

FLAGYL[®]
(metronidazole hydrochloride) 500 mg
FOR INJECTION, STERILE
For Intravenous Infusion

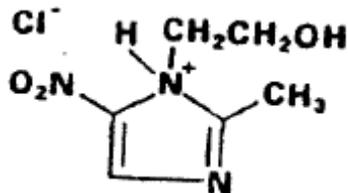
To reduce the development of drug-resistant bacteria and maintain the effectiveness of FLAGYL[®] (metronidazole) For Injection, Sterile 500 mg and other antibacterial drugs, FLAGYL[®] (metronidazole) For Injection, Sterile 500 mg should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

WARNING

Metronidazole has been shown to be carcinogenic in mice and rats (see **PRECAUTIONS**). Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the **INDICATIONS AND USAGE** section below.

DESCRIPTION

FLAGYL (metronidazole hydrochloride) For Injection, Sterile 500 mg is a parenteral dosage form of the synthetic nitroimidazole antibacterial agent 2-methyl-5-nitro-1H-imidazole-1-ethanol.



Metronidazole hydrochloride

Each single-dose vial of lyophilized FLAGYL I.V. contains sterile, nonpyrogenic metronidazole hydrochloride, equivalent to 500 mg metronidazole, and 415 mg mannitol.

CLINICAL PHARMACOLOGY

In patients treated with FLAGYL, using a dosage regimen of 15 mg/kg loading dose followed 6 hours later by 7.5 mg/kg every 6 hours, the average peak steady-state plasma concentrations (C_{max}) of metronidazole was 25 mcg/mL with trough (minimum) concentrations averaging 18 mcg/mL, respectively. Plasma concentrations of metronidazole are proportional to the administered dose. An eight-hour intravenous infusion of 100 mg to 4,000 mg of metronidazole in normal subjects showed a linear

relationship between dose and peak plasma concentration. The average elimination half-life of metronidazole in healthy subjects is eight hours.

Distribution:

Metronidazole is the major component appearing in the plasma, with lesser quantities of metabolites also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins.

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.

Following a single intravenous dose of metronidazole 500 mg, 4 healthy subjects who underwent gastrointestinal endoscopy had peak gastric juice metronidazole concentrations of 5 to 6 mcg/mL at one hour post-dose. 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.

Metabolism

The metabolites of metronidazole result primarily from side-chain oxidation [1-(β -hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-yl-acetic acid] and glucuronide conjugation. Both the parent compound and the hydroxyl metabolite possess *in vitro* antimicrobial activity.

Excretion

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose), with approximately 20% of the amount excreted appearing as unchanged metronidazole. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m². Fecal excretion accounts for 6-15% of the dose.

Renal Impairment:

Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole.

Subjects with end-stage renal disease (ESRD; $CL_{CR}=8.1 \pm 9.1$ mL/min) and who received a single intravenous infusion of metronidazole 500 mg had no significant change in metronidazole pharmacokinetics but had 2-fold higher C_{max} of hydroxy-metronidazole and 5-fold higher C_{max} of metronidazole acetate, compared to healthy subjects with normal renal function ($CL_{CR}=126 \pm 16$ mL/min). Thus, on account of the potential accumulation of metronidazole metabolites in ESRD patients, monitoring for metronidazole associated adverse events is recommended (see **PRECAUTIONS**).

Effect of Dialysis:

Following a single intravenous infusion or oral dose of metronidazole 500 mg, the clearance of metronidazole was investigated in ESRD subjects undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A hemodialysis session lasting for 4 to 8 hours removed 40% to 65% of the administered metronidazole dose, depending on the type of the dialyzer membrane used and the duration of the dialysis session. If the administration of metronidazole cannot be separated from the dialysis session, supplementation of metronidazole dose following hemodialysis should be considered (see **DOSAGE AND ADMINISTRATION**). A peritoneal dialysis session lasting for 7.5 hours removed approximately 10% of the administered metronidazole dose. No adjustment in metronidazole dose is needed in ESRD patients undergoing continuous ambulatory peritoneal dialysis.

