METRONIDAZOLE (Veterinary—Systemic)

Some commonly used *brand names* for human-labeled products are: *Apo-Metronidazole; Flagyl; Novonidazol;* and *PMS-Metronidazole.*

Note: For a listing of dosage forms and brand names by country availability, see the *Dosage Forms* section(s).

Category:
Antibacterial (systemic); antiprotozoal.

Indications
Note: Metronidazole is not specifically approved for veterinary use. In other USP information monographs the [EL]US and [EL]CAN designations refer to uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of veterinary products and, therefore, product labeling.

General considerations

Metronidazole is effective in the treatment of systemic and enteric obligate anaerobic bacterial infections, including *Clostridium* species, *Fusobacterium* species,{R-1} and penicillinase-producing strains of *Bacteroides.*{R-2; 3} Surgical therapy may be necessary to completely resolve isolated infections.{R-3}

Metronidazole is not clinically effective against facultative anaerobes or obligate aerobes.{R-1; 4} However, it is often combined with another antibiotic or antibiotics effective against aerobes to treat mixed bacterial infections.{R-2}

Metronidazole is considered effective in the treatment of some protozoal infections in animals.

Accepted

[EL]US,CAN Giardiasis (treatment)[EL]—*Cats* and *dogs:* Metronidazole is used to eliminate shedding of giardial cysts and treat associated diarrhea in cats and dogs.{R-6; 7; 36} Environmental eradication is necessary for effective treatment. The infection may not be completely cleared in all animals.{R-7}

Potentially effective

[EL]US,CAN Amebiasis, intestinal (treatment)[EL];

[EL]US,CAN Balantidiasis, intestinal (treatment)[EL]; or

[EL]US,CAN Trichomoniasis, intestinal (treatment)[EL]—*Cats* and *dogs:* In human patients, metronidazole is used in the treatment of susceptible *Balantidium coli, Entamoeba histolytica,* and *Trichomonas* species.{R-1; 4; 5} Metronidazole is also recommended in the treatment of enteric protozoal infections in cats and dogs, although the relationship between infection and clinical signs can be difficult to define.

[EL]US,CAN Bowel disease, inflammatory (treatment)[EL]—*Cats* and *dogs:* Although there are insufficient data to establish efficacy, metronidazole is used in the treatment of inflammatory bowel disease.

[EL]US,CAN Colitis, antibiotic-associated (treatment)[EL]; or

[EL]US,CAN Colitis, clostridial (treatment)[EL]—*Horses:* Although there are insufficient data to establish efficacy, metronidazole is used in the treatment of bacterial colitis caused by susceptible organisms, including *Clostridium difficile.*{R-10-12}

[EL]US,CAN Encephalopathy, hepatic (treatment)[EL]—*Cats* and *dogs:* Although there are insufficient data to establish efficacy, metronidazole is used to reduce gastrointestinal bacterial production of ammonia thought to contribute to clinical signs in hepatic encephalopathy.

[EL]US,CAN Endometritis (treatment)[EL]—*Horses:* Although there are insufficient data to establish efficacy, metronidazole is used in combination with other antibiotics in the treatment of endometritis, including infections caused by penicillinase-producing anaerobic bacteria.{R-13}

[EL]US,CAN *Helicobacter* species infections (treatment)[EL]—*Cats* and *dogs:* Although the treatment of *Helicobacter pylori* in human gastrointestinal disease has had major clinical impact, the relationship of *Helicobacter* species or *Helicobacter*-like organisms to gastric disease in cats and dogs has not been established. When evidence of infection with these organisms is found in a patient, a clinician may make a decision to treat with metronidazole, in combination with other drugs, such as bismuth-containing compounds, a proton-pump inhibitor, and another antibiotic, based on the data available.{R-22-26}

[EL]US,CAN Infections, bacterial (treatment)[EL], including

[EL]US,CAN Bone and joint infections (treatment)[EL];

[EL]US,CAN Central nervous system infections (treatment)[EL];

[EL]US,CAN Intra-abdominal infections (treatment)[EL];

[EL]US,CAN Perioperative infections, colorectal (prophylaxis)[EL];

[EL]US,CAN Respiratory tract infections, lower (treatment)[EL];

