

**METRONIDAZOLE
REDI-INFUSION™
(Metronidazole Injection)
FOR INTRAVENOUS INFUSION ONLY**

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats (See WARNINGS). Its use, therefore, should be reserved for the conditions described in the INDICATIONS AND USAGE section below.

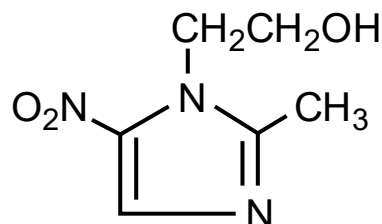
DESCRIPTION

Metronidazole Redi-Infusion™ is a parenteral dosage form of the synthetic anti-bacterial agent 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole.

The molecular formula is C₆H₉N₃O₃.

Metronidazole Redi-Infusion™, 100 mL single dose vial for intravenous infusion, is a sterile, nonpyrogenic, isotonic, buffered solution. Each mL contains metronidazole 5 mg, dibasic sodium phosphate, anhydrous 0.476 mg, citric acid anhydrous 0.229 mg and sodium chloride 7.9 mg in Water for Injection pH 4.5-7.0. Each vial contains 14 mEq of sodium and has a calculated tonicity of 310 mOsm/L.

The molecular weight of metronidazole is 171.16 and its structural formula is as follows:



CLINICAL PHARMACOLOGY

Metronidazole is a synthetic antibacterial compound. Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms, with an average elimination half-life in healthy humans of eight hours.

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose), with fecal excretion accounting for 6-15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(β-hydroxyethyl)-2-hydroxy-methyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m².

Metronidazole is the major component appearing in the plasma, with lesser quantities of the 2-hydroxymethyl metabolite also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Both the parent compound and the metabolite possess *in vitro* bactericidal activity against most strains of anaerobic bacteria.

Metronidazole appears in cerebrospinal fluid, saliva, and breast milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.

Plasma concentrations of metronidazole are proportional to the administered dose. An eight-hour intravenous infusion of 100-4,000 mg of metronidazole in normal subjects showed a linear relationship between dose and peak plasma concentration.

In patients treated with intravenous metronidazole using a dosage regimen of 15 mg/kg loading dose followed six hours later by 7.5 mg/kg every six hours, peak steady-state plasma concentrations of metronidazole averaged 25 mcg/mL with trough (minimum) concentrations averaging 18 mcg/mL.

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole. However, plasma clearance of metronidazole is decreased in patients with decreased liver function.

In one study newborn infants appeared to demonstrate diminished capacity to eliminate metronidazole. The elimination half-life, measured during the first three days of life, was inversely related to gestational age. In infants whose gestational ages were between 28 and 40 weeks, the corresponding elimination half-lives ranged from 109 to 22.5 hours.

Microbiology: Metronidazole is active *in vitro* against most obligate anaerobes, but does not appear to possess any clinically relevant activity against facultative anaerobes or obligate aerobes. Against susceptible organisms, metronidazole is generally bactericidal at concentrations equal to or slightly higher than the minimal inhibitory concentrations (MIC). Metronidazole has been shown to have *in vitro* and clinical activity against the following organisms:

Anaerobic gram-negative bacilli, including:

Bacteroides species, including the *Bacteroides fragilis* group (*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*) *Fusobacterium* species

Anaerobic gram-positive bacilli, including:

Clostridium species and susceptible strains of *Eubacterium*

Anaerobic gram-positive cocci, including:

Peptococcus species

Peptostreptococcus species

Susceptibility Testing

For specific information regarding susceptibility test interpretive criteria, and associated test methods and quality control standards recognized by FDA for this drug, please see: <http://www.fda.gov/STIC>.

INDICATIONS AND USAGE

Metronidazole Redi-Infusion™ is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with Metronidazole Redi-Infusion™ therapy. In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection should be used in addition to Metronidazole Redi-Infusion™.