Hepatic Impairment:

Following a single intravenous infusion of 500 mg metronidazole, the mean AUC_{24} of metronidazole was higher by 114% in patients with severe (Child-Pugh C) hepatic impairment, and by 54% and 53% in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to healthy control subjects. There were no significant changes in the AUC_{24} of hydroxy-metronidazole in these hepatically impaired patients. A reduction in metronidazole dosage by 50% is recommended in patients with severe (Child-Pugh C) hepatic impairment (see **DOSAGE AND ADMINISTRATION**). No dosage adjustment is needed for patients with mild to moderate hepatic impairment. Patients with mild to moderate hepatic impairment should be monitored for metronidazole associated adverse events (see **PRECAUTIONS and DOSAGE AND ADMINISTRATION**).

Geriatric Patients:

Following a single 500 mg oral or I.V. dose of metronidazole, subjects >70 years old with no apparent renal or hepatic dysfunction had a 40% to 80% higher mean AUC of hydroxy-metronidazole (active metabolite), with no apparent increase in the mean AUC of metronidazole (parent compound), compared to young healthy controls <40 years old. In geriatric patients, monitoring for metronidazole associated adverse events is recommended (see **PRECAUTIONS**).

Pediatric Patients:

In one study, newborn infants appeared to demonstrate diminished capacity to eliminate metronidazole. The elimination half-life, measured during the first 3 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

Mechanism of Action

Metronidazole, a nitroimidazole, exerts antibacterial effects in an anaerobic environment against most obligate anaerobes. Once metronidazole enters the organism by passive diffusion and activated in the cytoplasm of susceptible anaerobic bacteria, it is reduced; this process includes intra-cellular electron transport proteins such as ferredoxin, transfer of an electron to the nitro group of the metronidazole, and formation of a short-lived nitroso free radical. Because of this alteration of the metronidazole molecule, a concentration gradient is created and maintained which promotes the drug's intracellular transport. The reduced form of metronidazole and free radicals can interact with DNA leading to inhibition of DNA synthesis and DNA degradation leading to death of bacteria. The precise mechanism of action of metronidazole is unclear.

Drug Resistance

A potential for development of resistance exists against metronidazole.

Resistance may be due to multiple mechanisms that include decreased uptake of the drug, altered reduction efficiency, overexpression of the efflux pumps, inactivation of the drug, and/or increased DNA damage repair.

Metronidazole does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

Activity *In Vitro* and in Clinical Infections

Metronidazole has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Gram-positive anaerobes

Clostridium species
Eubacterium species
Peptococcus species
Peptostreptococcus species

Gram-negative anaerobes

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

The following *in vitro* data are available, **but their clinical significance is unknown**

Metronidazole exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 mcg/mL or less against most ($\geq 90\%$) isolates of the following bacteria; however, the safety and effectiveness of metronidazole in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-negative anaerobes

Bacteroides fragilis group (*B. caccae*, *B. uniformis*)

Prevotella species (*P. bivia*, *P. buccae*, *P. disiens*)

Susceptibility Tests

When available, the clinical microbiology laboratory should provide results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

For Anaerobes

Quantitative methods are used to determine antimicrobial inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. For anaerobic bacteria, the susceptibility to metronidazole can be determined by the reference broth and/or agar dilution method^{1,2}. The MIC values should be interpreted according to the criteria provided in the following Table:

Susceptibility Test Interpretive Criteria for Metronidazole against Anaerobes*†

MIC (mcg/mL)	Interpretation
≤ 8	Susceptible (S)
16	Intermediate (I)
≥ 32	Resistant (R)

*Agar dilution method is recommended for all anaerobes

†Broth dilution method is recommended for testing of *Bacteroides fragilis* group only; for this group, MIC values by agar and broth dilution methods are considered equivalent

A report of "Susceptible" (S) indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of "Intermediate" (I) implies that an infection due to the isolate may be appropriately treated in the body sites where the drugs are physiologically concentrated or when a high dosage of drug is used. A report of "Resistant" (R) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentration usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.^{1,2} Standard metronidazole powder should provide a value within the MIC ranges noted in the following table:

Acceptable Quality Control Ranges for Metronidazole against Anaerobes

Quality control strain	Minimum Inhibitory Concentration (mcg/mL)	
	Agar	Broth
<i>Bacteroides fragilis</i> ATCC 25285	0.25–1.0	0.25-2.0
<i>Bacteroides thetaiotaomicron</i> ATCC 29741	0.5–2.0	0.5-4.0
<i>Clostridium difficile</i> ATCC 700057	0.125-0.5	-
<i>Eggerthella lenta</i> ATCC 43055	-	0.125-0.5

INDICATIONS AND USAGE

Treatment of Anaerobic Bacterial Infections

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

FLAGYL I.V. 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 postsurgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group, *Clostridium* species, *Peptococcus* species, *Peptostreptococcus* species, and *Fusobacterium* 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 FLAGYL I.V. preoperatively, intra-operatively, 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 FLAGYL I.V. 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**).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of FLAGYL I.V. and other antibacterial drugs, FLAGYL I.V. should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Hypersensitivity:

FLAGYL I.V. 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 and products containing propylene glycol during and for at least three days after therapy with metronidazole (see **PRECAUTIONS, Drug Interactions**).

