Chemistry/Synonyms
A beta$_1$ specific adrenergic blocker, metoprolol tartrate occurs as a white, crystalline powder having a bitter taste. It is very soluble in water. Metoprolol succinate occurs as a white, crystalline powder and is freely soluble in water.

Metoprolol may also be known as: CGP-2175E; H-93/26, and metoprolol; many trade names are available.

Storage/Stability/Compatibility
Store all products protected from light. Store tablets in tight, light-resistant containers at room temperature. Avoid freezing the injection.

The injection is **compatible** with D5W and normal saline.

Dosage Forms/Regulatory Status
VETERINARY-LABELED PRODUCTS: None

The ARCI (Racing Commissioners International) has designated this drug as a class 3 substance. See the appendix for more information.

HUMAN-LABELED PRODUCTS:

Metoprolol Tartrate Tablets: 25 mg, 50 mg & 100 mg; *Lopressor*® (Novartis); generic; (Rx)

Metoprolol Succinate Extended-Release Tablets (equivalent to metoprolol tartrate): 25 mg, 50 mg, 100 mg & 200 mg; *Toprol XL*® (AstraZeneca); (Rx)

Metoprolol Tartrate Injection: 1 mg/mL in 5 mL amps and *Carpuject* sterile cartridge units; *Lopressor*® (Novartis); (Rx); generic; (Hospira); (Rx)

METRONIDAZOLE

(me-troe-***ni***-da-zole) Flagyl®

ANTIBIOTIC, ANTIPARASITIC

Prescriber Highlights
- Injectable & oral antibacterial (anaerobes) & antiprotozoal agent
- Prohibited by the FDA for use in food animals
- Contraindications: Hypersensitivity to it or nitroimidazole derivatives. Extreme caution: in severely debilitated, pregnant or nursing animals; hepatic dysfunction.
- Adverse Effects: Neurologic disorders, lethargy, weakness, neutropenias, hepatotoxicity, hematuria, anorexia, nausea, vomiting, & diarrhea
- May be a teratogen, especially in early pregnancy

Uses/Indications
Although there are no veterinary-approved metronidazole products, the drug has been used extensively in the treatment of Giardia in both dogs and cats. It is also used clinically in small animals for the treatment of other parasites (Trichomonas and *Balantidium coli*) as well as treating both enteric and systemic anaerobic infections.

In horses, metronidazole has been used clinically for the treatment of anaerobic infections.

Pharmacology/Actions
Metronidazole is bactericidal against susceptible bacteria. Its exact mechanism of action is not completely understood, but it is taken-up by anaerobic organisms where it is reduced to an unidentified polar compound. It is believed that this compound is responsible for the drug's antimicrobial activity by disrupting DNA and nucleic acid synthesis in the bacteria.

Metronidazole has activity against most obligate anaerobes including *Bacteroides* spp. (including *B. fragilis*), Fusobacterium, Veillonella, *Clostridium* spp., Peptococcus, and Peptostreptococcus. Actinomyces is frequently resistant to metronidazole.

Metronidazole is also trichomonacidal and amebicidal in action and acts as a direct amebicide. Its mechanism of action for its antiprotozoal activity is not understood. It has therapeutic activity against *Entamoeba histolytica*, Trichomonas, Giardia, and *Balantidium coli*. It acts primarily against the trophozoite forms of Entamoeba rather than encysted forms.

Finally, metronidazole has some inhibitive actions on cell-mediated immunity.

Pharmacokinetics
Metronidazole is relatively well absorbed after oral administration. The oral bioavailability in dogs is high, but interpatient variable, with ranges from 50–100% reported. The oral bioavailability of the drug in horses averages about 80% (range 57–100%). If given with food, absorption is enhanced in dogs, but delayed in humans. Peak levels occur about one hour after dosing.

Metronidazole is rather lipophilic and is rapidly and widely distributed after absorption. It is distributed to most body tissues and fluids, including bone, abscesses, the CNS, and seminal fluid. It is less than 20% bound to plasma proteins in humans.

Metronidazole is primarily metabolized in the liver via several pathways. Both the metabolites and unchanged drug are eliminated in the urine and feces. Elimination half-lives of metronidazole in patients with normal renal and hepatic function in various species are reported as: humans 6–8 hours, dogs 4–5 hours, and horses 2.9–4.3 hours.

Contraindications/Precautions/Warnings
Metronidazole is prohibited for use in food animals by the FDA.

