Because Vietnamese Pot Bellied pigs may have delayed absorption due to sequestration of the drug in body fat, re-dose with extreme caution; deaths have resulted after repeat dosing.

Adverse Effects
Transient salivation, piling, panting and shivering have been reported in pigs. Pigs should be left undisturbed after injection (for approximately 20 minutes) until the drug's full effects have been expressed; disturbances during this period may trigger excitement.

Azaperone has minimal analgesic effects and is not a substitute for appropriate anesthesia or analgesia. Doses above 1 mg/kg may cause the penis to be extruded in boars.

Overdosage/Acute Toxicity
Overdoses (>1 mg/kg) in boars may cause penis extrusion leading to damage.

Drug Interactions
No specific drug interactions have been reported for azaperone. The following interactions have been reported for the closely related compounds, haloperidol or droperidol:

- **CNS DEPRESSANT AGENTS** (**barbiturates, narcotics, anesthetics**, etc.) may cause additive CNS depression if used with butyrophenones

Doses
- **SWINE:**

For approved indication of mixing feeder or weanling pigs:

a) 2.2 mg/kg deeply IM (see client information below) (Package Insert; *Stresnil®—P/M* Mallinckrodt; **Note:** No longer on US market)

For labeled indications (*Stresnil®*—Janssen U.K.):

a) **Note:** all doses are to be given IM directly behind the ear using a long hypodermic needle and given as closely behind the ear as possible and perpendicular to the skin.

Aggression (prevention and cure of fighting; including regrouping of piglets, porkers, fattening pigs): 2 mg/kg (1 mL/20 kg)

Treatment of aggression in sows: 2 mg/kg (1 mL/20 kg)

Stress (restlessness, anxiety, etc.): 1–2 mg/kg (0.5–1 mL/20 kg)

Transport of boars: 1 mg/kg (0.5 mL/20 kg)

Transport of weaners: 0.4–2 mg/kg (0.4–1 mL/20 kg)

Obstetrics: 1 mg/kg (0.5 mL/20 kg)

As a premed: 1–2 mg/kg (0.5–1 mL/20 kg)

Monitoring
- Level of sedation

Client Information
- Must be injected IM deeply, either behind the ear and perpendicular to the skin or in the back of the ham. All animals in groups to be mixed must be treated.

Chemistry/Synonyms
A butyrophenone neuroleptic, azaperone occurs as a white to yellowish-white macrocrystalline powder with a melting point between 90–95°C. It is practically insoluble in water; 1 gram is soluble in 29 mL of alcohol.

Azaperone may also be known as azaperonum, R-1929, *Stresnil®*, or *Suicalm®*.

Storage/Stability/Compatibility
Azaperone should be stored at controlled room temperature (15–25°C) and away from light. Do not store above 25°C. Once the vial is opened it should be used within 28 days. No information was located regarding mixing azaperone with other compounds.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: Note: Not currently marketed in the USA: Azaperone 40 mg/mL for Injection in 20 mL vials (6 vials/box); *Stresnil®* (Schering-Plough); (Rx).

In the UK: Azaperone 40 mg/mL for Injection in 100 mL vials; *Stresnil®* (Janssen—UK); (POM-V) Pigs may be slaughtered for human consumption only after 10 days from the last treatment.

The ARCI (Racing Commissioners International) has designated this drug as a class 2 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS: None

AZATHIOPRINE
AZATHIOPRINE SODIUM

(ay-za-***thye***-oh-preen) Imuran®

IMMUNOSUPPRESSANT

Prescriber Highlights
- Purine antagonist immunosuppressive used for a variety of autoimmune diseases
- Known mutagen & teratogen; use with caution in patients with hepatic disease
- Bone marrow depression principal adverse effect; GI effects (including GI distress, pancreatitis & hepatotoxicity) also seen
- Usually not used in cats as they are very sensitive to bone marrow effects

Uses/Indications
In veterinary medicine, azathioprine is used primarily as an immunosuppressive agent in the treatment of immune-mediated diseases in dogs. See Doses below for more information. For autoagglutinizing immune mediated hemolytic anemia, azathioprine is generally recommended to start at the time of diagnosis. When used in combination with cyclosporine, azathioprine has been used to prevent rejection of MHC-matched renal allografts in dogs.

Although the drug can be very toxic to bone marrow in cats, it is sometimes used to treat feline autoimmune skin diseases.

