Metronidazole
Dazomet®

Rx

500 mg/100 mL Solution for IV Infusion
500 mg Film-Coated Tablet
ANTIBACTERIAL / ANTIPROTOZOAL

FORMULATIONS

Each 100 mL solution for intravenous (IV) infusion contains:
Metronidazole.. 500 mg
Each film-coated tablet contains:
Metronidazole.. 500 mg

PRODUCT DESCRIPTIONS

Metronidazole (Dazomet®) 500 mg/100 mL (5 mg/mL) Solution for IV Infusion is a clear, colorless to light yellow solution, free from extraneous matter.

Metronidazole (Dazomet®) 500 mg Tablet is a blue, film-coated, elliptical tablet that is plain on both sides.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Metronidazole is bactericidal, amebicidal and trichomonacidal. Its exact mechanism of action has not been fully determined. Metronidazole is reduced by low-redox-potential electron transfer proteins (e.g., nitroreductases such as ferredoxin) to unidentified polar products which lack the nitro group. The reduction products appear to be responsible for the cytotoxic and antimicrobial effects of the drug which include disruption of DNA and inhibition of nucleic acid synthesis. Metronidazole is equally effective against dividing and non-dividing cells.

Antimicrobial spectrum of activity
In general, metronidazole is active against most obligately anaerobic bacteria and many protozoa. Metronidazole has been shown to be active against strains of the following microorganisms both *in vitro* and in clinical infections:

Gram positive anaerobes	Gram negative anaerobes	Protozoal parasites
Clostridium perfringens	*Bacteroides fragilis* group, (*B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus, B. caccae, B. uniformis*)	*Entamoeba histolytica*
Clostridium difficile	*Porphyromonas asaccharolytica, P. gingivalis*	*Trichomonas vaginalis*
Eubacterium species	*Prevotella spp. (P. bivia, P. disiens, P. Intermedia, P. melaninogenica P. Oralis, P. Buccae)*	*Giardia intestinalis (G. lamblia)*
Peptococcus species	*Fusobacterium* species	*Balantidium coli*
Peptostreptococcus species	*Veillonella* species	*Blastocystis hominis*

Metronidazole exhibits in vitro minimum inhibitory concentration (MIC) of 8 mcg/mL or less against most strains (≥90%) of gram negative and gram positive anaerobes.

Metronidazole is active against most obligate anaerobes, but does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.

Pharmacokinetics

Metronidazole is rapidly and almost completely absorbed after oral administration; bioavailability is 90 to 100%. Peak plasma concentrations (C_{max}) of approximately 5 mcg/mL and 10 mcg/mL are achieved at an average of 1 to 2 hours after single oral doses of 250 mg and 500 mg, respectively. Some accumulation and consequently higher concentrations occur when multiple doses are given. Absorption may be delayed but is not reduced overall, by administration of food. On a regimen of 500 mg three times daily administered by the intravenous (IV) route, a steady state was achieved after approximately three days. Comparison of the pharmacokinetics of oral and IV metronidazole showed that the area under the plasma metronidazole concentration (AUC) against time curves were essentially identical.

Metronidazole is widely distributed in body tissues and fluids. It diffuses across the blood-brain barrier, crosses the placenta, and appears in the saliva and breast milk of breastfeeding mothers in concentrations equivalent to those found in the plasma. It attains therapeutic concentrations in the bile and the cerebrospinal fluid (CSF). No more than 20% is bound to plasma proteins.

An oral or IV dose of metronidazole is partially metabolized in the liver by hydroxylation, acid side-chain oxidation and glucuronide conjugation. The major metabolite, 2-hydroxymethyl metronidazole, has some antiprotozoal activity *in vitro*. The plasma elimination half-life of an oral metronidazole is about 6 to 9 hours; that of the hydroxyl metabolite is slightly longer. The half-life of metronidazole is reported to be longer in neonates and in patients with severe liver disease. The biological half-life of a single intravenously administered dose of metronidazole has been determined as 7.3 hours ± 1 hour.
The majority of metronidazole dose is excreted in the urine, mainly as metabolites; a small amount appears in the feces. Urine may be dark or reddish brown in color following oral and IV administration of the drug due to the presence of water-soluble pigments, which result from its metabolism.