[EL]US,CAN Septicemia, bacterial (treatment)[EL]; or

[EL]US,CAN Skin and soft tissue infections (treatment)[EL]—*Cats, dogs,* and *horses:* Although there are insufficient clinical research data to establish efficacy, metronidazole is used in the treatment of many types of anaerobic bacterial infections in animals. In human patients, metronidazole is indicated, usually in combination with other antibiotics, in the prevention of perioperative infections during colorectal surgery and in the treatment of bone and joint infections; central nervous system infections; intra-abdominal infections; lower respiratory tract infections, including pleuropneumonia and lung abscess; septicemia; and skin and soft tissue infections caused by susceptible species, including *Bacteroides* and *Clostridium* species.{R-1; 4} There are limited pharmacokinetic data and case reports available pertaining to the use of metronidazole in the treatment of these types of infections in animals, when caused by susceptible organisms.{R-8; 9; 12; 14; 16; 19-21; 28}

[EL]US,CAN Periodontal infections (treatment)[EL]—*Cats* and *dogs:* Metronidazole is used in the treatment of periodontal infections in cats and dogs.{R-15; 17; 18} It may be administered for destructive periodontal diseases as part of a treatment plan that also includes one or more of the following: dental scaling, gingival crevicular lavage, periodontal surgery, or regular teeth cleaning.{R-17}

Regulatory Considerations
U.S.—

The Food and Drug Administration has not approved the use of me-tronidazole in animals. **Federal law prohibits the extra-label use of nitroimidazoles in food-producing animals.**{R-27}

Canada—

Metronidazole is not approved for use in food-producing animals. There are no established withdrawal times.

Chemistry
Chemical group: Nitroimidazoles.

Chemical name:

Metronidazole—1*H*-Imidazole-1-ethanol, 2-methyl-5-nitro-.{R-29}

Metronidazole hydrochloride—1*H*-Imidazole-1-ethanol, 2-methyl-5-nitro-, hydrochloride.{R-29}

Molecular formula:

Metronidazole—$C_6H_9N_3O_3$.{R-29}

Metronidazole hydrochloride—$C_6H_9N_3O_3 \cdot HCl$.{R-29}

Molecular weight:

Metronidazole—171.15.{R-29}

Metronidazole hydrochloride—207.61.{R-29}

Description: Metronidazole USP—White to pale yellow, odorless crystals or crystalline powder. Is stable in air, but darkens on exposure to light.{R-30}

Solubility: Metronidazole USP—Sparingly soluble in water and in

alcohol; slightly soluble in ether and in chloroform.[R-30]

Pharmacology/Pharmacokinetics

Mechanism of action/Effect: Metronidazole is reduced as it enters the target cell where it interacts with bacterial or protozoal DNA, causing a loss of helical structure and strand breakage in the DNA; these effects inhibit nucleic acid synthesis and cause death of the cell.

Absorption: Metronidazole is moderately well absorbed from the gastrointestinal tract.[R-21; 33; 37]

Distribution: *Horses*—In one pharmacokinetic study of horses, peak metronidazole concentrations in peritoneal fluid, synovial fluid, and cerebrospinal fluid were 65%, 92%, and 30% of peak serum concentrations.[R-21] With an oral dose of 7.5 mg/kg every 6 hours, endometrial penetration was poor.[R-21]

Biotransformation: Hepatic, metabolized primarily by side-chain oxidation and glucuronide synthesis.

Pharmacokinetic data:

Table 1. Intravenous administration.

Species	Elimination half-life (hours)	Volume of distribution (L/kg)	Clearance (mL/min/kg)
Dogs[R-37]	4.48 ± 0.89	Area: 0.95 ± 0.10	2.49 ± 0.54
Horses[R-33]	2.9	Area: 1.70 ± 0.24	6.67 ± 0.83
[R-21]	3.11 ± 0.21	Area: 0.74 ± 0.01	2.8 ± 0.18
[R-39]	3.27 ± 0.65	Steady state: 0.69 ± 0.01	2.8 ± 0.8
		Steady state: 0.68 ± 0.16	

Table 2. Oral administration.

Species	Dose (mg/kg)	C_{max} (mcg/mL)	T_{max} (hour)	Bioavail-ability (%)
Dogs[R-37]	44	42*	1*	59 to 100
Horses[R-33]	25	12.6 ± 2.4	1 to 2	85.0 ± 18.6
[R-39]	20	22 ± 8	1.1 ± 0.6	74 ± 18
[R-21]†	15	13.9 ± 2.18	0.67	97 ± 5.7

* Read from graph.

† Two horses with pleuropneumonia yielded similar kinetic results to that of healthy mares in this study.