Metronidazole Redi-Infusion™ is effective in *Bacteroides fragilis* infections resistant to clindamycin, chloramphenicol, and penicillin.

Intra-Abdominal Infections, including peritonitis, intra-abdominal abscess, and liver abscess, caused by *Bacteroides* species including the *B. fragilis* group (*B. fragilis*, *B. distasonis*, *B. ovatus*, *B. thetaiotaomicron*, *B. vulgatus*), *Clostridium* species, *Eubacterium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Skin and Skin Structure Infections caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and *Fusobacterium* species.

Gynecologic Infections, including endometritis, endomyometritis, tubo-ovarian abscess, and post-surgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, and *Peptostreptococcus* species.

Bacterial Septicemia caused by *Bacteroides* species including the *B. fragilis* group, and *Clostridium* species.

Bone and Joint Infections, as adjunctive therapy, caused by *Bacteroides* species including the *B. fragilis* group.

Central Nervous System (CNS) Infections, including meningitis and brain abscess, caused by *Bacteroides* species including the *B. fragilis* group.

Lower Respiratory Tract Infections, including pneumonia, empyema, and lung abscess, caused by *Bacteroides* species including the *B. fragilis* group.

Endocarditis caused by *Bacteroides* species including the *B. fragilis* group.

Prophylaxis

The prophylactic administration of Metronidazole Redi-Infusion™ preoperatively, intraoperatively and postoperatively may reduce the incidence of postoperative infection in patients undergoing elective colorectal surgery which is classified as contaminated or potentially contaminated.

Prophylactic use of Metronidazole Redi-Infusion™ should be discontinued within 12 hours after surgery. If there are signs of infection, specimens for cultures should be obtained for the identification of the causative organism(s) so that appropriate therapy may be given (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Metronidazole is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

Psychotic Reaction with Disulfiram

Use of oral metronidazole is associated with psychotic reactions in alcoholic patients who were using disulfiram concurrently. Do not administer metronidazole to patients who have taken disulfiram within the last two weeks (see PRECAUTIONS-Drug Interactions).

Interaction with Alcohol

Use of oral metronidazole is associated with a disulfiram-like reaction to alcohol, including abdominal cramps, nausea, vomiting, headaches, and flushing. Discontinue consumption of alcohol or products containing propylene glycol during and for at least three days after therapy with metronidazole (see PRECAUTIONS-Drug Interactions).

Cockayne Syndrome

Metronidazole Injection is contraindicated in patients with Cockayne syndrome. Severe irreversible hepatotoxicity/acute liver failure with fatal outcomes have been reported after initiation of metronidazole in patients with Cockayne syndrome (see ADVERSE REACTIONS).

WARNINGS

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported with the use of metronidazole. Symptoms can be serious and potentially life threatening. If symptoms or signs of SCARs develop, discontinue Metronidazole injection immediately and institute appropriate therapy.

Convulsive Seizures and Peripheral Neuropathy: Convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity, have been reported in patients treated with metronidazole. The appearance of abnormal neurologic signs demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

Tumorigenicity in Rodents: Metronidazole has shown evidence of carcinogenic activity in studies involving chronic, oral administration in mice and rats, but similar studies in the hamster gave negative results. Also, metronidazole has shown mutagenic activity in a number of *in vitro* assay systems, but studies in mammals (*in vivo*) failed to demonstrate a potential for genetic damage.

PRECAUTIONS

General

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, administer, with caution, doses below those usually recommended.

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administering Metronidazole Redi-Infusion™ to patients receiving corticosteroids or to patients predisposed to edema.

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with Metronidazole Redi-Infusion™ and requires treatment with a candidicidal agent.

Information for Patients

Advise patients that Metronidazole injection may increase the risk of serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS). Instruct the patient to be alert for skin rash, blisters, fever or other signs and symptoms of these hypersensitivity reactions. Advise patients to stop Metronidazole injection immediately if they develop any type of rash and seek medical attention.