Special Population:

Renal Impairment: Subjects with end-stage renal disease (ESRD) (CL_{CR}=8.1±9.1 mL/min) who received a single 500 mg IV infusion of metronidazole had no significant change in metronidazole pharmacokinetics but had 2-fold higher C_{max} of hydroxyl-metronidazole and 5-fold higher C_{max} of metronidazole acetate, compared to healthy subjects with normal renal function (CL_{CR}=126±16 mL/min). Monitoring for metronidazole associated adverse events is recommended in ESRD patients due to accumulation of metronidazole metabolites.

Following a single 500 mg IV infusion or oral dose of metronidazole, the clearance of metronidazole was studied in ESRD patients 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 dialyzer membrane used and the duration of the dialysis session. Supplementation of metronidazole dose following hemodialysis should be considered if the administration of metronidazole cannot be separated from the dialysis session. A peritoneal dialysis session lasting for 7.5 hours removed approximately 10% of the administered metronidazole dose.

Hepatic Impairment: After a single 500 mg IV infusion of 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 subjects. There were no significant changes in the AUC_{24} of hydroxyl-metronidazole in these patients. In patients with severe (Child-Pugh C) hepatic impairment, a reduction in metronidazole dose by 50% is recommended. No dosage adjustment is needed for patients with mild to moderate hepatic impairment. Monitoring for metronidazole associated adverse events is recommended in patients with mild to moderate hepatic impairment.

Geriatric: After a single 500 mg oral or IV 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, with no apparent increase in the mean AUC of metronidazole, compared to young healthy subjects. Monitoring for metronidazole associated adverse events is recommended.

Pediatrics: Newborn infants showed 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 between 28 and 40 weeks, the corresponding elimination half-lives ranged from 10.9 to 22.5 hours.

USES / INDICATIONS

Format	Indications
Metronidazole (Dazomet®) 500 mg Tablet	Treatment of the following infections caused by susceptible microorganisms: • Prophylaxis and prevention of postoperative infection due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci. • Treatment of septicemia, bacteremia, peritonitis, brain abscess, necrotizing pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated. • Urogenital trichomoniasis, both symptomatic and asymptomatic • Amebiasis • Giardiasis • Balantidiasis and *Blastocystis hominis* infection • Vaginal infections including bacterial vaginosis • Acute ulcerative gingivitis • Acute dental infections (e.g., acute pericoronitis and acute apical infections • Anaerobically-infected leg ulcers and pressure sores • Treatment of *Helicobacter pylori* infection associated with peptic ulcer as part of triple therapy.
Metronidazole (Dazomet®) 500 mg/100 mL (5mg / mL) IV Infusion	• Prophylaxis and prevention of postoperative infection due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci. • Treatment of septicemia, bacteremia, peritonitis, brain abscess, necrotizing pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated. • Treatment of intestinal and extraintestinal or invasive amebiasis including amoebic liver abscess • Treatment of *Helicobacter pylori* infection associated with peptic ulcer as part of triple therapy.

DOSAGE AND ADMINISTRATION

A. Metronidazole (Dazomet®) 500 mg/100 mL (5 mg/mL) Solution for IV Infusion
- Metronidazole solution for IV infusion does not need to be diluted or neutralized prior to IV administration. IV infusions should be given at a rate of 5 mL/min.
- In the treatment of most serious anaerobic infections, IV metronidazole is usually administered initially. This may be followed by oral metronidazole therapy at the discretion of the physician.

	Usual Intravenous Metronidazole Adult Dose
Indications	**Dosing Regimen (Each dose is administered by slow IV infusion)**
Prophylaxis and prevention of postoperative anaerobic bacterial infections	Metronidazole is administered as a slow IV infusion (30 to 60 minutes). Initial **loading dose** of 15 mg/kg body weight completed approximately one hour before surgery; followed by 7.5 mg/kg body weight every 6 to 8 hours after the initial dose, **OR** 500 mg just before surgery and at 8 and 16 hours after the initial dose. It is important that 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 metronidazole injection be administered, if necessary, at 6-hour intervals to maintain effective drug levels. Prophylactic use of metronidazole injection should be limited to the day of surgery only and should not be continued for more than 12 hours after surgery. Prevention of infection at the surgical site requires adequate tissue concentrations of the drug being attained at the time of surgery. The dose and route of administration should be selected in each case to achieve this objective.
Treatment of infections caused by susceptible anaerobic microorganisms	Initial **loading dose** of 15 mg/kg body weight followed by maintenance doses of 7.5 mg/kg body weight per dose every 6 to 8 hours, doses being infused over 1 hour. A **maximum dose** of 4 g should not be exceeded during a 24-hour period. The first maintenance dose should be instituted six hours following the initiation of the loading dose. The usual duration of metronidazole therapy is 7 to 10 days; however, infections of the bone and joint, lower respiratory tract, and endocardium may require longer treatment.
Treatment of intestinal and hepatic amebiasis	400 mg to 800 mg three times daily for 5 to 10 days
	Or, as prescribed by a physician.

