Chemistry/Synonyms
A peripheral vasodilating agent, isoxsuprine occurs as an odorless, bitter-tasting, white, crystalline powder with a melting point of about 200°C. It is slightly soluble in water and sparingly soluble in alcohol.

Isoxsuprine HCl may also be known as: Caa-40, isoxsuprini hydrochloridum, phenoxyisopropylnorsuprifen, *Dilum®, Duvadilan®, Fadaespasmol®, Fenam®, Inibina®, Isodilan®, Isotenk®, Uterine®, Vadosilan®, Vasodilan®, Vasolan ®, Vasosuprina Ilfi®, Voxsuprine®*, and *Xuprin®*.

Storage/Stability
Tablets should be stored in tight containers at room temperature (15–30°C).

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 4 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Isoxsuprine HCl Tablets: 10 mg & 20 mg; *Vasodilan®* (Mead Johnson); *Voxsuprine®* (Major); generic; (Rx)

ITRACONAZOLE

(ey-tra-***kon***-a-zole) Sporanox®

ANTIFUNGAL

Prescriber Highlights
- Synthetic oral triazole antifungal used for systemic mycoses, including aspergillosis, cryptococcal meningitis, blastomycosis, & histoplasmosis
- Not amenable to compounding; be wary of compounded itraconazole dosage forms as bulk powder itraconazole may not be absorbed
- Contraindications (relative: risk vs. benefit): Hypersensitivity to it or other azole antifungal agents, hepatic impairment, or achlorhydria (or hypochlorhydria)
- Adverse Effects: DOGS: anorexia is the most common, but hepatic toxicity most significant adverse effect. At the higher dosage rate, some develop ulcerative skin lesions/vasculitis & limb edema. Rare, serious erythema multiforme or toxic epidermal necrolysis
- Adverse Effects: CATS: Dose related; GI effects (anorexia, weight loss, vomiting), hepatotoxicity (increased ALT, jaundice), & depression
- May be more efficacious than ketoconazole, but is also more expensive; long-term treatment may be required
- Maternotoxicity, fetotoxicity, & teratogenicity in lab animals at high dosages (5–20 times labeled)
- Drug interactions

Uses/Indications
Itraconazole may have use in veterinary medicine in the treatment of systemic mycoses, including aspergillosis, cryptococcal meningitis, blastomycosis, and histoplasmosis. Itraconazole is probably more effective than ketoconazole, but is significantly more expensive. It may also be useful for superficial candidiasis or dermatophytosis. Itraconazole does not have appreciable effects (unlike ketoconazole) on hormone synthesis and may have fewer side effects than ketoconazole in small animals.

It is considered by many to be the drug of choice for treating blastomycosis, unless moderate or severe hypoxemia is present (than amphotericin B).

In horses, itraconazole may be useful in the treatment of sporotrichosis and *Coccidioides immitis* osteomyelitis.

Pharmacology/Actions
Itraconazole is a fungistatic triazole compound. Triazole-derivative agents, like the imidazoles (clotrimazole, ketoconazole, etc.), presumably act by altering the cellular membranes of susceptible fungi, thereby increasing membrane permeability and allowing leakage of cellular contents and impaired uptake of purine and pyrimidine precursors. Itraconazole has efficacy against a variety of pathogenic fungi, including yeasts and dermatophytes. *In vivo* studies using laboratory models have shown that itraconazole has fungistatic activity against many strains of Candida, Aspergillus, Cryptococcus, Histoplasma, Blastomyces, and *Trypanosoma cruzi.*

Itraconazole has immune-suppressing activity, probably via suppressing T-lymphocyte proliferation.

Pharmacokinetics
Itraconazole absorption is highly dependent on gastric pH and presence of food. When given on an empty stomach, bioavailability may only be 50% or less; with food, it may approach 100%. In cats, the oral solution is more bioavailable and probably has fewer GI effects. The commercially available capsules are specially formulated to increase oral bioavailability. Compounding capsules from bulk powders may not yield a dosage form that is absorbed. The commercially available liquid preparation possesses adequate oral bioavailability.

