PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr METRONIDAZOLE

Metronidazole Tablets

Tablets, 250 mg, Oral

ANTIBACTERIAL - ANTIPROTOZOAL

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Date of Initial Authorization:
MAY 26, 2010

Date of Revision:
JUN 1, 2023

Submission Control Number: 270506

RECENT MAJOR LABEL CHANGES

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

METRONIDAZOLE (Metronidazole Tablets) is indicated for:

Bacterial Infections

Treatment: Culture and susceptibility studies should be performed to determine the causative organisms and their susceptibility to metronidazole. Based on clinical judgment and anticipated bacteriological findings, therapy may be started while awaiting the results of these tests. However, modification of the treatment may be necessary once these results become available.

In mixed aerobic and anaerobic infections, consideration should be given to the concomitant administration of an antibiotic appropriate for the treatment of the aerobic component of the infection. See 7 WARNINGS AND PRECAUTIONS, General.

Metronidazole has also been used in the treatment of a small number of cases of brain or lung infections (some with abscesses) caused by anaerobic bacteria.

Prophylaxis: If there are signs of infections, specimens for culture should be obtained for the identification of causative organisms so that appropriate therapy may be given.

Bacterial Vaginosis

Metronidazole is indicated for the treatment of bacterial vaginosis.

Protozoal Infections

- *Trichomonal* infections in men as well as in women (protozoal infection caused by *Trichomonas vaginalis*).
- Hepatic and intestinal amebiasis.
- Giardiasis.

To reduce the development of drug-resistant bacteria/protozoans and maintain the effectiveness of METRONIDAZOLE and other antibacterial/antiprotozoal drugs, METRONIDAZOLE should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria/protozoans. 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.

1.1 Pediatrics

Anaerobic infections, Bacterial vaginosis and Trichomoniasis

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Amebiasis and Giardiasis

Pediatrics (< 18 years of age): See 4.2 Recommended dose and Dosage adjustment.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

METRONIDAZOLE (metronidazole) is contraindicated in:

- Patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- 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 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic).
- Patients with active neurological disorders or a history of blood dyscrasia.
- Patients with hypothyroidism or hypoadrenalism.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

A rare case of reversible but profound neurological deterioration has been reported following a single oral dose of metronidazole; it is therefore advisable that a patient taking metronidazole for the first time not be left unattended for a period of two hours.

Patients administered metronidazole longer than the usually recommended duration, should be monitored for adverse reactions such as peripheral or central neuropathy (such as paresthesia, ataxia, dizziness, vertigo, convulsive seizures).

Treatment with metronidazole should be discontinued if ataxia or any other symptom of CNS involvement occurs (see 7 WARNINGS AND PRECAUTIONS, Neurologic).

4.2 Recommended Dose and Dosage Adjustment

Severe hepatic disease: Patients with severe hepatic disease metabolize metronidazole slowly, with resultant accumulation of metronidazole and its metabolites. Accordingly, doses below those usually recommended should be administered and with caution. However, due to a lack of pharmacokinetic information, specific dosage recommendations cannot be given for these patients. Therefore, close monitoring of blood metronidazole levels and of the patients for signs of toxicity are recommended. See 7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic.

Severe impairment of renal function and anuria: Patients with severe impairment of renal function who are not undergoing hemodialysis should be monitored closely for signs of toxicity. Dose adjustment may be necessary. See 7 WARNINGS AND PRECAUTIONS, Renal.

The elimination half-life of metronidazole in anuric patients is not significantly altered. However, the elimination half-lives of the metabolites of metronidazole are significantly increased (3- to 13-fold). Consequently, although metronidazole would not be expected to accumulate in these patients, accumulation of the metabolites would be expected. The potential for toxicity of these metabolites is not known.

Patients on hemodialysis: The dose of metronidazole need not be specifically reduced since accumulated metabolites may be rapidly removed by hemodialysis.

Patients on peritoneal dialysis: Peritoneal dialysis does not appear to reduce serum levels of metronidazole metabolites.

ANAEROBIC INFECTIONS

Adults

Treatment: TREATMENT SHOULD BE INITIATED BY THE I.V. ROUTE. Oral medication may be substituted when it is feasible and/or practical.

Duration of therapy depends upon clinical and bacteriological assessment. Treatment for seven days should be satisfactory for most patients. However, in cases where infection sites cannot be drained or which are liable to endogenous recontamination by anaerobic pathogens, a longer treatment may be required.

Oral Administration: 500 mg every 8 hours.

Pediatrics: The safety and effectiveness of metronidazole for anaerobic infections in pediatric patients is not known. Due to lack of pharmacokinetic data, no dosage recommendations can be made. See 7.1.3 Pediatrics.

BACTERIAL VAGINOSIS

Adults

500 mg orally twice a day for 7 days.

Concurrent treatment of sexual partners is not usually indicated.

TRICHOMONIASIS

Consideration should be given to use metronidazole therapy (oral or vaginal) in female patients, only when trichomonal infection has been confirmed by appropriate diagnostic techniques. In the male patient, oral metronidazole is recommended in those who are evidently the source of reinfection in female sexual partners and those with demonstrated urogenital trichomoniasis. See 7 WARNING AND PRECAUTIONS, General.

Single-Dose Treatment: For both women and men, 2g administered as a single dose after a meal.

Standard Ten-day Treatment: Women - One 250 mg tablet twice a day, morning and night for 10 consecutive days. Men - One 250 mg tablet twice a day for 10 consecutive days.

For both men and women, it may be occasionally necessary to give a second ten-day course after 4 to 6 weeks.

AMEBIASIS

Adults

Intestinal Amebiasis - Three 250 mg tablets (750 mg) three times daily for 5 to 7 days.

Amebic abscesses of the liver - Two to three 250 mg tablets (500 to 750 mg) three times daily for 5 to 7 days.

Pediatrics (< 18 years of age): Administer 35 to 50 mg/kg/day in three divided doses for 5 to 7 days.

