prednisolone should be used carefully.

In horses, in addition to the previously listed adverse effects, there may be an increased risk of laminitis, although documentation of this effect has been controversial and not supported by clinical evidence.

Contraindications and Precautions
Use cautiously in patients with a risk of GI ulcers or infection and in animals in which growing or healing is necessary. Use prednisolone cautiously in patients with kidney disease because it may increase azotemia. Use prednisolone cautiously in pregnant animals because fetal abnormalities have been reported in laboratory rodents. Use cautiously in dogs and cats with heart disease because in cats it can increase volume expansion in cats at risk of CHF, and in dogs, it can increase vascular resistance and blood pressure. Do not administer prednisolone acetate intravenously. In some species, particularly horses and cats, prednisolone (the active form) is preferred for oral treatment rather than prednisone.

Drug Interactions
Administration of corticosteroids with NSAIDs will increase the risk of GI injury. Corticosteroids may inhibit conversion of T4 thyroid hormone to the active form T3. However, in dogs, the concentration of total T4 but not free T4, is decreased. Therefore the effect on thyroid status in canine patients is expected to be minimal.

Instructions for Use
Doses for prednisolone are of a broad range and based on severity of underlying condition. Generally, after initial treatment, if the patient responds favorably, the doses for long-term maintenance treatment can be tapered to less than 0.5 mg/kg q48h PO.

Patient Monitoring and Laboratory Tests
Monitor patients for signs of secondary infections. Perform an ACTH stimulation test to monitor adrenal function. Corticosteroids can increase liver enzymes, especially ALP, without inducing liver pathology. Prednisone can increase white blood cell (WBC) count and decrease lymphocyte count. It can increase serum albumin, glucose,
triglycerides, and cholesterol. Corticosteroid administration may decrease conversion of thyroid hormones to active form, but free T$_4$ concentrations should be unaffected. Prednisolone and prednisone at high doses for several weeks may produce significant proteinuria and glomerular changes in some dogs.

**Formulations**
- Oral prednisolone is available in 5- and 20-mg tablets and 3-mg/mL syrup.
- Injection is available as a 25-mg/mL acetate suspension injection (10 and 50 mg/mL in Canada).
- Prednisolone sodium phosphate orally disintegrating tablets are available for people but not widely used in animals. These tablets are available in sizes of 5, 10, 15, and 30 mg.
- Prednisolone is also available in combination with trimeprazine (Temaril-P). (See Trimeprazine for more information.)

**Stability and Storage**
Store in a tightly sealed container, protected from light, and at room temperature. Prednisolone is slightly soluble in water, but it is more soluble in ethanol. If diluted first in ethanol, it may be compounded into oral liquid formulations with good stability for 90 days. Prednisolone acetate is insoluble in water. Do not freeze.

**Small Animal Dosage**
**Dogs**
- Anti-inflammatory: The induction dose is 0.5–1 mg/kg, per day, which may be split into q12h doses, IM, or PO. Then taper the dose to 0.3–0.5 mg/kg, q48h, for long-term treatment.
- Immunosuppressive: 2.2–6.6 mg/kg/day IV, IM, or PO initially; then taper to 2–4 mg/kg q48h. Initial dosages rarely need to exceed 4 mg/kg per day.
- Neurologic disease (steroid responsive): Start with 2 mg/kg q12h PO for 2 days followed by gradual tapering to 1 mg/kg, then 0.5 mg/kg, and eventually to 0.5 mg/kg every other day.
- Replacement therapy for adrenal insufficiency: 0.2–0.3 mg/kg/day PO.
- Cancer therapy (e.g., CHOP protocol): 40 mg/m$^2$ q24h for 7 days; then 20 mg/m$^2$ every other day PO.

**Cats**
- Same as for dogs, except that for many conditions they require twice the dog dose.

**Large Animal Dosage**
**Horses**
- Prednisolone acetate suspension: 100–200 mg total dosage IM.
- Prednisolone tablets: 0.5–1 mg/kg q12–24h PO. Taper to lower dose for long-term treatment.