Itraconazole has very high protein binding and is widely distributed throughout the body, particularly to tissues high in lipids (drug is highly lipophilic). Skin, sebum, female reproductive tract, and pus all have concentrations greater than those found in the serum. Only minimal concentrations are found in CSF, urine, aqueous humor, and saliva. However, many fungal infections in the CNS, eye, or prostate can be effectively treated with itraconazole.

Itraconazole is metabolized by the liver to many different metabolites, including to hydroxyitraconazole, which is active. In humans, itraconazole's serum half-life ranges from 21–64 hours. Elimination may be a saturable process. Because of its long half-life, itraconazole does not reach steady state plasma levels for at least 6 days after starting therapy. If loading doses are given, levels will approach those of steady-state sooner.

Contraindications/Precautions/Warnings
Itraconazole should not be used in patients hypersensitive to it or other azole antifungal agents.

Use itraconazole in patients with hepatic impairment or achlorhydria (or hypochlorhydria) only when the potential benefits outweigh the risks.

Compounding capsules from bulk powders may not yield a dosage form that is absorbed.

Adverse Effects
In dogs, anorexia is the most common adverse effect seen, especially at higher dosages, but hepatic toxicity appears to be the most significant adverse effect. Approximately 10% of dogs receiving 10 mg/kg/day and 5% of dogs receiving 5 mg/kg/day developed hepatic toxicosis serious enough to discontinue treatment (at least temporarily). Hepatic injury is determined by an increased ALT activity. Anorexia is often the symptomatic marker for toxicity and usually

occurs in the second month of treatment. Some dogs (7%) given itraconazole at the higher dosage rate (10 mg/kg/day) may develop ulcerative skin lesions/vasculitis and limb edema that may require dosage reduction. These generally resolve following drug discontinuation. Rarely, serious erythema multiforme or toxic epidermal necrolysis reactions have been noted.

In cats, adverse effects appear to be dose related. GI effects (anorexia, weight loss, vomiting), hepatotoxicity (increased ALT, jaundice) and depression have been noted. Should adverse effects occur and ALT is elevated, the drug should be discontinued. Increased liver enzymes in the absence of other signs do not necessarily mandate dosage reduction or drug discontinuation. Once ALT levels return to normal and other adverse effects have diminished, if necessary, the drug may be restarted at a lower dosage or use longer dosing intervals with intense monitoring.

Reproductive/Nursing Safety

In laboratory animals, itraconazole has caused dose-related maternotoxicity, fetotoxicity and teratogenicity at high dosages (5–20 times labeled). As safety has not been established, use only when the benefits outweigh the potential risks. In humans, the FDA categorizes this drug as category ***C*** for use during pregnancy (*Animal studies have shown an adverse effect on the fetus, but there are no adequate studies in humans; or there are no animal reproduction studies and no adequate studies in humans.*)

Itraconazole does enter maternal milk; significance is unknown.

Overdosage/Acute Toxicity

There is very limited information on the acute toxicity of itraconazole. Giving oral antacids may help reduce absorption. If a large overdose occurs, consider gut emptying and give supportive therapy as required. Itraconazole is not removed by dialysis.

In chronic toxicity studies, dogs receiving 40 mg/kg PO daily for 3 months demonstrated no overt toxicity.