Metronidazole is contraindicated in animals hypersensitive to the drug or nitroimidazole derivatives. It has been recommended not to use the drug in severely debilitated, pregnant or nursing animals. Metronidazole should be used with caution in animals with hepatic dysfunction. If the drug must be used in animals with significant liver impairment, consider using only 25–50% of the usual dose.

Adverse Effects
Adverse effects reported in dogs include neurologic disorders, lethargy, weakness, neutropenias, hepatotoxicity, hematuria, anorexia, nausea, vomiting, and diarrhea. Cats infrequently develop GI effects.

Neurologic toxicity in dogs may be manifested after acute high dosages or, more likely, with chronic moderate to high-dose therapy. Clinical signs reported are described below in the Overdosage section.

Metronidazole tablets have a sharp, metallic taste that animals find unpleasant. Placing in capsules or using compounded oral suspensions may alleviate the problem of dosing avoidance.

Reproductive/Nursing Safety
Metronidazole's potential for teratogenicity is somewhat controversial; some references state that it has been teratogenic in some laboratory animal studies, but others state that it has not. However, unless the benefits to the mother outweigh the risks to the fetus(es), it should not be used during pregnancy, particularly during the first 3 weeks of gestation. 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.) In a separate system evaluating the safety of drugs in canine and feline pregnancy (Papich 1989), this drug is categorized as 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.*)

Because of the potential for tumorigenicity, consider using alternative therapy or switching to milk replacer for nursing patients.

Overdosage/Acute Toxicity

Signs of intoxication associated with metronidazole in dogs and cats, include anorexia and/or vomiting, depression, mydriasis, nystagmus, ataxia, head-tilt, deficits of proprioception, joint knuckling, disorientation, tremors, seizures, bradycardia, rigidity and stiffness. These effects may be seen with acute overdoses or in some animals on chronic therapy when using "recommended" doses. Diazepam has been used successfully to decrease the CNS effects associated with metronidazole toxicity; see the Diazepam monograph or the reference by Evans, Levesque, et al for more information.

Acute overdoses should be handled by attempting to limit the absorption of the drug using standard protocols. Extreme caution should be used before attempting to induce vomiting in patients demonstrating CNS effects or aspiration may result. If acute toxicity is seen after chronic therapy, the drug should be discontinued and the patient treated supportively and symptomatically. Neurologic clinical signs may require several days before showing signs of resolving.

Drug Interactions

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

- **ALCOHOL**: May induce a disulfiram-like (nausea, vomiting, cramps, etc.) reaction when given with metronidazole.
- **CIMETIDINE**: May decrease the metabolism of metronidazole and increase the likelihood of dose-related side effects occurring.
- **PHENOBARBITAL** or **PHENYTOIN**: May increase the metabolism of metronidazole, thereby decreasing blood levels.
- **WARFARIN**: Metronidazole may prolong the PT in patients receiving warfarin or other coumarin anticoagulants. Avoid concurrent use if possible; otherwise, intensify monitoring.

Laboratory Considerations

- Metronidazole can cause falsely decreased readings of **AST** (SGOT) and **ALT** (SGPT) when determined using methods measuring decreases in ultraviolet absorbance when NADH is reduced to NAD.

Doses

- **DOGS:**

  For treatment of Giardia:
  a) 15–25 mg/kg PO q12–24h daily for 5–7 days (Lappin 2006b)
  b) 44 mg/kg PO initially, then 22 mg/kg PO q8h for 5 days (Todd, Paul, and DiPietro 1985)
  c) 25–65 mg/kg PO once daily for 5 days (Longhofer 1988)
  d) 30–60 mg/kg PO once daily for 5–7 days (also for trichomoniasis) (Chiapella 1988)

  For other protozoal infections:
  a) *Entamoeba histolytica* or *Pentatrichomas hominis*: 25 mg/kg PO q12h for 8 days (Lappin 2000)

  For anaerobic infections:
  a) For anaerobic bacterial meningitis: 25–50 mg/kg PO q12h (Schunk 1988)
  b) For suppurative cholangitis: 25–30 mg/kg PO two times a day; may be used with chloramphenicol. Therapy may be necessary for 4–6 weeks (Cornelius and Bjorling 1988)
  c) For sepsis: 15 mg/kg IV q12h (Hardie 2000)
  d) 44 mg/kg PO q12h (Aronson and Aucoin 1989)
  e) For anaerobic sepsis: 10 mg/kg IV three times daily as a CRI (Tello 2003a)