	Usual Intravenous Metronidazole Pediatric Dose	
Indications	**Dosing Regimen (Each dose is administered by slow IV infusion)**	
	AGE	**DOSE**
Treatment of infections caused by anaerobes, trichomoniasis, *Gardnerella vaginitis*, amebiasis, giardiasis, pseudomembranous colitis, prophylaxis in colon surgery and part of combination therapy for *Helicobacter pylori*	0 to 4 weeks: < 1,200 g	7.5 mg/kg per dose every 48 hours
	<7 days: 1,200 g to 2,000 g	7.5 mg/kg per day every 24 hours
	<7 days: >2,000 g	15 mg/kg per day every 12 hours
	>7 days: 1,200 g to 2,000 g	15 mg/kg per day every 12 hours
	>7 days: >2,000 g	30 mg/kg per day every 12 hours
	Infants and children	15 to 30 mg/kg per day every 6 hours; maximum dose of 4 g per day
	Or, as prescribed by a physician.	

Usual Duration of Treatment
- Total duration of treatment (including oral metronidazole) is based on the type and severity of infection and patient response.
- Treatment for seven days should be satisfactory for most patients but, depending upon clinical and bacteriological assessment, the clinician may decide to prolong treatment, e.g., for the eradication of infection from sites which cannot be drained or are prone to endogenous recontamination by anaerobic pathogens from the gut, nasopharynx or the female genital tract. Oral metronidazole should be substituted as soon as possible.

Incompatibility
- Do not use equipment containing aluminum components since metronidazole infusion is incompatible with aluminum.
- Do not use flexible container or plastic infusion bags in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.
- Metronidazole IV should not be mixed with cefamandole nafate, cefoxitin sodium, dextrose 10%, compound sodium lactate injection, penicillin G potassium, and other drugs.
- Discontinue other IV infusions during IV metronidazole infusion

Prior to administration, parenteral products should be inspected visually for particulate matter and discoloration. Use sterile equipment.

Metronidazole (Dazomet®) 500 mg Tablet
- Metronidazole tablet should be swallowed with water (not chewed). It is recommended that the tablets be taken during or after a meal.
- Dosing should be individualized.

Indications	Usual Oral Metronidazole Dose
Treatment of infections caused by susceptible anaerobic microorganisms	***Adults:*** 7.5 mg/kg body weight (approximately 500 mg for a 70 kg adult) every 6 to 8 hours OR 500 mg every 8 hours A maximum of 4 g should not be exceeded during a 24-hour period. ***Children (<12 years old):*** 7.5 mg/kg body weight per dose every 8 hours, OR 20 to 30 mg/kg body weight as a single dose The daily dose may be increased to 40 mg/kg depending on the severity of the infection. Duration of treatment is 7 to 10 days or longer for serious bacterial infections.
Prophylaxis and prevention of postoperative anaerobic bacterial infections	***Adults:*** 500 mg ***Children (<12 years old):*** 20 to 30 mg/kg body weight per day as a single dose given 1 to 2 hours before surgery. Treatment to be initiated 48 hours before surgery, repeated every 8 hours. Prophylactic use of metronidazole should not be continued for more than 12 hours before surgery.
Eradication of Helicobacter pylori in pediatric patients	As part of a combination therapy, 20 mg/kg body weight per day not to exceed 500 twice per day for 7 to 14 days.
	Or, as prescribed by a physician.