**Cattle**
- Treatment of ketosis: 100–200 mg total dosage IM.

**Regulatory Information**
Cattle withdrawal times for prednisolone acetate: 5 days for meat; 72 hours for milk (in Canada).
Withdrawal times are not established for animals that produce food in the United States. For extralabel use withdrawal interval estimates, contact FARAD at www.FARAD.org.
RCI Classification: 4
Patient Monitoring and Laboratory Tests
Monitor liver enzymes, blood glucose, and renal function during therapy. Monitor patients for signs of secondary infections. Perform an ACTH stimulation test to monitor adrenal function. Corticosteroids can increase liver enzymes, especially ALP, because of enzyme induction, without inducing liver pathology. Prednisolone can increase WBC count and decrease lymphocyte count. It can increase serum albumin, glucose, triglycerides, and cholesterol. Corticosteroid administration may decrease conversion of thyroid hormones to its active form. Prednisolone and prednisone at high doses for several weeks may produce significant proteinuria and glomerular changes in some dogs.

Formulations
- Prednisolone sodium succinate is available in 100- and 500-mg vials for injection (10, 20, and 50 mg/mL). For some indications, methylprednisolone sodium succinate (Solu-Medrol) has been substituted.

Stability and Storage
Store in a tightly sealed container, protected from light, and at room temperature. Prednisolone sodium succinate should be used immediately after reconstitution. Do not freeze. If solution becomes cloudy, do not administer intravenously.

Small Animal Dosage
Dogs and Cats
- Shock (effectiveness of this use is controversial): 15–30 mg/kg IV (repeat in 4–6 hours).
- CNS trauma: 15–30 mg/kg IV, taper to 1–2 mg/kg q12h.
- Anti-inflammatory: 1 mg/kg/day IV.
- Replacement therapy for adrenal insufficiency: 0.25–0.5 mg/kg/day IV.
- Intermittent treatment (pulse therapy) of pemphigus foliaceus: 10 mg/kg IV.

Large Animal Dosage
Horses
- 0.5–1 mg/kg q12–24h IM or IV. IV dose should be given slowly over 30–60 seconds.
- Treatment of shock (although efficacy for treating shock has not been established): 15–30 mg/kg IV; repeat dose in 4–6 hours.

Regulatory Information
Withdrawal times are not established for animals that produce food. For extralabel use withdrawal interval estimates, contact FARAD at www.FARAD.org. RCI Classification: 4

Prednisone
pred’nih-sone

Trade and other names: Deltasone, Meticorten, and generic brands

Functional classification: Corticosteroid

Pharmacology and Mechanism of Action
Prednisone is the inactive form of prednisolone. After administration in most animals (except horses and cats), prednisone is converted to prednisolone, and the effects listed for prednisolone are expected.
Prednisone is a glucocorticoid anti-inflammatory drug. The effect of prednisone is attributed to prednisolone. Anti-inflammatory effects are complex, but via binding to cellular glucocorticoid receptors, prednisolone acts to inhibit inflammatory cells and suppresses expression of inflammatory mediators. Prednisolone is approximately four times more potent than cortisol but only one seventh as potent as dexamethasone. Prednisone appears to be well absorbed and converted to active drug in dogs. However, in horses and cats, administration of prednisone results in low systemic levels of the active drug prednisolone, either because of poor absorption of prednisone or because of a deficiency in converting prednisone into prednisolone.

**Indications and Clinical Uses**
Prednisone, like other corticosteroids, is used to treat a variety of inflammatory and immune-mediated diseases. In cats, prednisone may produce therapeutic failures, and prednisolone (active drug) is preferred. There is evidence of poor conversion of prednisone to prednisolone or poor absorption of prednisone in cats and horses. Prednisolone or another active drug (e.g., triamcinolone, dexamethasone) should be used instead for these animals. There are several large animal doses cited (similar to prednisolone); however, because of poor activity in horses, the use is discouraged.

**Precautionary Information**

**Adverse Reactions and Side Effects**
There are many side effects from corticosteroids that include polyphagia, polydipsia and polyuria, behavior changes, and HPA axis suppression. Adverse effects include GI ulceration, diarrhea hepatopathy, diabetes, hyperlipidemia, decreased thyroid hormone (but not free T₄), decreased protein synthesis, delayed wound healing, and immunosuppression. Secondary infections can occur as a result of immunosuppression and include demodicosis, toxoplasmosis, fungal infections, and UTIs.