Precautions to Consider

Carcinogenicity/Mutagenicity

Metronidazole has been shown to be a carcinogen in mice and rats with chronic oral administration. It has also been shown to be mutagenic in *in vitro* assays.[R-1; 4]

Pregnancy/Reproduction

Pregnancy—Metronidazole readily crosses the placenta and enters the fetal circulation.[R-1] No teratogenic effects were seen in the pups of rats that had received 250 mg per kg of body weight (mg/kg) a day for 1 to 12 days, or 100 mg/kg a day for 40 days. However, spermatogenesis in male rats was affected by the administration of 100 mg/kg a day.

Lactation

Metronidazole is distributed into milk at concentrations similar to plasma concentrations.[R-1; 4] Risk-benefit should be considered carefully when metronidazole is used in nursing animals.

Drug interactions and/or related problems

The following drug interactions and/or related problems have been selected on the basis of their potential clinical significance (possible mechanism in parentheses where appropriate)—not necessarily inclusive:

Note: Combinations containing any of the following medications, depending on the amount present, may also interact with metronidazole.

Cimetidine

(hepatic metabolism of metronidazole may be decreased when metronidazole and cimetidine are used concurrently, possibly resulting in delayed elimination and increased serum metronidazole concentrations;[R-5] dosage of metronidazole may need to be adjusted)

Phenobarbital

(phenobarbital may induce microsomal liver enzymes, increasing metronidazole's metabolism and resulting in a decrease in half-life and plasma concentration;[R-5] dosage of metronidazole may need to be adjusted)

Side/Adverse Effects

The following side/adverse effects have been selected on the basis of their potential clinical significance (possible signs and, for humans, symptoms in parentheses where appropriate)—not necessarily inclusive:

Those indicating need for medical attention

Neurologic disturbances (ataxia, nystagmus, seizures, tremors, weakness)—usually with high dosage in cats, dogs, and horses,[R-31; 32] although signs have been reported with doses as low as 30 mg/kg.[R-41]

Those indicating need for medical attention only if they continue or are bothersome

Anorexia; neutropenia; vomiting

Those not indicating need for medical attention

Reddish brown urine

Human side/adverse effects[R-5]

In addition to the above side/adverse effects reported in animals, the following side/adverse effects have been reported in humans, and are included in the human monograph *Metronidazole (Systemic)* in *USP DI Volume I;* these side/adverse effects are intended for informational purposes only and may or may not be applicable to the use of metronidazole in the treatment of animals:

Incidence more frequent

Central nervous system (CNS) effects; gastrointestinal disturbance

Incidence less frequent or rare

Change in taste sensation; CNS toxicity, including ataxia and encephalopathy; dark urine; dryness of mouth; hypersensitivity; leukopenia; pancreatitis; peripheral neuropathy—usually with high doses or prolonged use; ***seizures***—usually with high doses; ***thrombocytopenia***—reversible; ***thrombophlebitis; unpleasant or sharp metallic taste; urinary tract effects, including frequent or painful urination and inability to control urine flow; vaginal candidiasis***

Overdose

For information in cases of overdose or unintentional ingestion, **contact the American Society for the Prevention of Cruelty to Animals (ASPCA) National Animal Poison Control Center** (888-426-4435 or 900-443-0000; a fee may be required for consultation) **and/or the drug manufacturer.**

Lethal dose

Dogs: 250 mg per kg of body weight (mg/kg) a day induced central nervous system dysfunction within 4 to 6 days and death within a week of onset of signs.[R-32]

Clinical effects of overdose

The following effects have been selected on the basis of their potential clinical significance—not necessarily inclusive:

Dogs, with doses of 65 to 129 mg/kg a day.[R-32]

Ataxia; head tilt; nystagmus (spontaneous, positional, vertical); ***seizures***

Note: Neurologic effects have also been reported with doses as low as 30 mg/kg.[R-41]

Ataxia and *nystagmus* were noted consistently in a report on five cases of toxicosis. Signs appeared within 7 to 12 days of initiating therapy. In dogs that survived complications of neurologic dysfunction, signs gradually resolved over 1 to 2 weeks after ending metronidazole administration.[R-32]

Oral Dosage Forms

Note: The dosing and strengths of the dosage forms available are expressed in terms of metronidazole base.

Metronidazole is not specifically approved for veterinary use. In other USP information monographs the [EL US] and [EL CAN] designations indicate uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of veterinary products and, therefore, product labeling.