Protozoal and other infections

Recommended Oral Metronidazole Dose			
Infection	**Duration of dosage in days**	**Adults and adolescents**	**Children**
Urogenital trichomoniasis *Sexual partners should also be treated*	1	2,000 mg as a single dose	15 to 30 mg/kg per day every 6 hours; maximum dose of 4 g per day
If treatment needs to be repeated, an interval of 4 to 6 weeks between courses has been recommended	5 to 7	400 mg to 500 mg two times per day	—
Bacterial vaginosis	1	2,000 mg as a single dose	—
	5 to 7	400 mg to 500 mg two times per day	
Amebiasis *Acute intestinal amebiasis (acute amebic dysentery)*	5 to 10	750 mg three times per day	15 to 30 mg/kg per day every 6 hours; maximum dose of 4 g per day
Amebic liver abscess	5 to 10	500 mg or 750 mg three times per day	
Giardiasis	3	2,000 mg as a single dose	15 to 30 mg/kg per day every 6 hours; maximum dose of 4 g per day
	7 to 10	500 mg two times per day	
Acute ulcerative gingivitis	3	200 mg to 250 mg three times per day	—
Balantidiasis and *Blastocystis hominis infection*	5 to 10 days	750 mg three times per day	—
Or, as prescribed by a physician.			

Special Population:

Geriatric: In elderly patients, the pharmacokinetics of metronidazole may be altered and, thus, monitoring of serum levels may be necessary to adjust the metronidazole dosage accordingly.

Hepatic impairment: Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma metronidazole levels and toxicity is recommended.

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

In patients on hemodialysis, the dose of metronidazole need not be specifically reduced since accumulated metabolites may be rapidly removed by hemodialysis. Peritoneal dialysis does not appear to reduce serum levels of metronidazole metabolites. Patients with severe impairment of renal function who are not undergoing hemodialysis should be monitored closely for signs of toxicity.

In patients receiving metronidazole injection 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.

CONTRAINDICATIONS

- Hypersensitivity to metronidazole or nitroimidazole derivatives or any ingredient of the product.
- Active neurological disorders, a history of blood dyscrasia, hypothyroidism, or hypoadrenalism
- First trimester of pregnancy in patients with trichomoniasis.

WARNINGS and PRECAUTIONS

Metronidazole like any other imidazole derivative, have been shown to be carcinogenic in rodents. Unnecessary use of the drug should be avoided.

General
Regular clinical and laboratory monitoring, particularly leukocyte count, are advised if administration of metronidazole for more than 10 days is considered to be necessary and patients should be monitored for adverse reactions such as peripheral or central neuropathy (e.g., paresthesia, ataxia, dizziness, convulsive seizures). If leukopenia or abnormal neurological signs occur, the drug should be discontinued immediately.

There is a possibility that after *Trichomonas vaginalis* has been eliminated, a gonococcal infection might persist. Where there is clinical evidence of a trichomonal infection in the sexual partner, he should be treated concomitantly to avoid reinfection.

Metronidazole has no direct activity against aerobic or facultative anaerobic bacteria. In patients with mixed aerobic-anaerobic infections, appropriate concomitant antibiotics active against the aerobic component should be considered.

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

Central and peripheral nervous system effects
Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system (CNS) disease due to risk of neurological aggravation.

Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole. Peripheral neuropathy, mainly of sensory type has been reported and is characterized by numbness or paresthesia of the extremities. Encephalopathy has been reported in associated with cerebellar toxicity characterized by ataxia, dizziness, and dysarthria. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible. It is therefore advisable that a patient taking metronidazole injection for the first time not be left unattended for a period of two hours. The appearance of abnormal neurologic signs demands prompt discontinuation of metronidazole therapy, and when severe, immediate medical attention is required.

Cases of convulsive seizures and aseptic meningitis have been reported with metronidazole. Symptoms of aseptic meningitis 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.

Treatment with metronidazole should be discontinued if ataxia or any other symptom of CNS involvement occurs.

Candidiasis
Candida overgrowth in the gastrointestinal or genital tract may occur during metronidazole therapy and may require treatment with an agent with activity against Candida.

Sodium Retention
Administration of solutions containing sodium ions may result in sodium retention. Caution should be taken when administering metronidazole injection to patients receiving corticosteroids and patients predisposed to edema.

Hepatic Impairment
Use with caution in patients with severe hepatic disease (including hepatic encephalopathy) since these patients metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Close monitoring of plasma metronidazole levels and toxicity is recommended.