In dogs, prednisolone administration increased vascular resistance, systolic blood pressure, and increase cardiac afterload. This could potentially exacerbate CHF in some dogs. Thus, in dogs with heart disease, prednisolone should be used carefully.

**Contraindications and Precautions**
Use corticosteroids cautiously in patients with a risk of GI ulcers or infections and in animals in which growing or healing is necessary. Use prednisone cautiously in patients with renal disease because it may cause azotemia. Use prednisone cautiously in pregnant animals because fetal abnormalities have been reported in laboratory rodents.

**Drug Interactions**
Administration of corticosteroids with NSAIDs increases the risk of GI injury. Corticosteroids may inhibit conversion of T₄ thyroid hormone to the active form T₃. However, in dogs, the concentration of total T₄, but not free T₄, is decreased. Therefore, the effect on thyroid status in a canine patient is expected to be minimal.

**Instructions for Use**
Prednisolone and prednisone can be used interchangeably in dogs. However, cats and horses may have problems converting prednisone to the active prednisolone or problems with oral absorption of prednisone, and prednisolone should be used instead. (Alternatively, methylprednisolone or triamcinolone can be used.) As for
prednisolone, the doses vary across a broad range based on severity of the underlying condition. Consult the dosing section for the range of doses administered for each condition.

**Patient Monitoring and Laboratory Tests**

Monitor liver enzymes, blood glucose, and renal function during therapy. Monitor patients for signs of secondary infections. Perform an ACTH stimulation test to monitor adrenal function. Corticosteroids can increase liver enzymes, especially ALP, without inducing liver pathology. Corticosteroid administration may decrease conversion of thyroid hormones to active form. However, in dogs receiving anti-inflammatory doses of prednisone, total T<sub>4</sub> concentrations, but not free T<sub>4</sub>, may be decreased.

**Formulations**

- Prednisone oral forms: 1-, 2.5-, 5-, 10-, 20-, 25-, and 50-mg tablets; 1-mg/mL syrup (Liquid Pred in 5% alcohol); and 1-mg/mL oral solution (in 5% alcohol)
- Prednisone for injection: 10- and 40-mg/mL prednisone suspension for injection (Meticorten; availability has been limited).

**Stability and Storage**

Store in a tightly sealed container, protected from light, and at room temperature. Prednisone is slightly soluble in water, and it is soluble in ethanol. Prednisone has been prepared by first dissolving in ethanol and then mixing with syrups and flavorings. No loss occurred, but crystallization is common in aqueous vehicles. Prednisone tablets have been crushed and mixed with syrups and other flavorings, stored for 60 days, and found to produce equal bioavailability as tablets in people.

**Small Animal Dosage**

**Dogs**

- Anti-inflammatory: 0.5–1 mg/kg, per day, which may be divided into twice-daily treatments, IM, or PO initially; then taper to q48h at a dose of 0.3–0.5 mg/kg.
- Immunosuppressive: 2.2–6.6 mg/kg/day IV, IM, or PO initially; then taper to 2–4 mg/kg q48h. Initial doses rarely need to exceed 4 mg/kg per day.
- Replacement therapy for adrenal insufficiency: 0.2–0.3 mg/kg/day PO.
- Neurologic disease (steroid responsive): Start with 2 mg/kg q12h PO for 2 days followed by gradual tapering to 1 mg/kg, then 0.5 mg/kg, and eventually to 0.5 mg/kg every other day.
- Cancer therapy (e.g., COAP protocol): 40 mg/m<sup>2</sup> q24h for 7 days; then 20 mg/m<sup>2</sup> every other day PO.

**Cats**

- Not recommended for cats because of an inability to form active metabolite. However, if use is attempted, higher doses than used in dogs are needed.

**Large Animal Dosage**

**Horses**

- Prednisone suspension (Meticorten) (label dosage): 100–400 mg per horse (0.22–0.88 mg/kg) as a single dose IM to be repeated every 3–4 days. No oral doses are listed for horses because of an inability of oral treatment to produce active prednisolone concentrations.

**Regulatory Information**

Withdrawal times are not established for animals that produce food. For extralabel use withdrawal interval estimates, contact FARAD at [www.FARAD.org](http://www.FARAD.org).

RCI Classification: 4