Pharmacology/Actions
While the exact mechanism how azathioprine exerts its immunosuppressive action has not been determined, it is probably dependent on several factors. Azathioprine antagonizes purine metabolism thereby inhibiting RNA, DNA synthesis and mitosis. It may also cause chromosome breaks secondary to incorporation into nucleic acids and cellular metabolism may become disrupted by the drug's ability to inhibit coenzyme formation. Azathioprine has greater activity on delayed hypersensitivity and cellular immunity than on humoral antibody responses. Clinical response to azathioprine may require up to 6 weeks.

Pharmacokinetics

Azathioprine is absorbed from the GI tract and is rapidly metabolized to mercaptopurine; it is then further metabolized to several other compounds. These metabolites are excreted by the kidneys. Only minimal amounts of either azathioprine or mercaptopurine are excreted unchanged.

Cats have low activity of thiopurine methyltransferase (TPMT), one of the routes used to metabolize azathioprine. Approximately 11% of humans have low thiopurine methyltransferase activity, and these individuals have a greater incidence of bone marrow suppression, but also greater azathioprine efficacy. Dogs have variable TMPT activity levels similar to that seen in humans, which may explain why some canine patients respond better and/or develop more myelotoxicity than others. However, one study (Rodriguez, Mackin et al. 2004) in dogs did not show significant correlation between TMPT activity in red blood cells and drug toxicity.

Contraindications/Precautions/Warnings

Azathioprine is contraindicated in patients hypersensitive to it. The drug should be used cautiously in patients with hepatic dysfunction. Use of azathioprine in cats is controversial; they seem to be more susceptible to azathioprine's bone marrow suppressive effects.

Adverse Effects

The principal adverse effect associated with azathioprine is bone marrow suppression. Cats are more prone to develop these effects and the drug is generally not recommended for use in this species. Leukopenia is the most prevalent consequence, but anemias and thrombocytopenia may also be seen. GI upset, poor hair growth, acute pancreatitis and hepatotoxicity have been associated with azathioprine therapy in dogs.

Because azathioprine depresses the immune system, animals may be susceptible to infections or neoplastic illnesses with long-term use.

In recovering dogs with immune-mediated hemolytic anemia, taper the withdrawal of the drug slowly over several months and monitor for early signs of relapse. Rapid withdrawal can lead to a rebound hyperimmune response.

Reproductive/Nursing Safety

Azathioprine is mutagenic and teratogenic in lab animals. In humans, the FDA categorizes this drug as category ***D*** for use during pregnancy (*There is evidence of human fetal risk, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.*) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as in class: ***C*** (*These drugs may have potential risks. Studies in people or laboratory animals have uncovered risks, and these drugs should be used cautiously as a last resort when the benefit of therapy clearly outweighs the risks.*)

Azathioprine is distributed into milk; it is recommended to use milk replacer while the dam is receiving azathioprine.

Overdosage/Acute Toxicity

No specific information was located regarding acute overdose of azathioprine. It is suggested to use standard protocols to empty the GI tract if ingestion was recent and to treat supportively. Contact an animal poison control center for more information.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving azathioprine and may be of significance in veterinary patients:

- **ACE INHIBITORS** (**benazepril, enalapril,** etc.): Increased potential for hematologic toxicity
- **ALLOPURINOL**: The hepatic metabolism of azathioprine may be decreased by concomitant administration of allopurinol; in humans, it is recommended to reduce the azathioprine dose to ¼–⅓ usual if both drugs are to be used together
- **AMINOSALICYLATES** (**sulfasalazine, mesalamine, olsalazine**): Increased risk for azathioprine toxicity
- **NON-DEPOLARIZING MUSCLE RELAXANTS** (*e.g.*, **pancuronium, tubocurarine**): The neuromuscular blocking activity of these drugs may be inhibited or reversed by azathioprine
- **CORTICOSTEROIDS**: Although azathioprine is often used with corticosteroids, there is greater potential risk for toxicity development
- **DRUGS AFFECTING MYELOPOIESIS** (*e.g.*, **trimethoprim/sulfa, cyclophosphamide,** etc.): Increased potential for hematologic toxicity
- **WARFARIN**: Potential for reduced anticoagulant effect