Renal Impairment
In patients undergoing hemodialysis, metronidazole and metabolites are efficiently removed during an 8-hour period of dialysis so that plasma concentration quickly falls below the therapeutic range. Thus, a further dose of metronidazole is needed after dialysis to restore an adequate plasma concentration.

In patients with renal failure, the half-life of metronidazole is unchanged, but those of its major metabolites are prolonged 4-fold or greater. The accumulation of the 2-hydroxymethyl metabolite could be associated with side effects and measurement of its plasma concentration by high pressure liquid chromatography has been recommended. In patients with renal failure undergoing intermittent peritoneal dialysis (IPD) or continuous ambulatory peritoneal dialysis (CAPD), no routine adjustment in metronidazole dose should be done.

In the absence of hemodialysis, the plasma clearance and elimination half-life of metronidazole are equivalent to those in patients with normal renal clearance. Thus, dosage adjustment is not necessary.

Pancreatitis
Treatment with metronidazole should be discontinued should pancreatitis occur once other causes of this disease are excluded.

Blood Dyscrasias
Patients with history of blood dyscrasias should use metronidazole with caution. Transient eosinophilia and leukopenia have been observed during treatment with metronidazole. Hematological tests, particularly regular total and differential leukocyte counts are recommended if administration for more than 10 days or a second course of therapy is considered to be necessary

Surgical Drainage
The use of metronidazole does not obviate the need for drainage of pus whenever indicated such as in amoebic liver abscess or abscess in other accessible positions.

Effects on the ability to drive and use machines
Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

Carcinogenicity, tumorigenicity, mutagenicity, fertility
Metronidazole has shown carcinogenic and tumorigenic activity in a number of studies involving chronic, oral administration in mice and rats, but similar studies in hamsters gave negative results. Prominent among the effects in mice was the promotion of pulmonary tumorigenesis. This has been observed in multiple studies, including one in which the animals were dose on an intermitten schedule (every fourth week only). The results of one of the mouse studies indicate a statistically significant increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding.

In the rats, there was a statistically significant increase in the incidence of various neoplasms, particularly mammary tumors, among females fed with metronidazole on a lifetime basis, over that observed in concurrent female control groups.

Metronidazole has been shown to be mutagenic in bacteria in vitro. In studies conducted in mammalian cells in vitro as well as in rodents in vivo, there was inadequate evidence of mutagenic effect of metronidazole.

A retrospective study of 771 women treated with metronidazole for Trichomonas vaginalis has revealed no statistically significant increase in cancer incidence over that expected in the normal population. An apparent increase in the incidence of cervical carcinoma observed in the metronidazole-treated group was no different from the incidence observed in women documented to have trichomoniasis not treated with metronidazole.

Fertility studies have been performed in mice at doses up to six times the maximum recommended human oral dose based on mg/m^2 and have revealed no evidence of impaired fertility.

INTERACTIONS WITH OTHER MEDICAMENTS

Alcohol: Patients taking metronidazole should be warned against consuming alcoholic beverages and products containing propylene glycol during therapy and for at least 3 days afterwards, because of the possibility of a disulfiram-like (antabuse effect) reaction (flushing, headache, nausea, vomiting, abdominal cramps, sweating, tachycardia). This reaction occurs due to the inhibition of the oxidation of acetaldehyde, the primary metabolite of alcohol.

Anticoagulants (e.g., warfarin, heparin): Oral or IV metronidazole potentiates the effects of oral anticoagulants resulting in prolongation of prothrombin time and increased hemorrhagic risk caused by decreased hepatic catabolism; thus concomitant administration should be avoided, if possible. If metronidazole is used in patients receiving an oral anticoagulant, prothrombin time and international normalized ratio (INR) should be monitored and the dosage of the anticoagulant adjusted accordingly.

There is no interaction with heparin. However, anticoagulant activity should be routinely monitored while patients receive metronidazole.

Antiepileptics: Concomitant administration of drugs which induce microsomal liver enzyme activity (e.g., phenobarbital, phenytoin) may accelerate the elimination of oral metronidazole, resulting in reduced plasma concentrations and increased concentrations of its 2-hydroxymethyl metabolite; impaired clearance of phenytoin has also been reported.