WARNINGS

Central and Peripheral Nervous System Effects

Encephalopathy and peripheral neuropathy: Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole.

Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, and dysarthria. CNS lesions seen on MRI have been described in reports of encephalopathy. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible.

Peripheral neuropathy, mainly of sensory type has been reported and is characterized by numbness or paresthesia of an extremity.

Convulsive seizures have been reported in patients treated with metronidazole.

Aseptic meningitis: Cases of aseptic meningitis have been reported with metronidazole. Symptoms can occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.

The appearance of abnormal neurologic signs and symptoms demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy (see **ADVERSE REACTIONS**).

PRECAUTIONS

General:

Hepatic Impairment

Patients with hepatic impairment metabolize metronidazole slowly, with resultant accumulation of metronidazole in the plasma. For patients with severe hepatic impairment (Child-Pugh C), a reduced dose of metronidazole is recommended. For patients with mild to moderate hepatic impairment, no dosage adjustment is needed but these patients should be monitored for metronidazole associated adverse events (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Renal Impairment

Patients with end-stage renal disease may excrete metronidazole and metabolites slowly in the urine, resulting in significant accumulation of metronidazole metabolites. Monitoring for metronidazole associated adverse events is recommended (see **CLINICAL PHARMACOLOGY**).

Fungal Superinfections

Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

Use in Patients with Blood Dyscrasias

Metronidazole is a nitroimidazole and FLAGYL I.V. should be used with caution in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administrations; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies.

Monitoring for Leukopenia

Total and differential leukocyte counts are recommended before and after prolonged or repeated courses of metronidazole therapy.

Sodium Retention

Administration of solutions containing sodium ions may result in sodium retention. Care should be taken when administering FLAGYL I.V. to patients receiving corticosteroids or to patients predisposed to edema.

Drug-Resistant Bacteria and Parasites:

Prescribing metronidazole in the absence of a proven or strongly suspected bacterial or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients

Interaction with Alcohol

Discontinue consumption of alcoholic beverages or products containing propylene glycol while taking FLAGYL I.V. and for at least three days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur (see **CONTRAINDICATIONS, PRECAUTIONS, Drug Interactions**).

Drug Interactions

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**).

Warfarin and other Oral Anticoagulants

Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants, resulting in a prolongation of prothrombin time. When metronidazole is prescribed for patients on this type of anticoagulant therapy, prothrombin time and INR should be carefully monitored.

Lithium

In patients stabilized on relatively high doses of lithium, short-term metronidazole therapy has been associated with elevation of serum lithium and, in a few cases, signs of lithium toxicity. Serum lithium and serum creatinine levels should be obtained several days after beginning metronidazole to detect any increase that may precede clinical symptoms of lithium intoxication.

Busulfan

Metronidazole has been reported to increase plasma concentrations of busulfan, which can result in an increased risk for serious busulfan toxicity. Metronidazole should not be administered concomitantly with busulfan unless the benefit outweighs the risk. If no therapeutic alternatives to metronidazole are available, and concomitant administration with busulfan is medically needed, frequent monitoring of busulfan plasma concentration should be performed and the busulfan dose should be adjusted accordingly.

Drugs that Inhibit CYP450 Enzymes

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.

Drugs that Induce CYP450 Enzymes

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

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 glucose hexokinase. 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 nicotinamide 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, Mutagenesis, Impairment of Fertility

Tumors affecting the liver, lung, mammary, and lymphatic tissues have been detected in several studies of metronidazole in rats and mice, but not hamsters.