Doses

- **DOGS:**

As an immunosuppressive:

a) For inflammatory bowel disease: Initially 2 mg/kg PO once daily for 2 weeks, then tapered to 2 mg/kg PO every other day for 2–4 weeks, then 1 mg/kg PO every other day. May take 2–6 weeks before beneficial effects are seen. (Moore 2004)

b) For immune-mediated anemia, colitis, immune-mediated skin disease, and acquired myasthenia gravis: 2 mg/kg PO once daily (q24h); long-term therapy 0.5–1 mg/kg PO every other day, with prednisolone administered on the alternate days (Papich 2001)

c) For adjunctive therapy in myasthenia gravis in non-responsive patients: Initially, 1 mg/kg PO once daily. CBC is evaluated every 1–2 weeks. If neutrophil and platelet counts are normal after 2 weeks, dose is increased to 2 mg/kg PO once daily. CBC is repeated every week for the first month and then monthly thereafter. Recommend to discontinue azathioprine if WBC falls below 4,000 cells/mcL or neutrophil count is less than 1,000 cells/mcL. Serum ACHR antibody concentrations reevaluated q4–6 weeks. Azathioprine dose is tapered to every other day when clinical remission occurs and serum ACHR antibody concentrations are normalized. (Coates 2000)

d) For lymphoplasmacytic enteritis if clinical response to prednisolone is poor or the adverse effects (of prednisolone) predominate: azathioprine 2 mg/kg PO once daily for 5 days, then on alternate days to prednisolone (Simpson 2003a)

e) For severe cases (autoagglutination, hemolytic crisis with rapid decline of hematocrit, intravascular hemolysis, Cocker Spaniels) of immune-mediated hemolytic anemia: 2.2 mg/kg PO once daily (q24h) in addition to prednisone (initially at 2.2 mg/kg PO q12h until hematocrit reaches 25–30%; then dose is gradually tapered by approximately 25% q2–3 weeks until a dose of 0.5 mg/kg PO q48h is reached). (Macintire 2006d)

f) For adjunctive therapy in immune-mediated hemolytic anemia: 2 mg/kg PO once daily or on alternate days; continue until remission; then attempt to reduce prednisone to alternate day therapy. Azathioprine may be given on the days prednisone is not. If remission persists for 4 weeks, azathioprine may be discontinued. For dogs sensitive to the side effects of glucocorticoids, azathioprine may be used on alternate days. (Miller 2000)

g) For severe and refractory inflammatory bowel disease: 2.2 mg/kg PO once daily; a lag time of 3–5 weeks is expected before clinical improvement is noted (Jergens and Willard 2000)

h) For adjunctive treatment of ocular fibrous histiocytomas: 2 mg/kg PO daily for 2 weeks, reevaluate, and reduce to 1 mg/kg every other day for 2 weeks, then 1 mg/kg once weekly for 1 month (Riis 1986)

i) In combination with cyclosporine, to prevent rejection of MHC-matched renal allografts in dogs: 1–5 mg/kg PO every other day (Gregory 2000)

j) For perianal fistulas (anal furunculosis): In the study, initially 2 mg/kg PO once daily (q24h) until a reduction in the size, number or inflammation of the fistulas was seen or total WBC <5000 cells/mcL or neutrophil count was <3500 cells/mcL or platelet count <160,000 cells/mcL. Then reduce to 2 mg/kg PO every other day (q48h) and continued for 12 weeks as long as myelosuppression doesn't develop. After 12 weeks, reduce dose to 1 mg/kg PO every other day (q48h) with a planned therapy duration of 12 months. Prednisone was given at 2 mg/kg PO once daily for the first two weeks of therapy; then at 1 mg/kg PO once daily for another 2 weeks and then discontinued. All dogs were placed on a limited antigen diet. No correlation with efficacy and lymphocyte blastogenesis effect. Complete or partial remission in 64% of treated dogs, which is less than systemic cyclosporine or topical tacrolimus treatment, but azathioprine treatment is less expensive. (Harkin, Phillips et al. 2007)

k) For treatment of glomerulonephritis: 2 mg/kg PO once daily. Immunosuppressive treatment is controversial. (Labato 2006)

■ **CATS:**

Note: Most do not recommend azathioprine for use in cats because of the potential for development of fatal toxicity and the difficulty in accurately dosing.