Patients receiving phenobarbital metabolize metronidazole at a much greater rate than normally, reducing the half-life to approximately three hours. It is recommended that increased doses of metronidazole injection be considered in such cases.

Metronidazole injection did not interfere with the biotransformation of diazepam, antipyrine, or phenytoin. However, oral metronidazole inhibits metabolism of phenytoin (increases plasma-phenytoin concentration).

Primidone accelerates the metabolism of metronidazole causing reduced plasma concentrations.

Busulfan: Plasma levels of busulfan may be increased by metronidazole, which may lead to severe 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 required, frequent monitoring of busulfan plasma concentration should be done and the busulfan dose should be adjusted accordingly.

Ciclosporin: Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary

Cimetidine: The concomitant administration of drugs that decrease microsomal liver enzyme activity such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole. It is not clear if ranitidine exerts a similar effect.

Corticosteroids: Care should be taken when administering metronidazole infusion to patients receiving corticosteroid therapy or to patients predisposed to edema since administration of solutions containing sodium ions may result in sodium retention.

Cyclophosphamide and carmustine (BCNU): Metronidazole should be used with caution in patients who are receiving cyclophosphamide or carmustine as a drug interaction showed in mice leads to increased toxicity.

Disulfiram: Administration of disulfiram with metronidazole has been associated with acute psychoses and confusion in some patients, thus these drugs should not be administered concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

Estrogens: Broad spectrum antibiotics may reduce the contraceptive effect of estrogens.

5-Fluorouracil and azathioprine: Transient neutropenia has been reported in patients who received oral and IV metronidazole in conjunction with IV fluorouracil and in a patient who received oral metronidazole in conjunction with azathioprine.

Metronidazole has been reported to reduce the clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil.

Lithium: Concomitant use of lithium and metronidazole may result in lithium intoxication due to decreased renal clearance of lithium. Persistent renal damage may develop. When metronidazole is to be administered to patients on lithium therapy, it may be prudent to consider tapering or discontinuing lithium temporarily when feasible. Otherwise, frequent monitoring of lithium, creatinine, electrolyte levels, and urine osmolality should be obtained several days after commencing metronidazole therapy to detect any increase that may precede clinical symptoms of lithium intoxication.

Vecuronium: A slight potentiation of the neuromuscular blocking activity of vecuronium has been reported in patients administered with metronidazole at a dose of 15 mg/kg.

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 which are based on the decrease in ultraviolet absorbance which occurs when NADH is oxidized to NAD. Metronidazole causes an increase in absorbance at the peak of NADH (340 nm) resulting in falsely decreased values.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy
Pregnancy Category B. There are no adequate and well controlled studies of metronidazole in pregnant women. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. Although metronidazole has been given to pregnant women without apparent complication, its effects on the human fetal organogenesis are not known. Administration of metronidazole should be avoided in pregnant patients and be withheld during the first trimester of pregnancy.

In serious anaerobic infections, if the administration of metronidazole to pregnant patients is considered to be necessary, its use requires that the potential benefits to the mother be weighed against possible risks to the fetus.

Screening and/or treatment for bacterial vaginosis in pregnant women as clinically indicated should be conducted during the first prenatal visit. Although intravaginal therapy may be used solely for symptomatic relief (and not for prevention of adverse pregnancy outcomes) in women at low risk for preterm delivery, the use of systemic therapy for all pregnant women, regardless of degree of risk for complications of pregnancy is recommended, because of systemic treatment may be required to eradicate upper genital tract infection that may associated with bacterial vaginosis. For the treatment of bacterial vaginosis and reduction in the incidence of adverse pregnancy outcomes associated with bacterial vaginosis (e.g., preterm birth), particularly in pregnant women at high risk for complications of pregnancy, a 7-day regimen of oral clindamycin is recommended.

Use of metronidazole for trichomoniasis in the second and third trimesters should be restricted to those in whom local palliative treatment has been inadequate to control symptoms.

Lactation
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. Breastfeeding should be interrupted for 12 to 24 hours after a single 2 g dose, or discontinued during multiple dose therapy.

Geriatrics
Monitoring for metronidazole associated adverse events is recommended in elderly patients. Decreased liver function in elderly patients can result in increased concentrations of metronidazole that may require adjustment of metronidazole dosage.