Pulmonary tumors have been observed in all six reported studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). Malignant liver tumors were increased in male mice treated at approximately 1500 mg/m^2 (similar to the maximum recommended daily dose, based on body surface area comparisons). Malignant lymphomas and pulmonary neoplasms were also increased with lifetime feeding of the drug to mice (published data). Mammary and hepatic tumors were increased among female rats administered oral metronidazole compared to concurrent controls. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Metronidazole has shown mutagenic activity in *in vitro* assay systems including the Ames test. Studies in mammals *in vivo* have failed to demonstrate a potential for genetic damage.

Metronidazole failed to produce any adverse effects on fertility or testicular function in male rats at doses up to 400 mg/kg/day (approximately 2 times the maximum recommended daily dose based on body surface area comparisons) for 28 days. However, rats treated at the same dose for 6 weeks or longer were infertile and showed severe degeneration of the seminiferous epithelium in the testes as well as marked decreases in testicular spermatid counts and epididymal sperm counts. Fertility was restored in most rats after an eight week, drug-free recovery period.

Fertility studies have been performed in male mice at doses up to six times the maximum recommended human dose based on mg/m^2 and have revealed no evidence of impaired fertility. However, metronidazole was associated with reversible adverse effects on the male reproductive system (significantly decreased testes and epididymides weight, decreased sperm viability, and increased the incidence of abnormal sperm).

Pregnancy

Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of FLAGYL I.V. in pregnant women. There are published data from case-control studies, cohort studies, and 2 meta-analyses that include more than 5000 pregnant women who used metronidazole during pregnancy. Many studies included first trimester exposures. One study showed an increased risk of cleft lip, with or without cleft palate, in infants exposed to metronidazole *in utero*; however, these findings were not confirmed. In addition, more than ten randomized placebo-controlled clinical trials enrolled more than 5000 pregnant women to assess the use of antibiotic treatment (including metronidazole) for bacterial vaginosis on the incidence of preterm delivery. Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy. Three studies conducted to assess the risk of infant cancer following metronidazole exposure during pregnancy did not show an increased risk; however, the ability of these studies to detect such a signal was limited.

Metronidazole crosses the placental barrier and its effects on the human fetal organogenesis are not known. Reproduction studies have been performed in rats, rabbits and mice at doses similar to the maximum recommended daily dose based on body surface area comparisons. There was no evidence of harm to the fetus due to metronidazole.

Nursing Mothers

Metronidazole is present in human milk at concentrations similar to maternal serum levels, and infant serum levels can be close to or comparable to infant therapeutic levels. 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. Alternatively, a nursing mother may choose to pump and discard human milk for the duration of metronidazole therapy, and for 24 hours after therapy ends and feed her infant stored human milk or formula.

Geriatric Use

In geriatric patients, monitoring for metronidazole associated adverse events is recommended (see **CLINICAL PHARMACOLOGY, PRECAUTIONS**). Decreased liver function in geriatric patients can result in increased concentrations of metronidazole that may necessitate adjustment of metronidazole dosage (see **DOSAGE AND ADMINISTRATION**).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The following reactions have been reported during treatment with metronidazole:

Central Nervous System: The most serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures, encephalopathy, aseptic meningitis, optic 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 administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur. In addition, patients have reported headache, syncope, dizziness, vertigo, incoordination, ataxia, confusion, dysarthria, irritability, depression, weakness, and insomnia (see **WARNINGS**).

The following reactions have also been reported during treatment with metronidazole.

Gastrointestinal: The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly 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.

Dermatologic: Erythematous rash and pruritus.

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

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

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Hypersensitivity: Urticaria, erythematous rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.

Renal: Dysuria, cystitis, polyuria, incontinence, a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. 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.

Other: Proliferation of *Candida* in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness". Rare cases of pancreatitis, which abated on withdrawal of the drug, have been reported. Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some 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 FLAGYL I.V.

OVERDOSAGE

Use of dosages of FLAGYL I.V. 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 included 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 of Overdosage

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

DOSAGE AND ADMINISTRATION

Treatment of Anaerobic Bacterial Infections

The recommended dosage schedule for adults is:

Loading Dose	15 mg/kg infused over 1 hour (approximately 1 g for a 70 kg adult).
Maintenance Dose	7.5 mg/kg infused over 1 hour every 6 hours (approximately 500 mg for a 70 kg adult). The first maintenance dose should be instituted 6 hours following the initiation of the loading dose.

Parenteral therapy may be changed to oral FLAGYL (metronidazole) when conditions warrant, based upon the severity of the disease and the response of the patient to FLAGYL I.V. treatment. The usual adult oral dosage is 7.5 mg/kg every 6 hours (approximately 500 mg for a 70-kg adult).