Note: Pediatric dosing may not be possible for all weights.

GIARDIASIS

Adults

One 250 mg tablet twice daily for 5 to 7 days.

Pediatrics (< 18 years of age): Administer 25 to 35 mg/kg/day in two divided doses for 5 to 7 days.

Note:

- Pediatric dosing may not be possible for all weights.
- The efficacy of the recommended dosages for the treatment of amebiasis and giardiasis has been demonstrated. However, the optimal dose, the duration of treatment and the risk of recurrence have not been completely established.

4.4 Administration

Tablets are for oral administration.

Warn patients not to take alcohol or alcohol-containing medicines during metronidazole therapy and for at least one day afterwards (See 7 WARNINGS AND PRECAUTIONS, Neurologic).

4.5 Missed Dose

If the patient misses a dose, instruct the patient to take the dose as soon as they remember. If it is almost time for the next dose, inform the patient to skip the missed dose and continue the regular dosing schedule.

5 OVERDOSAGE

Symptom

Single oral doses of metronidazole, up to 12 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.

Treatment

There is no specific antidote. Early gastric lavage may remove a large amount of the drug; otherwise, symptomatic treatment.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet 250 mg of metronidazole	colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and microcrystalline cellulose

METRONIDAZOLE (Metronidazole Tablets), 250 mg: Each round, white biconvex, film coated, engraved "250"one one side and plain on the other, contains 250 mg of metronidazole. Available in bottles of 100 and 500 tablets.

7 WARNINGS AND PRECAUTIONS

General

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.

Carcinogenesis and Mutagenesis

Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided. The use of metronidazole for longer treatment than usually required should be carefully weighed.

Metronidazole has been shown to be carcinogenic in the mouse and in the rat. However similar studies in the hamster have given negative results. Metronidazole has been shown to be mutagenic in bacteria *in vitro*. In studies conducted in mammalian cells *in vitro* as well as in rodent *in vivo,* there was inadequate evidence of mutagenic effect of metronidazole.

Prominent among the effects in the mouse was the promotion of pulmonary tumorigenesis. This has been observed in all six reported studies in that species, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). At very high dose levels (approximately 1500 mg/m^2 which is approximately 3 times the most frequently recommended human dose for a 50 kg adult based on mg/m^2), there was a statistically significant increase in the incidence of malignant liver tumors in males. Also, the published results of one of the mouse studies indicate an increase in the incidence of malignant lymphomas as well as pulmonary neoplasms associated with lifetime feeding of the drug. All these effects are statistically significant.

Several long-term oral dosing studies in the rat have been completed. There were statistically significant increases in the incidence of various neoplasms, particularly in mammary and hepatic tumors, among female rats administered metronidazole over those noted in the concurrent female control groups. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.

Driving and Operating Machinery

Patients should be advised not to drive or operate machinery due to the potential for confusion, dizziness, vertigo, hallucinations, convulsions, or eye disorders when treated with metronidazole.

Genitourinary

Patients should be warned that METRONIDAZOLE may darken urine. This is probably due to a metabolite of metronidazole and seems to have no clinical significance. See 8.2 Clinical trial Adverse Reactions, Renal and urinary disorders.

Known or previously unrecognized moniliasis may present more prominent symptoms after treatment with metronidazole. It is recommended that in the treatment of trichomoniasis, the use of metronidazole should be confined to those patients in whom significant T. vaginalis infection has been confirmed by appropriate diagnostic techniques.

Hematologic

Transient eosinophilia neutropenia, leukopenia, agranulocytosis and thrombocytopenia have been observed during treatment with metronidazole. Hematological tests, especially regular total and differential leukocyte counts are advised if administration for more than 10 days or a second course of therapy is considered to be necessary.

Hepatic/Biliary/Pancreatic

Metronidazole should be used with great caution in patients with a history of hepatic enzyme increase or liver injury associated with previous administration of metronidazole. See 8.2 Clinical Trial Adverse Reactions, Hepatobiliary disorders.

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome, with very rapid onset after treatment initiation, in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, METRONIDAZOLE is contraindicated (see 2 CONTRAINDICATIONS).

Patients with severe hepatic disease (including hepatic encephalopathy) metabolize metronidazole slowly with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses of metronidazole below those usually recommended should be administered and with caution.

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

Monitoring and Laboratory Tests

Regular clinical and laboratory monitoring (including blood count) are advised in cases of high-dose, prolonged, or repeated treatment as the risk for adverse reactions is increased.

Metronidazole interferes with serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), triglycerides and hexokinase glucose determinations which are based on the decrease in ultraviolet absorbance which occurs when nicotinamide adenine dinucleotide hydrogen (NADH) is oxidized to nicotinamide adenine dinucleotide (NAD). Metronidazole causes an increase in absorbance at the peak of NADH (340 nm) resulting in falsely decreased values (see 9 DRUG INTERACTIONS).

Neurologic

A rare case of reversible but profound neurological deterioration has been reported following a single oral dose of metronidazole; it is therefore advisable that a patient taking metronidazole 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. Gastric lavage may be considered if no more than two or three hours have elapsed since administration of the drug.

Severe neurological disturbances (i.e. convulsive seizures and peripheral neuropathy) have been reported in patients treated with metronidazole. These have been observed very infrequently.

Metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system diseases due to the risk of neurological aggravation.

If for compelling reasons, metronidazole must be administered longer than the usually recommended duration, it is recommended that patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paresthesia, ataxia, dizziness, vertigo, convulsive seizures).

Warn patients not to take alcohol or alcohol-containing medicines during metronidazole therapy and for at least one day afterwards because of the possibility of a disulfiram-like (Antabuse effect) reaction.

Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, dysarthria, and accompanied by CNS lesions seen on magnetic resonance imaging (MRI). CNS symptoms and CNS lesions are generally reversible within days to weeks upon discontinuation of metronidazole.

Aseptic meningitis can occur with metronidazole. Symptoms can start within hours of dose administration and generally resolve after metronidazole therapy is discontinued.