METRONIDAZOLE CAPSULES

Usual dose:

[EL US,CAN]Bacterial infections, anaerobic[EL]; or

[EL US,CAN]Protozoal infections[EL]—

Cats and *dogs:* Oral, 15 mg (base) per kg of body weight every twelve hours.[R-38]

Horses: Oral, 15 to 25 mg (base) per kg of body weight every six hours.[R-33]

Note: Anorexia may occur in horses treated with the above dose; therefore, some clinicians recommend use of a lower oral dose of 10 mg per kg of body weight every twelve hours.[R-40]

For susceptible *gram-negative anaerobic infections* in horses, one study recommended an alternative dosage regimen of 15 mg per kg of body weight as an initial dose, followed by 7.5 mg per kg of body weight every six hours.[R-21]

Contents of the capsule can be mixed with molasses or administered via nasogastric tube.[R-31; 33; 34]

[EL US,CAN]Hepatic encephalopathy[EL]; or

[EL US,CAN]Inflammatory bowel disease[EL]—*Cats* and d*ogs:* Oral, 7.5 mg (base) per kg of body weight every twelve hours.

Strength(s) usually available:

U.S.—

Veterinary product(s):

Not commercially available.

Human product(s):

375 mg (base) (Rx) [*Flagyl;* GENERIC].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (base) (Rx) [*Apo-Metronidazole; Flagyl; PMS-Metronidazole*].

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), in a well-closed container, unless otherwise specified by manufacturer. Store in a light-resistant container.

USP requirements: Not in USP.[R-30]

METRONIDAZOLE TABLETS USP

Usual dose: See *Metronidazole Capsules*.

Note: *Cats*—The typical way to give 15 mg per kg of body weight to an eight- to nine-pound cat is to administer one-fourth of a 250-mg tablet.

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (base) (Rx) [*Flagyl;* GENERIC].

500 mg (base) (Rx) [*Flagyl;* GENERIC].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

250 mg (base) (Rx) [*Apo-Metronidazole; Novonidazol* (scored); *PMS-Metronidazole;* GENERIC].

Packaging and storage: Store below 40 ºC (104 ºF), preferably between 15 and 30 ºC (59 and 86 ºF), in a well-closed container, unless otherwise specified by manufacturer. Store in a light-resistant container.

Additional information: For cats, tablets should not be crushed for administration, because metronidazole is bitter and often unpalatable.

USP requirements: Preserve in well-closed, light-resistant containers. Contain the labeled amount, within ±10%. Meet the requirements for Identification, Dissolution (85% in 60 minutes in 0.1 *N* hydrochloric acid in Apparatus 1 at 100 rpm), and Uniformity of dosage units.[R-30]

Parenteral Dosage Forms

Note: The dosing and strengths of the dosage forms available are expressed in terms of metronidazole base.

Metronidazole is not specifically approved for veterinary use. In other USP information monographs the [EL US] and [EL CAN] designations indicate uses that are not included in U.S. and Canadian product labeling; however, in this monograph they reflect the lack of veterinary products and, therefore, product labeling.

METRONIDAZOLE INJECTION USP

Usual dose:

Note: Reliable dosing information is not available for the use of parenteral metronidazole in animals. However, for situations in which oral administration is not a viable option, injectable forms are used by following dosing regimens similar to oral dosage forms.

Strength(s) usually available:

U.S.—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (base) per 100 mL (Rx) [GENERIC].

Canada—

Veterinary-labeled product(s):

Not commercially available.

Human-labeled product(s):

500 mg (base) per 100 mL (Rx) [GENERIC].

Withdrawal times: There are no established withdrawal times since metronidazole is not approved for use in food-producing animals.

Packaging and storage: Store below 40 ºC (104 ºF), preferably

between 15 and 30 ºC (59 and 86 ºF), unless otherwise specified by manufacturer. Protect from light. Protect from freezing.

Incompatibilities: Intravenous admixtures of metronidazole and other medications are not recommended.{R-35}

Additional information: Metronidazole Injection USP is an isotonic (297 to 310 mOsm per L), ready-to-use solution, requiring no dilution or buffering prior to administration.{R-35}

USP requirements: Preserve in single-dose containers of Type I or Type II glass, or in suitable plastic containers, protected from light. A sterile, isotonic, buffered solution of Metronidazole in Water for Injection. Contains the labeled amount, within ±10%. Meets the requirements for Identification, Bacterial endotoxins, pH (4.5–7.0), and Particulate matter, and for Injections.{R-30}

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04/05/03; 02/28/07

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