As an immunosuppressive:

a) For immune-mediated dermatologic diseases: Cats are prone to develop bone marrow toxicity from azathioprine and the drug is generally recommended not to be used in this species. However, if the drug is to be used, the dose is 1.1 mg/kg PO every other day. (Rosenkrantz 1989)

b) For severe and refractory inflammatory bowel disease: Must be used with caution; myelotoxicity with severe neutropenia is possible. Azathioprine at 0.3 mg/kg PO once every other day; may take 3–5 weeks before any beneficial effects. Administration can be enhanced by crushing one 50 mg tablet and suspending it in 15 mL of syrup resulting in a concentration of 3.3 mg/mL. Must be shaken well before each use. If cat becomes ill, rectal temperature and WBC should be determined immediately. (Willard 2002)

■ **FERRETS:**

As an immunosuppressive:

a) For treating inflammatory bowel disease: Treatments include prednisone (1 mg/kg PO q12–24h), azathioprine (0.9 mg/kg PO q24–72h), and dietary management. (Johnson 2006c)

■ **HORSES:**

As an immunosuppressive:

a) For various autoimmune skin diseases (*e.g.*, pemphigus foliaceous): 1–3 mg/kg PO q24h for 1 month, then every other day (q48h). May cause thrombocytopenia. Azathioprine used as a steroid-sparing drug; used with corticosteroids in an attempt to eventually decrease the amount of steroid needed. (White 2006)

Monitoring

- Hemograms (including platelets) should be monitored closely; initially every 1–2 weeks and every1–2 months (some recommend q2 weeks) once on maintenance therapy. It is recommended by some clinicians that if the WBC count drops to between 5,000–7,000 cells/mm^3 the dose be reduced by 25%. If WBC count drops below 5,000 cells/mm^3 treatment should be discontinued until leukopenia resolves.
- Liver function tests; serum amylase, if indicated
- Efficacy

Client Information

- There is the possibility of severe toxicity developing from this drug including drug-related neoplasms or mortality; routine testing to detect toxic effects are necessary
- Contact veterinarian should the animal exhibit symptoms of abnormal bleeding, bruising, lack of appetite, vomiting or infection
- Although, no special precautions are necessary with handling intact tablets, wash hands after administering the drug; if using a compounded formulation, wear protective gloves or wash hands immediately after administration

Chemistry/Synonyms

Related structurally to adenine, guanine and hypoxanthine, azathioprine is a purine antagonist antimetabolite that is used primarily for its immunosuppressive properties. Azathioprine occurs as an odorless, pale yellow powder that is insoluble in water and slightly soluble in alcohol. Azathioprine sodium powder for injection occurs as a bright yellow, amorphous mass. After reconstituting with sterile water for injection to a concentration of 10 mg/mL, it has an approximate pH of 9.6.

Azathioprine/Azathioprine sodium may also be known as: azathioprinum, BW-57322, or NSC-39084; many trade names are available.

Storage/Stability/Compatibility

Azathioprine tablets should be stored at room temperature in well-closed containers and protected from light.

The sodium powder for injection should be stored at room temperature and protected from light. It is reportedly stable at neutral or acidic pH, but will hydrolyze to mercaptopurine in alkaline solutions. This conversion is enhanced upon warming or in the presence of sulfhydryl-containing compounds (*e.g.*, cysteine). After reconstituting, the injection should be used within 24-hours as no preservative is present.

Azathioprine sodium is reportedly **compatible** with the following intravenous solutions: dextrose 5% in water, and sodium chloride 0.45% or 0.9%. Compatibility is dependent upon factors such as pH, concentration, temperature and diluent used; consult specialized references or a hospital pharmacist for more specific information.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Azathioprine Tablets: 25 mg, 50 mg, 75 mg & 100 mg; *Azasan*®(aaiPharma); *Imuran*® (Prometheus); (Rx)

Azathioprine Sodium Injection: 100 mg (as sodium)/vial in 20 mL vials; generic; (Rx)

AZITHROMYCIN

(ay-zith-roe-*my*-sin) Zithromax®

MACROLIDE ANTIBIOTIC

Prescriber Highlights

- Oral & parenteral human macrolide antibiotic; potentially useful for a wide range of infections in veterinary patients
- Very long tissue half-lives in dogs & cats
- Contraindications: Hypersensitivity to macrolides
- Caution: Hepatic disease
- Adverse Effects: Potentially GI distress, but less so than with erythromycin
- Relatively expensive, but prices are dropping secondary to the availability of generic products

Uses/Indications

Azithromycin with its relative broad spectrum and favorable pharmacokinetic profile may be useful for a variety of infections in veterinary species. Little data is published at this time, however. Azithromycin has been shown to be ineffective in the treatment of *Mycoplasma haemofelis* in cats.

Azithromycin may be potentially useful for treating Rhodococcus infections in foals.

Pharmacology/Actions

Like other macrolide antibiotics, azithromycin inhibits protein synthesis by penetrating the cell wall and binding to the 50S ribosomal subunits in susceptible bacteria. It is considered a bacteriostatic antibiotic.