Drug Interactions

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

- **AMPHOTERICIN B:** Lab animal studies have shown that itraconazole used concomitantly with amphotericin B may be antagonistic against Aspergillus or Candida; the clinical importance of these findings is not yet clear
- **ANTACIDS:** May reduce oral absorption of itraconazole; administer itraconazole at least 1 hour before or 2 hours after antacids
- **BENZODIAZEPINES** (**alprazolam, diazepam, midazolam, triazolam**): Itraconazole may increase levels
- **BUSPIRONE:** Plasma concentrations may be elevated
- **BUSULFAN:** Itraconazole may increase levels
- **CALCIUM-CHANNEL BLOCKING AGENTS** (**amlodipine, verapamil**): Itraconazole may increase levels
- **CISAPRIDE:** Itraconazole may increased cisapride levels and possibility for toxicity; use together contraindicated in humans
- **CORTICOSTEROIDS:** Itraconazole may inhibit the metabolism of corticosteroids; potential for increased adverse effects
- **CYCLOPHOSPHAMIDE:** Itraconazole may inhibit the metabolism of cyclophosphamide and its metabolites; potential for increased toxicity
- **CYCLOSPORINE:** Increased cyclosporine levels
- **DIGOXIN:** Itraconazole may increase digoxin levels; use together considered contraindicated in humans
- **FENTANYL/ALFENTANIL:** Itraconazole may increase fentanyl or alfentanil levels
- **H2-BLOCKERS** (**ranitidine, famotidine**, etc.): Increased gastric pH may reduce itraconazole absorption
- **IVERMECTIN:** Itraconazole may increase risk for neurotoxicity
- **MACROLIDE ANTIBIOTICS** (**erythromycin, clarithromycin**): May increase itraconazole concentrations
- **PHENOBARBITAL/PHENYTOIN:** May decrease itraconazole levels
- **PROTON-PUMP INHIBITORS** (**omeprazole**, etc.): Increased gastric pH may reduce itraconazole absorption
- **QUINIDINE:** Itraconazole may increase digoxin levels; use together considered contraindicated in humans
- **RIFAMPIN:** May decrease itraconazole levels; itraconazole may increase rifampin levels
- **SULFONYLUREA ANTIDIABETIC AGENTS** (*e.g.,* **glipizide, glyburide**): Itraconazole may increase levels; hypoglycemia possible
- **VINCRISTINE/VINBLASTINE:** Itraconazole may inhibit vinca alkaloid metabolism and increase levels
- **WARFARIN:** Itraconazole may cause increased prothrombin times in patients receiving warfarin or other coumarin anticoagulants

Laboratory Considerations

- Itraconazole may cause **hypokalemia** or increases in **liver function tests** in a small percentage of patients.

Doses

- **DOGS:**

For systemic mycoses:

a) For Malassezia dermatitis: 5–10 mg/kg PO once daily (Muse 2000)

b) Pulse therapy for Malassezia dermatitis: 5 mg/kg for 2 consecutive days per week for 3 weeks (Foil 2003a)

c) For dermatophytosis: 5 mg/kg PO once daily. Prolonged course of therapy required. Begin taking cultures after 4 weeks of treatment. Continue therapy for 2 weeks beyond clinical cure and when 2–3 negative cultures are obtained at weekly intervals. (Frank 2000)

d) For dermatophytosis: 5 mg/kg PO once daily on an every other week schedule. Treatment is generally continued for three "pulses" of one week on, one week off. Toxicity problems are rare with this protocol. (DeBoer 2006)

e) For Blastomycosis: 5 mg/kg PO once daily for at least 30 days after all signs of disease have resolved (treatment must persist for at least 60–90 days). Give with food.

For Nasal Aspergillosis: 5 mg/kg pO twice daily for at least 90 days. Because of expense, larger dogs may require a more cost effective treatment such as 1% topical clotrimazole in nasal passages and sinuses. (Davidson and Mathews 2000)

f) For Histoplasmosis: 10 mg/kg daily PO; given with food; if dog has intestinal histoplasmosis, treat with amphotericin B (0.5 mg/kg IV over 3–4 hours in D5W every other day) initially. Usually after six doses of amphotericin B, may switch to itraconazole. Total treatment times (amphotericin B and itraconazole) should be for at least 30 days after all signs of disease have resolved (treatment must persist for at least 90 days). (Legendre and Toal 2000)

g) For Blastomycosis: 5 mg/kg PO once a day or divided twice a day. Continue for 2–3 months or until active disease is not apparent. A loading dose of 10 mg/kg once a day (or divided twice a day) for the first three days may reduce the "lag" phase of effectiveness.