  For eliminating Helicobacter gastritis infections:
  a) Using triple therapy: Metronidazole 15.4 mg/kg q8h, amoxicillin 11 mg/kg q8h and bismuth subsalicylate (original *Pepto-Bismol®*) 0.22 mL/kg PO q4–6h. Give each for 3 weeks. (Hall 2000)
  b) Using triple therapy: Metronidazole 33 mg/kg once daily, amoxicillin 11 mg/kg q12h and either sucralfate (0.25–0.5 grams q8h) or omeprazole 0.66 mg/kg once daily (Hall 2000)

  For adjunctive therapy of plasmacytic/lymphocytic enteritis:
  a) 10 mg/kg PO three times daily for 2–4 weeks (Magne 1989)
  b) 10–30 mg/kg PO q8–24h for 2–4 weeks in refractory cases (Leib, Hay, and Roth 1989)

  For inflammatory bowel disease:
  a) For ulcerative colitis in dogs refractory to other therapies (*e.g.*, sulfasalazine, immunosuppressants, diet, etc.): 10–20 mg/kg PO twice daily–three times a day; may be beneficial in treating for 2–4 weeks those dogs with chronic colitis having unexplained diarrhea (Leib 2000).
  b) Starting dose of 10–15 mg/kg PO q12h and then tapered to the lowest effective dose. (Moore 2004)
  c) 10–15 mg/kg PO q8–12h; combine with prednisone to manage moderate to severe cases. (Marks 2007b)

  For adjunctive therapy of hepatic encephalopathy:
  a) 20 mg/kg PO q8h (Hardy 1989)

- **CATS:**

  For treatment of Giardia:
  a) 15–25 mg/kg PO q12–24h daily for 5–7 days (Lappin 2006b)
  b) 25 mg/kg PO q12h for 7 days (Zoran 2007)

  For other protozoal infections:
  a) *Entamoeba histolytica* or *Pentatrichomas hominis*: 25 mg/kg PO q12h for 8 days (Lappin 2000)

  For treating *H. pylori*:
  a) Metronidazole 10–15 mg/kg PO two times a day; clarithromycin 7.5 mg/kg PO two times a day; amoxicillin 20 mg/kg PO twice daily for 14 days (Simpson 2003b)

  For anaerobic infections:
  a) For sepsis: 15 mg/kg IV q12h (Hardie 2000)

For adjunctive therapy of GI conditions:

a) For inflammatory bowel disease: Initially, metronidazole at 11–22 mg/kg PO twice daily with prednisolone (initially at 1.1–2.2 mg/kg twice daily for first 2–8 weeks until clinical signs improve). Usually at least several months of metronidazole therapy is needed. (Taboada 2000)
b) Starting dose of 10–15 mg/kg PO q12h and then tapered to the lowest effective dose. (Moore 2004)
c) For inflammatory bowel disease: With a change of diet to "hypoallergenic", may give metronidazole at 62.5 mg (total dose) PO per cat once daily for 10–20 days. Resistant cats or those with severe disease are given immunosuppressive doses of prednisolone (1–2 mg/kg initially twice daily). (Gaschen 2006)
d) 10–15 mg/kg PO q8–12h; combine with prednisone to manage moderate to severe cases. (Marks 2007b)
e) For adjunctive therapy of hepatic lipidoses: 25–30 mg/kg PO twice daily for 2–3 weeks (unproven, but may be of benefit) (Cornelius and Bjorling 1988)
f) For hepatic encephalopathy: 7.5 mg/kg PO q8–12h (Cornelius, Bartges et al. 2000)

■ **FERRETS:**

For eliminating Helicobacter gastritis infections:

a) Using triple therapy: Metronidazole 22 mg/kg, amoxicillin 22 mg/kg and bismuth subsalicylate (original *Pepto-Bismol®*) 17.6 mg/kg PO. Give each 3 times daily for 3–4 weeks. (Hall 2000)

For susceptible infections:

a) 10–30 mg/kg PO once to twice daily. Very bitter; mask flavor. (Williams 2000)

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

a) Rabbits: For anaerobic infections: 20 mg/kg PO q12h for 3–5 days or 40 mg/kg PO once daily; 5 mg/kg slow IV q12h (Ivey and Morrisey 2000)
b) Chinchillas: 10–40 mg/kg PO once daily as an antimicrobial; 50–60 mg/kg PO twice daily for 5 days as an antiparasiticide (Giardia) (Hayes 2000)
c) Chinchillas, Gerbils, Guinea Pigs, Hamsters, Mice, Rats: 20–60 mg/kg PO q8–12h. Mice: 3.5 mg/mL in water for 5 days. Rats: 10–40 mg per rat PO once daily. Chinchillas, Guinea pigs: 10–40 mg/kg PO once daily. Gerbils, Hamsters: 7.5 mg/70–90 grams of body weight PO q8h. Add sucrose to improve palatability. (Adamcak and Otten 2000)