Psychiatric

Cases of suicidal ideation with or without depression have been reported during treatment with METRONIDAZOLE. Patients should be advised to discontinue treatment and contact their healthcare provider immediately if they experience psychiatric symptoms during treatment.

Renal

Use with caution in patients with severe renal impairment. Dose adjustment may be necessary.

Patients with severe renal impairment who are not undergoing hemodialysis should have their blood metronidazole and metronidazole metabolite levels monitored; monitor for signs of toxicity.

Hemodialysis removes significant amounts of metronidazole and its metabolites from systemic circulation. Therefore, supplementation of metronidazole following a hemodialysis session may be necessary.

Patients receiving peritoneal dialysis should be monitored for signs of toxicity due to the potential accumulation of metronidazole metabolites.

Reproductive Health: Female and Male Potential

Where there is clinical evidence of a trichomonal infection in the sexual partner, he/she should be treated concomitantly to avoid reinfection.

Sensitivity/Resistance

Development of Drug Resistant Bacteria
Prescribing METRONIDAZOLE in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of resistant organisms.

Potential for Microbial Overgrowth
Prolonged use of METRONIDAZOLE may result in overgrowth of non-susceptible bacteria and protozoans. If the infection is not improved following 2 treatment courses of 10 days, cultures should be obtained to guide further treatment. If such infections occur, discontinue use and institute alternate therapy.

Skin

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), or acute generalized exanthematous pustulosis (AGEP) have been reported with metronidazole. See 8.2 Clinical Trial Adverse Reactions, Skin and subcutaneous tissue disorders. If symptoms or signs of SJS, TEN or AGEP are present, METRONIDAZOLE treatment must be immediately discontinued.

7.1 Special Populations

7.1.1 Pregnant Women

Metronidazole should not be administered in pregnant patients during the first trimester of pregnancy.

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 human fetal organogenesis are not known; Its use in pregnancy should be carefully evaluated. 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 the possible risks to the fetus.

7.1.2 Breast-feeding

Administration of metronidazole should be avoided in the breast-feeding mother. Metronidazole is secreted in breast milk in concentrations similar to those found in plasma.

7.1.3 Pediatrics

Pediatrics (≤ 18 years of age): Clinical experience in children is very limited. The monitoring of this group of patients is particularly important.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following adverse reactions have been reported with the use of metronidazole:

Blood and lymphatic system disorders: transient eosinophilia, neutropenia, leukopenia, very rare cases of agranulocytosis and thrombocytopenia have been reported.

Cardiac disorders: palpitation and chest pain.

Ear and labyrinth disorders: hearing impairment/hearing loss (including hypoacusis, deafness, deafness neurosensory), tinnitus.

Eye disorders: transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision. Optic neuropathy/neuritis has been reported.

Gastrointestinal disorders: diarrhea, nausea, vomiting, epigastric distress, epigastric pain, dyspepsia, constipation. Reversible cases of pancreatitis have been reported infrequently.

Coated tongue, tongue discoloration/furred tongue (e.g. due to fungal overgrowth), dry mouth, taste disorders including unpleasant metallic taste, glossitis, oral mucositis.

General disorders and administration site conditions: fever has been reported.

Hepatobiliary disorders: increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis and hepatocellular liver injury, sometimes with jaundice have been reported.

Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome, in patients with Cockayne syndrome have been reported with products containing metronidazole.

Immune system disorders: angioedema, exceptional anaphylactic shocks.

Infections and infestations: rare cases of pseudomembranous colitis have been reported.

Investigations: reversible lowering of serum lipids has been reported.

Metabolism and nutrition disorders: an antithyroid effect has been reported by some investigators but three different clinical studies failed to confirm this. Anorexia has been reported.

Nervous system disorders: convulsive seizures, peripheral sensory neuropathy, transient ataxia, dizziness, drowsiness, insomnia, headache, aseptic meningitis.

Peripheral neuropathies have been reported in a few patients on moderately high to high-dose prolonged oral treatment with metronidazole. It would appear that the occurrence is not directly related to the daily dosage and that an important predisposing factor is the continuation of oral and/or I.V. medication for several weeks or months.

Profound neurological deterioration, within 2 hours after metronidazole administration has been reported. The occurrence is not directly related to the dosage level.

Psychiatric disorders: psychotic disorders including confusion and hallucinations, depressed mood.

Renal and urinary disorders: dysuria. Darkening of the urine has been reported. This is probably due to a metabolite of metronidazole and seems to have no clinical significance.

Reproductive system and breast disorders: proliferation of *Candida albicans* in the vagina, vaginal dryness and burning.

A single case of gynecomastia has been reported which resolved on discontinuing metronidazole administration.

Skin and subcutaneous tissue disorders: hypersensitivity reactions including flushing, urticaria, rash, and pruritus, very rare pustular eruptions, acute generalized exanthematous pustulosis

(AGEP), fixed drug eruption. Cases of Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Many of these case reports revealed the use of concomitant medications known to be associated with SJS or TEN.

Vascular disorders: thrombophlebitis has occurred with I.V. administration, occasional flushing and headaches, especially with concomitant ingestion of alcohol; altered taste of alcoholic beverages.

8.5 Post-Market Adverse Reactions

Cardiac disorders: tachycardia, dyspnea. QT interval 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.

General disorders and administration site conditions: malaise, face edema, edema peripheral, chills, asthenia.

Musculoskeletal and connective tissue disorders: muscle spasms, arthralgia, myalgia.

Nervous system disorders: vertigo, somnolence, hypoesthesia, paresthesia, dysgeusia.

Skin and subcutaneous disorders: hyperhidrosis, erythema.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

The drugs listed are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Patients taking metronidazole should be warned against consuming alcohol during therapy and for at least one day afterwards (see 9.3 Drug-Behavioural interactions).

Metronidazole can increase potency of CYP2C9 substrates (for example, phenytoin and warfarin in Table 2 of 9.4 Drug-Drug Interactions).