Laboratory Tests

Metronidazole is a nitroimidazole, and should be used with care in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy.

Drug Interactions

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when Metronidazole Redi-Infusion™ is prescribed for patients on this type of anticoagulant therapy.

The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

Disulfiram

Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks (see CONTRAINDICATIONS).

Alcoholic Beverages

Abdominal cramps, nausea, vomiting, headaches and flushing may occur if alcoholic beverages or products containing propylene glycol are consumed during or following metronidazole therapy (see CONTRAINDICATIONS).

QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

Drug/Laboratory Test Interactions

Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides and hexokinase glucose. Values of zero may be observed.

All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotine adenine dinucleotide ($\text{NAD}^+ \rightleftharpoons \text{NADH}$). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

Carcinogenesis

See WARNINGS.

Pregnancy

Teratogenic Effects. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Reproduction studies have been performed in rabbits and rats at doses up to five times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to metronidazole. Metronidazole administered intraperitoneally to pregnant mice at approximately the human dose caused fetotoxicity; administered orally to pregnant mice, no fetotoxicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and because metronidazole is a carcinogen in rodents, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Because of the potential for tumorigenicity shown for metronidazole in mouse and rat studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Metronidazole is secreted in breast milk in concentrations similar to those found in plasma.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The two most serious adverse reactions reported in patients treated with intravenous metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged oral administration of metronidazole, patients should be observed carefully if neurologic symptoms occur and a prompt evaluation made of the benefit/risk ratio of the continuation of therapy.

The following reactions have also been reported during treatment with intravenous metronidazole:

Gastrointestinal: Nausea, vomiting, abdominal discomfort, diarrhea, and an unpleasant metallic taste.

Hematopoietic: Reversible neutropenia (leukopenia).

Dermatologic: Erythematous rash and pruritus.

Central Nervous System: Headache, dizziness, syncope, ataxia, and confusion.

Local Reactions: Thrombophlebitis after intravenous infusion. This reaction can be minimized or avoided by avoiding prolonged use of indwelling intravenous catheters.

Other: Fever. Instances of a darkened urine have also been reported, and this manifestation has been the subject of a special investigation. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

The following adverse reactions have been reported during treatment with oral metronidazole:

Gastrointestinal: Nausea, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea, epigastric distress, abdominal cramping, and constipation.

Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of *Candida* which may occur during effective therapy.

Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.

Cardiovascular: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval. Flattening of the T-wave may be seen in electrocardiographic tracings.

Central Nervous System: Convulsive seizures, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, tinnitus, hearing impairment, hearing loss, confusion, irritability, depression, weakness, and insomnia.

Hypersensitivity: Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) (see WARNINGS). Urticaria, erythematous rash, flushing, nasal congestion, dryness of mouth (or vagina or vulva), and fever.

Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure, and darkened urine.

Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported.

The following adverse reactions have been reported during treatment with oral and IV metronidazole:

Hepatic: Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne Syndrome (latency from drug start to signs of liver failure as short as 2 days) (see Contraindications).

Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for Metronidazole Redi-Infusion™.

OVERDOSAGE

Use of dosages of intravenous metronidazole higher than those recommended has been reported. These include the use of 27 mg/kg three times a day for 20 days, and the use of 75 mg/kg as a single loading dose followed by 7.5 mg/kg maintenance doses. No adverse reactions were reported in either of the two cases.

Single oral doses of metronidazole, up to 15 g, have been reported in suicide attempts and accidental overdoses. Symptoms reported include nausea, vomiting, and ataxia.

Oral metronidazole has been studied as a radiation sensitizer in the treatment of malignant tumors. Neurotoxic effects, including seizures and peripheral neuropathy, have been reported after 5 to 7 days of doses of 6 to 10.4 g every other day.