■ **HORSES:**

For susceptible anaerobic infections:

a) 20–25 mg/kg PO q8–12h; for treatment of colitis due to *Clostridium* spp., may dose at 15 mg/kg PO q8h. Can also dose at same dosages rectally if unable to dose PO. Metronidazole is uncommonly associated with diarrhea and neurologic side effects. (Bentz 2007)
b) 10–25 mg/kg PO 2–4 times a day (Chaffin 1999)
c) Foals: 15 mg/kg PO or IV q6–12h (Brumbaugh 1999)
d) Foals with *C. perfringens*: 10–15 mg/kg PO 3–4 times a day (dose depends on severity); if animal has an ileus and is intolerant of oral feeding give IV at 10 mg/kg IV 4 times a day (Slovis 2003a)
e) For *L. intracellularis* infections: metronidazole 10–15 mg/kg PO q8–12h with either oxytetracycline (10–18 mg/kg via slow IV q24h) or chloramphenicol (44 mg/kg PO q6–8h). (Frazer 2007)

■ **BIRDS:**

For susceptible infections (anaerobes):

a) 50 mg/kg PO once daily for 5 days (Bauck and Hoefer 1993)
b) Ratites (not to be used for food): 20–25 mg/kg PO twice daily (Jenson 1998)

■ **REPTILES:**

a) For anaerobic infections in most species: 150 mg/kg PO once; repeat in one week

   For amoebae and flagellates in most species: 100–275 mg/kg PO once; repeat in 1–2 weeks.

   In *Drymarchon* spp., *Lampropeltis pyromelana*, and *L. zonata*: 40 mg/kg PO once; repeat in 2 weeks (Gauvin 1993)

Monitoring

■ Clinical efficacy
■ Adverse effects (clients should report any neurologic symptomatology)

Client Information

■ Report any neurologic clinical signs to veterinarian (see Overdose section).

Chemistry/Synonyms

A synthetic, nitroimidazole antibacterial and antiprotozoal agent, metronidazole occurs as white to pale yellow crystalline powder or crystals with a pK_a of 2.6. It is sparingly soluble in water or alcohol. Metronidazole base is commercially available as tablets or solution for IV injection and metronidazole HCl is available as injectable powder for reconstitution. The hydrochloride is very soluble in water.

Metronidazole may also be known as: Bayer-5360, metronidazolum, SC-32642, NSC-50364, RP-8823, and SC-10295; many trade names are available.

Storage/Stability/Compatibility

Metronidazole tablets and HCl powder for injection should be stored at temperatures less than 30°C and protected from light. The injection should be protected from light and freezing and stored at room temperature.

Specific recommendations on the reconstitution, dilution, and neutralization of metronidazole HCl powder for injection are detailed in the package insert of the drug and should be referred to if this product is used. Do not use aluminum hub needles to reconstitute or transfer this drug as a reddish-brown discoloration may result in the solution.

The following drugs and solutions are reportedly physically **compatible** with metronidazole ready-to-use solutions for injection: amikacin sulfate, aminophylline, carbenicillin disodium, cefazolin sodium, cefotaxime sodium, cefoxitin sodium, cefuroxime sodium, cephalothin sodium, chloramphenicol sodium succinate, clindamycin phosphate, disopyramide phosphate, gentamicin sulfate, heparin sodium, hydrocortisone sodium succinate, hydromorphone HCl, magnesium sulfate, meperidine HCl, morphine sulfate, moxalactam disodium, multielectrolyte concentrate, multivitamins, netilmicin sulfate, penicillin G sodium, and tobramycin sulfate.

The following drugs and solutions are reportedly physically **incompatible** (or compatibility data conflicts) with metronidazole ready-to-use solutions for injection: aztreonam, cefamandole naftate, and dopamine HCl.

Dosage Forms/Regulatory Status

VETERINARY-LABELED PRODUCTS: None

Metronidazole is prohibited for use in food animals by the FDA.