ADVERSE EFFECTS / UNDESIRABLE EFFECTS

Body as a whole: Fever, thrombophlebitis after IV infusion (this reaction can be minimized or avoided by limiting the duration of infusion and frequent resiting of the indwelling IV cannula)

Cardiovascular: Flattening of the T-wave and prolongation of the QT interval may be seen in ECG tracings, syncope, palpitation, chest pain

Dermatological/Hypersensitivity: Erythematous rash, pruritus, urticaria, Stevens-Johnson Syndrome, toxic epidermal necrolysis, flushing, pustular eruptions, dryness of the mouth (or vagina or vulva), angioedema, anaphylactic shock

Endocrine/Metabolic: Anorexia, decrease of libido

Gastrointestinal: Dry mouth, oral mucositis, vomiting, stomatitis, diarrhea, epigastric distress, epigastric pain, abdominal cramping, abdominal discomfort, dyspepsia, constipation, proctitis, pancreatitis, pseudomembranous colitis. 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. Crohn's disease patients are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers.

Genitourinary/Reproductive: Dysuria, cystitis, polyuria, pyuria, incontinence, sense of pelvic pressure, proliferation of *Candida* in the vagina, vaginal dryness and burning, dyspareunia, gynecomastia. Instances of darkened urine have also been reported; although the pigment which is responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.

Hematologic: Reversible neutropenia (leukopenia); thrombocytopenia, pancytopenia, transient eosinophilia, agranulocytosis, aplastic anemia, bone marrow aplasia

Hepatic: Increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis, hepatocellular liver injury, jaundice. Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Musculoskeletal: Fleeting joint pains sometimes resembling "serum sickness", myalgia, arthralgia

Nervous system: Convulsive seizures, encephalopathy (e.g., confusion, fever, headache, hallucination, paralysis, light sensitivity, disturbances in sight and movement, stiff neck), aseptic meningitis, peripheral sensory neuropathy, nausea, dizziness, vertigo, incoordination, subacute cerebellar syndrome (e.g., ataxia, dysarthria, gait impairment, nystagmus, tremor), irritability, depression, weakness, insomnia, drowsiness, paresthesia, vertigo

Respiratory: Nasal congestion

Special Senses: Sharp, unpleasant metallic taste; glossitis; tongue discoloration/furry tongue (due to fungal overgrowth); transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision, optic neuropathy/neuritis; tinnitus

OVERDOSE AND TREATMENT

Single oral doses of metronidazole of up to 15 g have been reported in accidental overdoses. Symptoms were limited to vomiting, ataxia and slight disorientation. Neurotoxic effects, including seizures and peripheral neuropathy have been reported after 5 to 7 days of oral doses of 6 to 10.4 g every other day. Overdosage with metronidazole appears to be associated with very few abnormal signs or symptoms.

Acute lethal dose in humans is unknown; oral LD50 of metronidazole in albino rats is 5 g/kg or greater.

There is no specific antidote for metronidazole overdosage. Activated charcoal may be administered to aid in the removal of unabsorbed drug. In cases of suspected massive overdose, symptomatic and supportive therapy may be instituted.

CAUTION
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

STORAGE CONDITION
Store at temperatures not exceeding 30°C

ADVERSE DRUG REACTION REPORTING STATEMENT
For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at (+632) 858-1000 or productsafety@unilab.com.ph.
By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY
Metronidazole (Dazomet®) 500 mg/100 mL Solution for IV Infusion in 100 mL glass vial.
Metronidazole (Dazomet®) 500 mg Tablet in flex foil, box of 100s.

DATE OF REVISION: April 10, 2014

DATE OF FIRST AUTHORIZATION:
Metronidazole (Dazomet®)
- 500 mg/100 mL Solution for IV Infusion: October 2, 2007 / DRXY33847
- 500 mg Tablet: December 2, 2009 / DR XY33848

Manufactured by:
Metronidazole (Dazomet®) 500 mg/100 mL Solution for IV Infusion
AMHERST PARENTERALS, INC.
Sta. Rosa-Tagaytay Road, Don Jose Sta. Rosa City, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

Metronidazole (Dazomet®) 500 mg Tablet
AMHERST LABORATORIES, INC.
UNILAB Pharma Campus, Barangay Mamplasan
Biñan, Laguna, Philippines
for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines

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