Treatment: There is no specific antidote for overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

DOSAGE AND ADMINISTRATION

Treatment of Anaerobic Infections

The recommended dosage schedule for *adults* is:

Loading Dose – 15 mg/kg infused over one hour (approximately 1 g for a 70 kg adult).

Maintenance Dose – 7.5 mg/kg infused over one hour every six hours (approximately 500 mg for a 70 kg adult). The first maintenance dose should be instituted six hours following the initiation of the loading dose.

Parenteral therapy may be changed to oral metronidazole when conditions warrant based upon the severity of the disease and the response of the patient to intravenous metronidazole treatment. The usual adult oral dosage is 7.5 mg/kg every six hours.

A maximum of 4 g should not be exceeded during a 24 hour period.

Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, administer, with caution, doses below those usually recommended. Close monitoring of plasma metronidazole levels² and toxicity is recommended.

In patients receiving intravenous metronidazole in whom gastric secretions are continuously removed by nasogastric aspiration, sufficient metronidazole may be removed in the aspirate to cause a reduction in serum levels.

The dose of metronidazole should not be specifically reduced in anuric patients since accumulated metabolites may be rapidly removed by dialysis.

The usual duration of therapy is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.

Prophylaxis

For surgical prophylactic use, to prevent postoperative infection in contaminated or potentially contaminated colorectal surgery, the recommended dosage schedule for adults is:

- a. 15 mg/kg infused over 30 to 60 minutes and completed approximately one hour before surgery; followed by
- b. 7.5 mg/kg infused over 30 to 60 minutes at 6 and 12 hours after the initial dose.

It is important that (1) administration of the initial preoperative dose be completed approximately one hour before surgery so that adequate drug levels are present in the serum and tissues at the time of initial incision, and (2) Metronidazole Redi-Infusion™ be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of Metronidazole Redi-Infusion™ should be limited to the day of surgery only, following the above guidelines.

CAUTION

Metronidazole Redi-Infusion™ is to be administered by slow intravenous drip infusion only, either as a continuous or intermittent infusion. IV admixtures containing metronidazole and other drugs should be avoided. Additives should not be introduced into the Metronidazole Redi-Infusion™ solution. If used with a primary intravenous fluid system, the primary solution should be discontinued during metronidazole infusion.

DO NOT USE EQUIPMENT CONTAINING ALUMINUM (e.g., NEEDLES, CANNULAE) THAT WOULD COME IN CONTACT WITH THE DRUG SOLUTION.

Metronidazole Redi-Infusion™ is a ready-to-use, isotonic solution. NO DILUTION OR BUFFERING IS REQUIRED. Each vial of Metronidazole Redi-Infusion™ contains 14 mEq of sodium.

Parenteral drug products should be Inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if cloudy or precipitated or if the seal is not intact.

Use sterile equipment It is recommended that the intravenous administration apparatus be replaced at least once every 24 hours.

HOW SUPPLIED

100 mL SINGLE USE vials (preservative-free) 500 mg/100 mL (5 mg/mL) packaged individually, without IV infusion set (NDC 0641-2337-41)

100 mL SINGLE USE vials (preservative-free) 500 mg/100 mL (5 mg/mL) packaged individually, with one standard secondary disposable vented IV infusion set (NDC 0641-2337-61)

STORAGE

Store at controlled room temperature 15° to 30°C (59° to 86°F). Avoid freezing. If freezing occurs, please contact the Professional Services Department. Protect from light. Store in box until ready to use.

REFERENCES

1. Ralph, E.D., and Kirby, W.M.M.: Bioassay of Metronidazole With Either Anaerobic or Aerobic Incubation, J. Infect Dis. 132:587-591 (Nov.) 1975; or Gulaid, et al.: Determination of Metronidazole and Its Major Metabolites in Biological Fluids by High Pressure Liquid Chromatography, Br. J. Clin. Pharmacol. 6:430-432, 1978.

Additional package inserts may be obtained by contacting the Professional Services Department.

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