9.3 Drug-Behavioural Interactions

Alcohol: Patients taking metronidazole should be warned against consuming alcohol during therapy and for at least one day afterwards, because of the possibility of a disulfiram-like reaction (flushing, vomiting, tachycardia). This reaction appears to be due to-the inhibition of the oxidation of acetaldehyde, the primary metabolite of alcohol.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e.,

those identified as contraindicated).

Table 2 - Established or Potential Drug-Drug Interactions

Proper/Common name	Source of Evidence	Effect	Clinical comment
Busulfan	T	Plasma levels of busulfan may be increased by metronidazole.	Concomitant use may lead to severe busulfan toxicity.
Cyclosporin	T	Risk of elevation of cyclosporin serum levels.	Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.
Cytochrome P450 inhibitors	T	Concomitant administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may cause decreased metabolism and reduced plasma clearance of metronidazole which may result in metronidazole toxicity.	
Cytochrome P450 3A4 (CYP3A4) substrates	T	Concomitant use of metronidazole and CYP3A4 substrates (e.g., amiodarone, tacrolimus, cyclosporine, carbamazepine, and quinidine) may increase respective CYP3A4-substrate plasma levels.	Monitoring of plasma concentrations of CYP3A4 substrates may be necessary.
Disulfiram	C	Administration of disulfiram and metronidazole has been associated with acute psychoses and confusion in some patients.	Disulfiram and METRONIDAZOLE should not be used concomitantly.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Drugs that prolong QT interval	T	QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.	
5-fluorouracil	CT	Metronidazole has been reported to reduce the clearance of 5-fluorouracil.	Concomitant use may increase toxicity of 5-fluorouracil.
Lithium	T	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 must be administered to patients on lithium therapy, it may be prudent to consider tapering or discontinuing lithium temporarily when feasible.	Frequent monitoring of lithium, creatinine and electrolyte levels and urine osmolality should be done.
Phenobarbital	CT	The metabolism of metronidazole has been reported to be increased by concurrent administration of phenobarbital.	It is recommended that increased doses of metronidazole Injection be considered in such cases.

Proper/Common name	Source of Evidence	Effect	Clinical comment
Phenytoin	CT	The metabolism of metronidazole has been reported to be increased by concurrent administration of phenytoin. Patients maintained on phenytoin were found to have toxic blood levels after oral metronidazole administration. Phenytoin concentration returned to therapeutic blood level after discontinuance of metronidazole.	Patients should be closely monitored when coadministration is necessary.
Vecuronium	CT	A slight potentiation of the neuromuscular blocking activity of vecuronium has been reported in patients administered metronidazole at a dose of 15 mg/kg.	
Warfarin	CT	Metronidazole has been reported to potentiate the anticoagulant effect of warfarin (a CYP2C9 substrate) resulting in a prolongation of prothrombin time. This possible drug interaction should be considered when metronidazole is prescribed for patients on this type of anticoagulant therapy.	In case of coadministration, prothrombin time should be more frequently monitored and anticoagulant therapy adjusted during treatment with metronidazole. Metronidazole potentiates potency of other CYP2C9 substrates.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Metronidazole may interfere with certain types of blood test determinations in blood (alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], triglycerides, glucose), which may lead to false negative or an abnormally low result. These analytical determinations are based on a decrease in ultraviolet absorbance, a fact that occurs when nicotinamide adenine dinucleotide hydrogen (NADH) is oxidized to nicotinamide adenine dinucleotide (NAD). The interference is due to the similarity in the absorption peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7. See 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Metronidazole is bactericidal against anaerobic bacteria, it exerts trichomonacidal activity and is also active against *Giardia lamblia* and *Entamoeba histolytica.* Its exact mechanism of action has not been entirely determined as yet. It has been proposed that an intermediate in the reduction of metronidazole, produced only in anaerobic bacteria and protozoa is bound to deoxyribonucleic acid and electron-transport proteins, inhibits subsequent nucleic acid synthesis.

10.2 Pharmacodynamics

Animal: Metronidazole exerted no central nervous system activity except at very high doses. At doses of 0.5 g/kg and above, some anticonvulsant activity was demonstrated in mice and rats, spinal reflexes were inhibited in the anaesthetized cat and hypnosis was produced in the rat.

Metronidazole at doses of 40 to 50 mg/kg administered by intravenous infusion to 4 anaesthetized dogs produced a slight fall in blood pressure and heart rate for 30 to 60 minutes after the infusion. There was little or no effect on the electrocardiographic tracings. With both metronidazole and the vehicle, there was a tendency for dogs to bleed more readily than untreated animals although plasma prothrombin times remained within normal limits.

10.3 Pharmacokinetics

Absorption

Human: Following oral administration, metronidazole is completely absorbed with plasma concentration usually reaching a peak within 1 to 2 hours. After single oral 500 mg doses, peak plasma levels of approximately 13 mg/L were obtained. On a regimen of 500 mg t.i.d. administered by the i.v. route, a steady state was achieved after approximately three days. The mean peak and trough concentrations measured at that time were 26 and 12 mg/L respectively,

and the elimination half-life was approximately 7 to 8 hours. Comparison of the pharmacokinetics of oral and i.v. metronidazole revealed that the area under the plasma metronidazole concentration against time curves were essentially identical.

There is negligible percutaneous absorption following topical application of metronidazole 1 % cream. In healthy volunteers who applied a single 100 mg dose of ^{14}C-labelled metronidazole 2 % cream to intact skin, no metronidazole could be detected in plasma after 12 hours. Only about 1 % and 0.1 % of the applied dose could be found in urine and feces, respectively. After once-daily application of the 1 % cream for 1 month, only traces (about 1% of the C_{max} of a 200 mg oral dose) could be detected in 25% of patients. In the rest of the patients, no detectable plasma levels were found.

Distribution

Protein Binding: Less than 20 % of the circulating metronidazole is bound to plasma proteins.