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

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.

Dosage Adjustments:

Patients with Severe Hepatic Impairment

Patients with Severe Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh C), the metronidazole dose should be reduced by 50% (see **CLINICAL PHARMACOLOGY and PRECAUTIONS**).

Patients Undergoing Hemodialysis

Hemodialysis removes significant amounts of metronidazole and its metabolites from systemic circulation. The clearance of metronidazole will depend on the type of dialysis membrane used, the duration of the dialysis session, and other factors. If the administration of metronidazole cannot be separated from the hemodialysis session, supplementation of metronidazole dosage following the hemodialysis session should be considered, depending on the patient's clinical situation (see **CLINICAL PHARMACOLOGY**).

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 1 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 1 hour before surgery so that adequate drug levels are present in the serum and tissues at the time of initial incision, and (2) FLAGYL I.V. be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of FLAGYL I.V. should be limited to the day of surgery only, following the above guidelines.

CAUTION: FLAGYL I.V. (metronidazole hydrochloride) is to be administered by slow intravenous drip infusion only, either as a continuous or intermittent infusion. Intravenous admixtures containing metronidazole and other drugs should be avoided. 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.

FLAGYL I.V. cannot be given by direct intravenous injection (I.V. bolus) because of the low pH (0.5-2.0) of the reconstituted product. FLAGYL I.V. MUST BE FURTHER DILUTED AND NEUTRALIZED FOR I.V. INFUSION.

FLAGYL I.V. is prepared for use in two steps:

NOTE: ORDER OF MIXING IS IMPORTANT

- A. Reconstitution
- B. Dilution in intravenous solution followed by pH neutralization with sodium bicarbonate injection into the dilution.

Reconstitution: To prepare the solution, add 4.4 mL of one of the following diluents and mix thoroughly: Sterile Water for Injection, USP; Bacteriostatic Water for Injection, USP; 0.9% Sodium Chloride Injection, USP; or Bacteriostatic 0.9% Sodium Chloride Injection, USP. The resultant approximate withdrawal volume is 5.0 mL with an approximate concentration of 100 mg/mL.

The pH of the reconstituted product will be in the range of 0.5 to 2.0. Reconstituted FLAGYL I.V. is clear, and pale yellow to yellow-green in color.

Dilution in Intravenous Solutions: Properly reconstituted FLAGYL I.V. (metronidazole hydrochloride) may be added to a glass or plastic I.V. container not to exceed a concentration of 8 mg/mL. Any of the following intravenous solutions may be used: 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; or Lactated Ringer's Injection, USP. **NEUTRALIZATION IS REQUIRED PRIOR TO ADMINISTRATION.** The final product should be mixed thoroughly and used within 24 hours.

Neutralization for Intravenous Infusion: Neutralize the intravenous solution containing FLAGYL I.V. with approximately 5 mEq of sodium bicarbonate injection for each 500 mg of FLAGYL I.V. used. Mix thoroughly. The pH of the neutralized intravenous solution will be approximately 6.0 to 7.0. Carbon dioxide gas will be generated with neutralization. It may be necessary to relieve gas pressure within the container.

Note: When the contents of one vial (500 mg) are diluted and neutralized to 100 mL, the resultant concentration is 5 mg/mL. Do not exceed an 8 mg/mL concentration of FLAGYL I.V. in the neutralized intravenous solution, since neutralization will decrease the aqueous solubility and precipitation may occur. **DO NOT REFRIGERATE NEUTRALIZED SOLUTIONS;** otherwise, precipitation may occur.

Storage and Stability: Reconstituted vials of FLAGYL I.V. are chemically stable for 96 hours when stored below 86°F (30°C) in room light.

Use diluted and neutralized intravenous solutions containing FLAGYL I.V. within 24 hours of mixing.

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

FLAGYL (metronidazole hydrochloride) I.V. sterile, is supplied in single-dose lyophilized vials each containing 500 mg metronidazole equivalent, individually packaged in cartons of 10 vials.

FLAGYL I.V. prior to reconstitution, should be stored below 77°F (25°C) and protected from light.

REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard—Eighth Edition*. CLSI document M11-A8, CLSI, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087-1898 USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fifth Informational Supplement*, CLSI document M100-S25. CLSI, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.

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