For coccidiomycosis: 5–10 mg/kg PO once daily; may need to treat for 6–12 months (Taboada 2000)

h) For sporotrichosis: 5–10 mg/kg once daily for 30 days beyond complete resolution of detectable lesions.

For pythiosis or lagendiosis (after lesion resection): 10 mg/kg PO once daily (with terbinafine at 5–10 mg/kg PO q24h) for at least 2 months after surgery.

For zygomycosis (after aggressive surgical resection: 5–10 mg/kg PO q24h. For non-resectable lesions, either itraconazole for 3–6 months or amphotericin B lipid complex. Recurrence is possible with either surgical or medical therapy. (Grooters 2005)

■ **CATS:**

For susceptible systemic mycoses:

a) For Histoplasmosis: 10 mg/kg daily PO; given with food

For Cryptococcosis: 50–100 mg per cat per day PO for many months. Mean treatment time is 8.5 months. If response inadequate, may add flucytosine (at 100–125 mg/kg divided into three doses per day). (Legendre and Toal 2000)

b) For Blastomycosis: 10 mg/kg PO once a day or divided twice a day. Continue for 2–3 months or until active disease is not apparent (**Note:** cats usually require longer treatment than dogs)

For Histoplasmosis: 10 mg/kg once daily or divided twice daily PO; at least 2–4 months of treatment required

For coccidiomycosis: 5–10 mg/kg PO once daily; may need to treat for 6–12 months (Taboada 2000)

c) For sporotrichosis: 5–10 mg/kg once daily for 30 days beyond complete resolution of detectable lesions. (Grooters 2005)

d) For Cryptococcosis: For mild to moderate disease where cats are eating and do not have CNS involvement: Cats weighing 3.5 kg or less receive 50 mg PO once daily or 100 mg PO every other day; medium to large cats get 100 mg PO once daily. Give with food; may be mixed with tasty food treat. Monitor ALT; itraconazole hepatotoxicity is reversible upon discontinuation of the drug and it can usually be restarted safely at 50% of the original dose. Continue treatment until cat appears completely normal; generally takes 3–12 months. Then obtain serum sample to determine decline in antigen titer. A 4–5 fold reduction suggests successful therapy. Then restart therapy (possibly at a reduced dose) or change to ketoconazole (50 mg/day) until antigen level declines to zero. (Malik 2006b)

For generalized dermatophytosis:

a) 10 mg/kg PO once daily; prolonged course of therapy required. Begin taking cultures after 4 weeks of treatment. Continue therapy for 2 weeks beyond clinical cure and when 2–3 negative cultures are obtained at weekly intervals. (Frank 2000)

b) 5 mg/kg PO twice daily or 10 mg/kg with food. Give until culture is negative 2 times at two week intervals; generally 3–5 weeks. Open capsule and measure out calculated portion; give in butter or *a/d*®. Can be stored in the freezer.

Pulse therapy: 5 mg/kg PO for 2 consecutive days per week, increasing interval gradually is useful in the management of dermatophytosis in longhaired cats and in cats in a heavily contaminated environment.

For dermatophyte granuloma (TOC): 10 mg/kg PO once daily for weeks to months, at least one month beyond clinical resolution and until brush culture is negative x 2. (Foil 2003b)

c) For dermatophytosis: 5 mg/kg PO once daily on an every other week schedule. Treatment is generally continued for three "pulses" of one week on, one week off. Toxicity problems are rare with this protocol. (DeBoer 2006)

■ **RABBITS, RODENTS, SMALL MAMMALS:**

a) Mice: For blastomycosis: 50–150 mg/kg q24h; Rats: For vaginal candidiasis: 2.5–10 mg/kg q24h; Guinea pigs: 5 mg/kg q24h for systemic candidiasis (Adamcak and Otten 2000)

■ **HORSES:**

For aspergillosis:

a) 3 mg/kg twice a day (Legendre 1993)