Tissue distribution: The concentrations of metronidazole found in various tissues and body fluids are given in the following table:

Table 3 – Concentrations of metronidazole in various tissues and body fluids

TISSUE OR FLUID	DOSE ADMINISTRATION	TISSUE OR FLUID LEVEL	PLASMA LEVEL
Bile	500 mg q.i.d. p.o. x 10 days	26 mg/L (on day 5) 20 mg/L (on day 15)	N/A* N/A
Saliva	500 mg p.o. single dose	7 mg/L (at 2-3 hour)	N/A
Placenta	250 mg p.o. single dose	0 to 1.4 mg/kg (at 4-5 hour)	3.0 – 6.9 mg/L (maternal)
Embryo	250 mg p.o. single dose	0 to 1.0 mg/kg	3.0 – 6.9 mg/L (maternal)
Breast Milk	200 mg p.o.	1.3 to 3.4 mg/L	1.8 – 3.9 mg/L
Cerebrospinal fluid	500 mg p.o. b.i.d.	11.0 to 13.9 mg/L	8.3 – 15.4 mg/L
Pus (brain abscess)	400 mg p.o. t.i.d. 600 mg p.o. t.i.d.	35 mg/L inflamed meninges 43 mg/L	N/A N/A
Pus (pulmonary empyema)	400 mg p.o. q.i.d.	24.2 mg/L	N/A

*Not available

Metabolism and Elimination

The major route of elimination of metronidazole and its metabolites is via the urine (60 to 80 % of the dose) with fecal excretion accounting for 6 to 15% of the dose. The metabolites that appear in the urine result primarily from side chain oxidation (i.e. 1-(β-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5 nitroimidazole-1-yl-acetic acid) and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20 % of the total.

Metronidazole is the major component appearing in the plasma with lesser quantities of the 2-hydroxymethyl metabolite also being present. The ratio of these components varies with time but the maximum concentration of the metabolite (C_{max}) is approximately 20 % of the C_{max} of metronidazole for the oral route of administration.

Special Populations and Conditions

- **Hepatic Insufficiency:** In patients with impaired liver function, the plasma clearance of metronidazole is decreased and accumulation can therefore result.
- **Renal Insufficiency:** Decreased renal function does not appear to alter the single dose pharmacokinetics of metronidazole, although the elimination half-life of the metabolites is prolonged.

  Haemodialysis: During haemodialysis, the hydroxy metabolite is removed from the plasma about three times more rapidly than in normal subjects. Comparison of the elimination half-lives of metronidazole and two metabolites are given in the following table.

Table 4 – Metronidazole elimination in normal subjects and in patients with renal insufficiency following a single intravenous dose of metronidazole (500 mg)

	ELIMINATION HALF LIFE (hours)		
	Patients		
Compound	Normal Subjects	on dialysis	between dialysis
Metronidazole	7.3 ± 1.0	2.6 ± 0.7	7.2 ± 2.4
1-(β-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole	9.8 ± 1.3	7.8 ± 4.1	34 ± 43
2-methyl-5 nitroimidazole-1-yl-acetic acid	—	7.9 ± 4.1	138 ± 82

Therefore, no accumulation should occur in anuric patients undergoing regular dialysis.

Continuous Ambulatory Peritoneal Dialysis: Metronidazole was given I.V. at 750 mg to five patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Insignificant changes were noted in the pharmacokinetic parameters of metronidazole (apparent volume of distribution, elimination half-life, total body clearance). Peritoneal dialysis does not appear to reduce the serum levels of metronidazole metabolites.

11 STORAGE, STABILITY AND DISPOSAL

METRONIDAZOLE (Metronidazole Tablets) should be stored at 15°C to 25°C.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

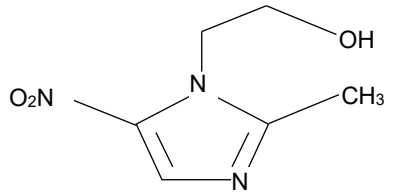
Drug Substance

Proper name: Metronidazole

Chemical name: 2-methyl-5-nitroimidazole-1-ethanol

Molecular formula and molecular mass: $C_6H_9O_3N_3$ and 171.15

Structural formula:



Physicochemical properties:

Physical Form:	White crystalline powder with slight yellow tint.
Solubility:	Slightly soluble in water, alcohol, chloroform and ether.
pka:	2.6
pH:	5.8
Melting Point:	159-163°C

14 CLINICAL TRIALS

Information is not available.

15 MICROBIOLOGY

BACTERIOLOGY

Metronidazole is active *in vitro* against most obligate anaerobes but does not appear to possess any relevant clinical activity against facultative anaerobes or obligate aerobes.

In one study the minimum inhibitory concentrations of metronidazole were determined in 730 strains of anaerobic bacteria isolated from clinical specimens. The results are summarized in the following table:

Table 5 - Activity* of metronidazole against anaerobic bacteria

BACTERIA	No of strains tested	CUMULATIVER PER CENT SUSCEPTIBLE AT THE INDICATED CONCENTRATION (mg/mL)										
		0.1	0.5	1.0	2.0	4.0	8.0	16.0	32.0	64.0	128	256
Bacteroides fragilis group	77	1	12	27	56	84	97	99	100			
Bacteroides melaninogenicus	69	15	81	93	99	100						
Other bacteroides	72	6	42	68	85	93	96	96	99			100
Fusobacterium nucleatum	19	58	95			100						
Other fusobacterium	46	15	76	100								
Peptococcus and Gaffkya	73	3	69	88	96						96	100
Peptostreptococcus	41	29	66	76	81	83	88	90				100
Microaerophilic and anaerobic streptococci	11		27			36					46	100
Gram-negative cocci (Acidaminococcus, Megashaera, Veillonella)	28	4	57	89	96	100						
Eubacterium	59	7	44	61	66		71		75	80	86	100
Arachnia	3		33									100
Propionibacterium	12		8			17						100
Actinomyces	16					13		19	50	56	63	100
Bifidobacterium	8					36		66	75	87		100
Lactobacillus	20	10	35	55		65	75			80	90	100
Clostridium perfringens	12		25	67	100							
Other clostridium	164	32	54	65	74	84	93	98	100			

*Determined using an agar dilution technique described in the Wadsworth Anaerobic Bacteriology Manual 2nd Ed. University of California, Los Angeles, Extension Division, 1975.