HUMAN-LABELED PRODUCTS:

Metronidazole Tablets: 250 mg & 500 mg; *Flagyl*® (Pharmacia); generic; (Rx)

Metronidazole Capsules: 375 mg; *Flagyl 375*® (Pharmacia); generic (Able); (Rx)

Metronidazole Extended-Release Tablets: 750 mg; *Flagyl ER*® (Pharmacia); generic (Able); (Rx)

Metronidazole HCl Powder for Injection: 500 mg/vial; *Flagyl*®*IV* (Pharmacia); (Rx)

Metronidazole Injection: 5 mg/mL in 100 mL vials and single-dose vials; *Flagyl*®*I.V.* (Pharmacia); generic; (B. Braun); (Rx)

Bismuth Subsalicylate, Metronidazole & Tetracycline HCl Combination Tablets & Capsules: 262.4 mg bismuth subsalicylate, 250 mg metronidazole; 500 mg tetracycline; *Helidac*® (Procter & Gamble); (Rx)

Lotions, gels, vaginal products and creams also available.

MEXILETINE HCL

(mex-***ill***-i-teen) Mexitil®

ORAL ANTIARRHYTHMIC

Prescriber Highlights

- Oral antiarrhythmic with similar effects as lidocaine; used for V tach, PVC's; often used with atenolol
- Extreme caution: Pre-existing 2nd or 3rd degree AV block (without pacemaker), or in patients with cardiogenic shock
- Caution: Severe congestive heart failure or acute myocardial infarction, hepatic function impairment, hypotension, intraventricular conduction abnormalities, sinus node function impairment, seizure disorder, or sensitivity to the drug
- Adverse Effects: GI distress, including vomiting (give with meals to alleviate); Potentially: CNS effects (trembling, unsteadiness, dizziness, depression), shortness of breath, PVC's & chest pain could occur; rarely (reported in humans): seizures, agranulocytosis, & thrombocytopenia
- Relatively expensive (compared to quinidine)
- Drug-drug; drug-lab interactions

Uses/Indications

Mexiletine may be useful to treat some ventricular arrhythmias, including PVC's and ventricular tachycardia in small animals. Ventricular tachycardias that have responded to lidocaine usually (but not always) respond to mexiletine as well. Mexiletine may have less cardiodepressant effects and appears to have fewer adverse effects than either procainamide or quinidine, but it is much more costly.

Mexiletine may be useful treating certain myopathies in dogs such as myotonia congenita (most studied in miniature schnauzers and Chow Chows) and myokymia in Jack Russell Terriers.

Pharmacology/Actions

Mexiletine is considered a class IB antiarrhythmic agent and is similar to lidocaine in its mechanism of antiarrhythmic activity. It inhibits the inward sodium current (fast sodium channel), thereby reducing the rate of rise of the action potential, Phase O. In the Purkinje fibers, automaticity is decreased, action potential is shortened and, to a lesser extent, effective refractory period is decreased. Usually conduction is unaffected, but may be slowed in patients with preexisting conduction abnormalities.

Pharmacokinetics

Mexiletine is relatively well absorbed from the gut and has a low first-pass effect. In humans, it is moderately bound to plasma proteins (60–75%), and is metabolized in the liver to inactive metabolites with an elimination half-life of about 10–12 hours. Half-lives may be significantly increased in patients with moderate to severe hepatic disease, or in those having severely reduced cardiac outputs. Half-lives may be slightly prolonged in patients with severe renal disease or after acute myocardial infarction.

Contraindications/Precautions/Warnings

Mexiletine should be used with extreme caution, if at all, in patients with pre-existing 2nd or 3rd degree AV block (without pacemaker), or with cardiogenic shock. It should be used only when the benefits of therapy outweigh the risks when the following medical conditions exist: severe congestive heart failure or acute myocardial infarction, hepatic function impairment, hypotension, intraventricular conduction abnormalities, sinus node function impairment, seizure disorder, or sensitivity to the drug.

Adverse Effects

The most likely adverse effect noted in animals is GI distress, including vomiting. Giving with meals may alleviate this. Potentially (reported in humans): CNS effects (trembling, unsteadiness, dizziness, depression), shortness of breath, PVC's and chest pain could occur. Rarely, seizures, agranulocytosis, and thrombocytopenia have been reported in humans.

Reproductive/Nursing Safety

Lab animal studies have not demonstrated teratogenicity. 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.*)

Because mexiletine is secreted into maternal milk, it has been recommended to use milk replacer if the mother is receiving the drug.

Overdosage/Acute Toxicity

Toxicity associated with overdosage may be significant. Case reports in humans have noted that CNS signs always preceded cardiovascular signs. Treatment should consist of GI tract emptying protocols when indicated, acidification of the urine to enhance urinary excretion, and supportive therapy. Atropine may be useful if hypotension or bradycardia occur.