■ **BIRDS:**

a) Ratites: 6–10 mg/kg PO once daily; if neuro signs develop reduce dose or discontinue (Jenson 1998)

b) 10–20 mg/kg PO q12–24h (based upon extrapolation from mammalian kinetics). Use with caution in African grey parrots. (Flammer 2003a)

Monitoring

- Clinical Efficacy
- With long-term therapy, routine liver function tests are recommended (monthly ALT)
- Appetite
- Physical assessment for ulcerative skin lesions in dogs

Client Information

- Compliance with treatment recommendations must be stressed
- Have clients report any potential adverse effects
- Give with food
- Do not give with any other medications without veterinarian's approval

Chemistry/Synonyms

A synthetic triazole antifungal, itraconazole is structurally related to fluconazole. It has a molecular weight of 706 and a pKa of 3.7.

Itraconazole may also be known as: itraconazolum, oriconazole, R-51211, or *Sporanox*®; many other trade names are available.

Storage/Stability/Compatibility

Itraconazole capsules should be stored between 15–25°C and protected from light an moisture.

Itraconazole oral solution should be stored at temperatures less than 26°C, and protected from freezing.

Itraconazole for injection should be stored at temperatures less than 26°C, and protected from light and freezing. After diluting with the 0.9% sodium chloride injection supplied, the resulting solution may stored at 2–8°C or 15–25°C for up to 48 hours. Protect solution from light during storage. It may be exposed to normal room light during administration.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

HUMAN-LABELED PRODUCTS:

Itraconazole Capsules: 100 mg; *Sporanox*® (Janssen-Ortho); generic; (Rx)

Itraconazole Oral Solution: 10 mg/mL in 150 mL; *Sporanox*® (Ortho Biotech); (Rx)

Itraconazole Injectable Solution: 10 mg/mL in Kits of 25 mL amps, & 50 mL bags of 0.9% NaCl Injection and 1 filtered infusion set; *Sporanox*® (Ortho Biotech); (Rx)

IVERMECTIN

(eye-ver-*mek*-tin) Heartgard®, Ivomec®

ANTIPARASITIC

Prescriber Highlights

- Prototype avermectin drug used in variety of species as an antiparasiticide
- Contraindications: Label specific due to lack of safety data (foals, puppies, etc.) or public health safety (lactating dairy animals)
- Caution in breeds susceptible to MDR1-allele mutation (Collies, Australian Shepherds, Shelties, Long-haired Whippet, "white feet"); at higher risk for CNS toxicity
- Adverse Effects: HORSES: Swelling & pruritus at the ventral mid-line can be seen approximately 24 hours after ivermectin administration due to a hypersensitivity reaction to dead *Onchocerca* spp. microfilaria. DOGS: May exhibit a shock-like reaction when ivermectin is used as a microfilaricide, presumably due to a reaction associated with the dying microfilaria. CATTLE: Ivermectin can induce serious adverse effects by killing the larva when they are in vital areas; may also cause discomfort or transient swelling at the injection site. MICE & RATS: May cause neurologic toxicity at doses slightly more than usually prescribed. BIRDS: Death, lethargy, or anorexia may be seen. Orange-cheeked Waxbill Finches & budgerigars may be more sensitive to ivermectin than other species

Uses/Indications

Ivermectin is approved in horses for the control of: large strongyles (adult) (*Strongylus vulgaris, S. edentatus, S. equinus, Triodontophorus* spp.), small strongyles, pinworms (adults and 4th stage larva), ascarids (adults), hairworms (adults), large-mouth stomach worms (adults), neck threadworms (microfilaria), bots (oral and gastric stages), lungworms (adults and 4th stage larva), intestinal threadworms (adults), and summer sores (cutaneous 3rd stage larva) secondary to *Hebronema* or *Draschia* Spp.

In cattle, ivermectin is approved for use in the control of gastrointestinal roundworms (adults and 4th stage larva), lungworms (adults and 4th stage larva), cattle grubs (parasitic stages), sucking lice, and mites (scabies). For a listing of individual species covered, refer to the product information.