With rare exceptions, anaerobic gram-negative non-spore forming bacilli and cocci as well as Clostridium species were susceptible to concentrations of metronidazole of 16 mg/L or less. A few strains of *Peptococcus* and *Peptostreptococcus* required 128 mg or more per litre of metronidazole for inhibition. Metronidazole was relatively ineffective against Streptococcus strains and the gram-positive non-spore forming bacilli.

A series of *in vitro* determinations demonstrated that the minimum bactericidal concentrations against susceptible strains are generally within one dilution of the minimum inhibitory concentrations.

With Bacteroides fragilis 10^3 fold increases in inoculum size have resulted in two to four fold increases in M.I.C. and M.B.C. values. The bactericidal effect of metronidazole is not significantly affected by pH changes within the range of 5.5 to 8.0.

Susceptibility testing

Quantitative methods give the most precise estimate of susceptibility to antibacterial drugs. A standardized agar dilution method and a broth microdilution method are recommended. A bacterial isolate may be considered susceptible if the M.I.C. value for metronidazole is not more than 16 mg/L. An organism is considered resistant if the M.I.C. is greater than 16 mg/L.

PARASITOLOGY

Trichomonacidal Activity

In Vitro activity was studied using decreasing concentrations of metronidazole which were added to a series of *Trichomonas vaginalis* cultures maintained at 37°C. A 1:400,000 dilution of metronidazole killed up to 99% of the *trichomonads* in 24 hours.

In Vivo, 0.5 mL of a 48-hour culture of *Trichomonas vaginalis* injected under the dorsal skin in a control and a test group of mice revealed, seven days later, extensive abscess-like lesions swarming with *trichomonads* in the control group and normal sub-cutaneous tissue free of *trichomonads* in the animals which had received oral metronidazole in a daily dosage of 12.5 mg/kg of body weight.

Amebicidal Activity

In Vitro: The minimum inhibitory concentration of metronidazole required to immobilize over a 48-hour period a culture of *Entamoeba histolytica* maintained at 37°C was 3 mg/L.

In Vivo: The amebicidal activity of metronidazole has been demonstrated in various tests.

In the young rat, an intestinal infestation was induced in the caecum by the inoculation of an amebic culture or of a homogenate of caecums obtained from young rats previously infested in the same manner. Metronidazole, 100 mg/kg/day p.o. administered during 4 consecutive days, the first dose being given 24 hours after infestation, protected all the animals. On the other hand, when the drug was administered on 4 consecutive days, starting on the day that the animals were infested, it had a CD_{50} of 22 mg/kg/day in the intestinal amebiasis of the young rat. Finally, the CD_{50} when the product was given in a single dose 24 hours after infestation was 49 mg/kg/day p.o.

In the hamster, hepatic amebiasis was induced by the inoculation of a culture of amebae under the capsule of Glisson; metronidazole administered orally during 4 consecutive days protected all the animals at a dosage of 35 mg/kg/day while its CD_{50} was 15 mg/kg/day.

Activity Against Giardiasis

The activity of metronidazole against giardiasis has been demonstrated in mice infested by *Lamblia muris.* The product administered once a day on two consecutive days had a CD_{50} of 30 mg/kg/day while its therapeutic index was 1/100.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity

The LD_{50} values for metronidazole are given in the following Table:

Table 6 – Values of LD_{50} for metronidazole

SPECIES	SEX	ROUTE	LD_{50} (mg/kg)
Mouse	—	p.o.	4350
	M	i.p.	3650
	M	i.v.	1170
	F	i.v.	1260
Rat	—	p.o.	5000
	M	i.p.	5000
	M	i.v.	1575
	F	i.v.	1575

Signs of toxicity following oral and intravenous administration of metronidazole were sedation, ataxia and death in mice, and sedation and death in rats.

The acute toxicity of metronidazole was also tested in dogs. Beagle dogs (male or female, 1 dog per dose) were administered single oral doses of 500, 750, 1000, 1500, 3000 or 5000 mg/kg of metronidazole by gastric intubation. The highest oral dosage which did not produce neurological disturbances and severe vomiting was 500 mg/kg. At the higher doses, ataxia, loss of spatial judgment, dozing, walking blindly, a general state of unawareness, convulsion, retching and/or vomiting were observed. There were no deaths but the dogs which received 1500 and 5000 mg/kg were killed on humane grounds 48 and 2½ hours after dosing, respectively.

Pairs of one male and one female beagle were administered total doses of 125, 200 or 250 mg/kg of metronidazole. These were given as 4 or 5 separate injections at hourly intervals, except for the 125 mg/kg dose which was given at half-hourly intervals. At 200 mg/kg, the male trembled during the third injection, the female appeared slightly lethargic following the third injection and its heart rate was rapid during the final injection. Following the 125 mg/kg and 250 mg/kg doses, no sign nor evidence of intolerance at the injection sites was observed.

The ocular irritant effects of 0.5%, 1% and 2% topical metronidazole cream and placebo cream were tested in rabbits. An aliquot (0.1 mL) of one of the cream formulations was placed in the

lower lid of one eye of each of three animals. The eyes were subsequently examined for the appearance and severity of ocular lesions after 1 hour, and 1, 2, 3, 4, and 7 days after instillation. Mild conjunctival irritation was noted in several animals in both the active and placebo cream groups. The eyes of the animals in all treatment groups normalized within 1 to 3 days of instillation. None of the rabbits showed any corneal or inidial inflammation.