Azithromycin has a relatively broad spectrum. It has *in vitro* activity (does not necessarily indicate clinical efficacy) against gram-positive organisms such as *Streptococcus pneumoniae*, *Staph aureus*; gram-negative organisms such as *Haemophilus influenzae*; *Bordetella* spp.; and *Mycoplasma pneumoniae*, *Borrelia burgdorferi* and *Toxoplasma* spp.

Pharmacokinetics

The pharmacokinetics of azithromycin have been described in cats and dogs. In dogs, the drug has excellent bioavailability after oral administration (97%). Tissue concentrations apparently do not mirror those in the serum after multiple doses and tissue half-lives in the dogs may be up to 90 hours. Greater than 50% of an oral dose is excreted unchanged in the bile. In cats, oral bioavailability is 58%. Tissue half-lives are less than in dogs, and range from 13 hours in adipose tissue to 72 hours in cardiac muscle. As with dogs, cats excrete the majority of a given dose in the bile.

In foals, azithromycin is variably absorbed after oral administration with a mean systemic bioavailability ranging from 40–60%. It has a very high volume of distribution (11.6–18.6 L/kg). Elimination half-life is approximately 20–26 hours. The drug concentrates in bronchoalveolar cells and pulmonary epithelial fluid. Elimination half-life in PMN's is about 2 days. In adult horses, oral bioavailability is low (1–7%).

When compared to erythromycin, azithromycin has better absorption characteristics, longer tissue half-lives, and higher concentrations in tissues and white blood cells.

Goats have an elimination half-life of 32.5 hours (IV), 45 hours (IM), an apparent volume of distribution (steady-state) of 34.5 L/kg and a clearance of 0.85 L/kg/hr.

Rabbits have an elimination half-life of 24.1 hours (IV), and 25.1 hours (IM). IM injection has a high bioavailability, but causes some degree of muscle damage at the injection site.

Sheep have an elimination half-life average of 48 hours (IV), 61 hours (IM), an apparent volume of distribution (steady-state) of 34.5 L/kg and a clearance of 0.52 L/kg/hr.

Contraindications/Precautions/Warnings

Azithromycin is contraindicated in animals hypersensitive to any of the macrolides. It should be used with caution in patients with impaired hepatic function.

Adverse Effects

Azithromycin can cause vomiting in dogs if high doses are given. When compared to erythromycin, azithromycin has less GI adverse effects. Other adverse effects, particularly those associated with the liver, may become apparent in dogs and cats as more experience is attained. Local IV site reactions have occurred in patients receiving IV azithromycin.

Reproductive/Nursing Safety

Safety during pregnancy has not been fully established; use only when clearly necessary. In humans, the FDA categorizes this drug as category ***B*** for use during pregnancy (*Animal studies have not yet demonstrated risk to the fetus, but there are no adequate studies in pregnant women; or animal studies have shown an adverse effect, but adequate studies in pregnant women have not demonstrated a risk to the fetus in the first trimester of pregnancy, and there is no evidence of risk in later trimesters.*)

Overdosage/Acute Toxicity

Acute oral overdoses are unlikely to cause significant morbidity other than vomiting, diarrhea and GI cramping.

Drug Interactions

The following drug interactions have either been reported or are theoretical in humans or animals receiving azithromycin and may be of significance in veterinary patients:

- **ANTACIDS (oral; magnesium- and aluminum-containing)**: May reduce the rate of absorption of azithromycin; suggest separating dosages by 2 hours
- **CISAPRIDE**: No data on azithromycin, but other macrolides contraindicated with cisapride; use with caution
- **CYCLOSPORINE**: Azithromycin may potentially increase cyclosporine blood levels; monitor carefully
- **DIGOXIN**: No data on azithromycin, but other macrolides can increase digoxin levels; monitor carefully
- **PIMOZIDE**: Azithromycin use is contraindicated in patients taking pimozide (unlikely to be used in vet med—used for Tourette's disorder in humans). Acute deaths have occurred.

Doses

- **DOGS:**

  For susceptible infections:

  a) 5–10 mg/kg PO once daily for 3–5 days (Trepanier 1999), (Sykes 2003)

  b) 5 mg/kg PO once daily for 2 days, then every 3–5 days for a total of 5 doses (Aucoin 2002b)

  c) For "Derm" infections: 5–10 mg/kg PO once daily for 5–7 days. For animals that are difficult to pill, a dose given every 5 days (after the initial 5–7 day course of therapy) may be effective if continued treatment is necessary. (Merchant 2000)