In swine, ivermectin is approved for use to treat GI roundworms, lungworms, lice, and mange mites. For a listing of individual species covered, refer to the product information.

In reindeer, ivermectin is approved for use in the control of warbles.

In American Bison, ivermectin is approved for use in the control of grubs.

In dogs and cats, ivermectin is approved only for use as a preventative for heartworm. It has also been used as a microfilaricide, slow-kill adulticide, ectoparasiticide, and endoparasiticide.

Pharmacology/Actions

Ivermectin enhances the release of gamma amino butyric acid (GABA) at presynaptic neurons. GABA acts as an inhibitory neurotransmitter and blocks the post-synaptic stimulation of the adjacent neuron in nematodes or the muscle fiber in arthropods. By stimulating the release of GABA, ivermectin causes paralysis of the parasite and eventual death. As liver flukes and tapeworms do not use GABA as a peripheral nerve transmitter, ivermectin is ineffective against these parasites.

Pharmacokinetics

In simple-stomached animals, ivermectin is up to 95% absorbed after oral administration. Ruminants only absorb ¼–⅓ of a dose due to inactivation of the drug in the rumen. While there is greater bioavailability after SC administration, absorption after oral dosing is more rapid than SC. It has been reported that ivermectin's bioavailability is lower in cats than in dogs, necessitating a higher dosage for prophylaxis of heartworm in this species.

Ivermectin is well distributed to most tissues, but does not readily penetrate into the CSF, thereby minimizing its toxicity. Collie-breed dogs with a specific gene defect allow more ivermectin into the CNS than other breeds/species.

Ivermectin has a long terminal half-life in most species (see below). It is metabolized in the liver via oxidative pathways and is primarily excreted in the feces. Less than 5% of the drug (as parent compound or metabolites) is excreted in the urine.

Pharmacokinetic parameters of ivermectin have been reported for various species:

Cattle: Volume of distribution = 0.45–2.4 L/kg; elimination half-life = 2–3 days; total body clearance = 0.79 L/kg/day.

Dogs: Bioavailability = 0.95; volume of distribution = 2.4 L/kg; elimination half-life = 2 days.

Swine: Volume of distribution = 4 L/kg; elimination half-life = 0.5 days.

Sheep: Bioavailability = 1 (intra-abomasal), 0.25 (intra-ruminal); volume of distribution = 4.6 L/kg; elimination half-life = 2–7 days.

Contraindications/Precautions/Warnings

The manufacturer recommends that ivermectin not be used in foals less than 4 months old, as safety of the drug in animals this young has not been firmly established. However, foals less than 30 days of age have tolerated doses as high as 1 mg/kg without signs of toxicity.

Ivermectin is not recommended for use in puppies less than 6 weeks old. After receiving heartworm prophylaxis doses, the manufacturer recommends observing Collie-type breeds for at least 8 hours after administration. Most clinicians feel that ivermectin should not be used in breeds susceptible (Collies, Shelties, Australian shepherds, etc.) to the mdr1 gene mutation at the doses specified for treating microfilaria or other parasites unless the patient has been tested and found not to have the gene defect. A specific test for identifying dogs that have the gene defect (deletion mutation of the mdr1 gene) is now available. Contact the veterinary clinical pharmacology lab at www.vetmed.wsu.edu.

Ivermectin is reportedly contraindicated in chelonian species.

Because milk withdrawal times have not been established, the drug is not approved for use in lactating dairy animals or females of breeding age.

The injectable products for use in cattle and swine should be given subcutaneously only; do not give IM or IV.

If using a product in a species not labeled for that product (extra-label), be certain of the dosage and/or dilutions. There are many reports of overdoses in small animals when large animal products have been used.

Adverse Effects

In horses, swelling and pruritus at the ventral mid-line can be seen approximately 24 hours after ivermectin administration due to a hypersensitivity reaction to dead *Onchocerca* spp. microfilaria. The reaction is preventable by administering a glucocorticoid just prior