Subacute and Chronic Toxicity

Rats were administered metronidazole orally at doses of 0, 25 and 50 mg/kg for a month, 100 mg/kg for fifteen days, and 1000 mg/kg for thirty days. Except for testicular changes which consisted of minor epithelial desquamation and fewer spermatocytes in the epididymus in the 100 and 1000 mg/kg groups, no other abnormalities were observed. No interference with fertility or embryogenesis was observed.

Twenty male and 20 female rats were administered metronidazole intravenously at a dose of 30 mg/kg/day for 4 weeks. There was no evidence of local intolerance at the injection site. A statistically significant decrease in body weight gain was noted in the males only, with their overall weight increase being about 90% that of controls. Mean absolute and relative (to bodyweight) thyroid weights were significantly lower (by approximately 25 %) than the control values in both sexes in the treated group. However, at microscopic examination, the architecture of the thyroid glands of treated animals was within normal limits. In another study conducted under the same experimental conditions, assessment of the thyroid function before and at the end of the dosing period revealed no effect of metronidazole in rats.

Dogs were administered metronidazole orally at doses of 0, 25 and 50 mg/kg for a period of one month. They showed no physical or biological alteration and no tissue modification. Other dogs dosed at 75, 110 and 225 mg/kg for a period of six months developed ataxia, muscular rigidity and tremor. No apparent dulling of the sensorium was noted.

Two male and 2 female dogs were administered metronidazole intravenously at doses of 37.5 mg/kg 5 days per week for 4 weeks. In the two males and in one of the 2 females, the relative weights of the thyroids were below control values (31% decrease for males and 26% decrease for females).

Carcinogenicity

Tumorigenicity Studies

Two separate tumorigenic studies were carried out in two different strains of mice with metronidazole. Metronidazole was administered in the diet at daily doses of 75,150 and 600 mg/kg in both experiments.

A study with the strain of Swiss mice was terminated after 78 weeks, while the other experiment with CF_1 mice was terminated at 92 weeks.

There was no evidence that the administration of metronidazole at any dosage level produced an adverse effect upon the physical appearance, behavior, body weight and food consumption. However, the survival in mice in the treated groups was better than that in the controls.

Statistical analysis of necropsy data, gross and microscopic, using life-table and other techniques revealed a significant increase in the rate of benign lung tumors in the groups of mice treated with 600 mg/kg. With the lower dosage, there was also a trend for increased rate; however, the changes were not significant. It should, though, be noted that this type of tumor was also seen in up to 30% of mice in the untreated groups.

In the rat, dose levels of 75, 150 and 300 mg/kg/day were administered orally in the diet for 80 consecutive weeks; a dosage of 600 mg/kg was administered for 13 weeks only. No consistent deleterious effects were observed with doses of 75 and 150 mg/kg for 28 to 80 weeks on physical, behavioral, clinical laboratory or post-mortem examinations. At the dosage of 300 mg/kg, testicular dystrophy was regularly encountered at 13 weeks or longer and was not reversed by a 28 week recovery (no drug) period; prostatic atrophy was also seen at 26 weeks. The 600 mg/kg dosage group showed a high incidence of testicular dystrophy and prostatic atrophy with a pronounced reduction in the rate of body weight gain. There was a significant increase in the number of benign mammary tumors only in the females of the 300 mg/kg group.

Two independent tumorigenicity studies conducted in the hamster gave negative results.

Genotoxicity

Mutagenicity Studies

The mutagenic potential of metronidazole has been measured in two test systems. In a study using a bacterial indicator strain to detect mutagenic effects, positive results were reported. The inherent antimicrobial property of metronidazole further complicates the interpretation respecting genetic and carcinogenic hazard to man. The other test system, the dominant lethal test, measured the effect of metronidazole on mammalian germ cells. Male rats administered doses of metronidazole up to 600 mg/kg/day for five consecutive days, were mated to untreated females. Fetal deaths, the primary measure of dominant lethality, were not increased in those females mated to treated males.

Reproductive and Developmental Toxicology

Teratogenicity Studies

Metronidazole has been evaluated for its embryotoxic and teratogenic potential in the rat, rabbit and mouse. In four studies performed in the rabbit, the compound was administered orally by capsule, by buccal intubation or by gastric intubation at doses of 30 to 200 mg/kg/day for periods ranging from 3 to 13 days during pregnancy. Neither embryotoxic nor teratogenic effects related to drug administration were observed.

In one study metronidazole was administered intravenously to rabbits (18 per group) at doses of 15 or 30 mg/kg/day from days 6-18 of pregnancy inclusive. There were no statistically significant differences between control and treated groups for any foetal parameter, but discrepancies between the numbers of corpora lutea and implantation sites suggested that the drug may have caused a 10 to 15% increase in pre-implantation loss. No embryotoxic or teratogenic effects were observed.

In five rat studies, metronidazole was administered either at a dietary concentration of 0.13% for 18 days of gestation, or by gastric intubation at dose levels from 50 to 200 mg/kg/day for periods ranging from 10 days (mid-gestation) to 40 days (before and during pregnancy). Drug-related embryotoxic or teratogenic effects were not observed in any of the five studies.

In rats, metronidazole was administered intravenously at doses of 15 or 30 mg/kg/day from days 5 to 17 of pregnancy inclusive. There was a statistically significant increase in the mean numbers of implantations and live foetuses per litter in the metronidazole treated groups, but no difference in any other foetal parameter.

In one mouse study, two groups of mice were treated from the sixth to the fifteenth day of gestation. Metronidazole was administered by gastric intubation at doses of 10 and 20 mg/kg/day. At the dosage utilized, metronidazole was devoid of any teratogenic activity.

In humans, data has been accumulated on 2500 women who received Metronidazole at various stages during pregnancy. The overall incidence of congenital abnormalities remained within the expected limits for untreated mothers and an examination of the reports revealed that there was no trend or consistent pattern in the reported defects nor was there any evidence of causal relationship.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr] METRONIDAZOLE

Metronidazole Tablets

Read this carefully before you start taking **METRONIDAZOLE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **METRONIDAZOLE**.

What is METRONIDAZOLE used for?

METRONIDAZOLE is used to treat adults with:

- infections of the genital tract (such as trichomoniasis: a sexually transmitted infection, bacterial vaginosis: bacterial infection of the vagina).
- infections of the brain or lung.

It is also used treat adults and children with:

- Amebiasis (a parasitic infections of the liver or intestine).
- Giardiasis (a parasitic infection in the intestines).

Antibacterial drugs like METRONIDAZOLE treat only bacterial infections. They do not treat viral infections.

How does METRONIDAZOLE work?

METRONIDAZOLE belongs to a group of medicines called antibacterial - antiprotozoal.

METRONIDAZOLE works by killing bacteria and parasites (protozoans) that cause infections in your body.

What are the ingredients in METRONIDAZOLE?

Medicinal ingredient: metronidazole

Non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate and microcrystalline cellulose.

METRONIDAZOLE comes in the following dosage forms:

Tablets: 250 mg

Do not use METRONIDAZOLE if:

- you are allergic (hypersensitive) to metronidazole, nitroimidazoles (e.g. tinidazole) or any of the ingredients in METRONIDAZOLE or components of the container (see What are the ingredients in METRONIDAZOLE).
- you have a genetic disorder called Cockayne Syndrome. Severe liver damage that may be fatal has happened when people with Cockayne syndrome have taken metronidazole.
- you have a disease of the nervous system.
- you have a history of blood disorders.
- you have hypothyroidism (underactive thyroid gland) or hypoadrenalism (underactive adrenal glands).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take METRONIDAZOLE. Talk about any health conditions or problems you may have, including if you:

- are pregnant, think you are pregnant, or plan to get pregnant.
- are breastfeeding, or planning to breastfeed, as metronidazole is excreted in human breast milk.
- have other infections.
- have liver problems.
- have kidney problems.
- are sexually active.
- are taking METRONIDAZOLE for the first time or have any nervous system problems.
- have any blood disorder (e.g. leukemia, hemophilia, or other).

Other warnings that you should know about:

Driving and Operating Machinery:

- METRONIDAZOLE may make you experience confusion, dizziness, vertigo (spinning sensation), hallucinations, convulsions (seizures) or problems with your eyesight (blurred vision). Do not drive or operate heavy machinery while taking METRONIDAZOLE.

Medical Tests

- Your healthcare professional may order medical tests based on your medical history and how long you have been taking METRONIDAZOLE.
- METRONIDAZOLE may affect the results of certain medical tests. Tell your healthcare professional if you are taking METRONIDAZOLE and you need a medical test for another health condition.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with METRONIDAZOLE:

- Amiodarone – used to treat certain heart rhythm conditions.
- Busulfan, a medicine used to treat certain blood cancer.
- Carbamazepine – used to treat epilepsy and nerve pain.
- Corticosteroids, medicines used to treat allergies, skin problems, asthma and arthritis.
- Cyclosporin, a medicine used to prevent organ rejection after a transplant.
- Disulfiram, a medicine used to treat alcoholism.
- Lithium, a medicine used as a psychiatric medication.
- Phenytoin, a medicine used to treat seizures.
- Phenobarbital, a medicine used to treat insomnia, anxiety or tension or to control seizures.
- Quinidine – used to treat malaria and certain heart rhythm conditions.
- Tacrolimus – used to help with organ transplants.
- Vecuronium, an agent used to relax muscles during surgical procedures.
- Warfarin, a blood thinner used treat heart conditions.
- 5-fluorouracil, a medicine used to treat cancer.
- Medications that may cause heart rhythm changes (QT prolongation), like certain antiarrhythmics (medicines for heart rhythm disorders), certain antibiotics, and psychotropic medicines.

Do not drink alcohol while taking METRONIDAZOLE and for at least 1 day after your last dose. Drinking alcohol while using METRONIDAZOLE might cause side effects, such as feeling sick (nausea), being sick (vomiting), stomach pain, hot flushes, very fast or uneven heartbeat (palpitations) and headache.

How to take METRONIDAZOLE:

- You should not be left unattended for 2 hours after your first use of METRONIDAZOLE.
- Although you may feel better early in treatment, METRONIDAZOLE should be used exactly as directed.
- Misuse or overuse of METRONIDAZOLE could lead to the growth of bacteria that will not be killed by METRONIDAZOLE (resistance). This means that METRONIDAZOLE may not work for you in the future.
- Do not share your medicine.

Usual dose:

Your healthcare professional will decide how much METRONIDAZOLE you should take depending on the type of infection you have and your medical history.

Adults:

The usual dose is 250 mg to 500 mg every 8 to 12 hours for 5 to 10 days.

Children (under 18 years old):

The usual dose is 25 to 50 mg / kg / day divided into 2 to 3 doses each day for 5 to 7 days.

Overdose:

If you think you, or a person you are caring for, have taken too much METRONIDAZOLE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take METRONIDAZOLE, take them as soon as you remember. However, if it is almost time for your next dose, skip the missed dose. Do not use a double dose to make up for a forgotten dose.

What are possible side effects from using METRONIDAZOLE?

These are not all the possible side effects you may have when taking METRONIDAZOLE. If you experience any side effects not listed here, tell your healthcare professional.

Like all medicines, METRONIDAZOLE can cause side effects, although not everybody gets them.

These side effects may include:

- Constipation
- Unpleasant taste in the mouth
- Dry mouth
- Furred tongue or tongue discoloration
- Chest pain
- Feeling sick (nausea), being sick (vomiting)
- Upset stomach
- Stomach pain
- Noise such as buzzing, ringing, or whistling heard in the ear
- Loss of appetite
- Feeling sleepy or dizzy
- Unpleasant metallic taste
- Dark urine
- Painful urination
- Flushing
- Headache
- Trouble sleeping

- Itching, hives, rash

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Allergic reaction: swelling of the face, mouth, tongue or throat, hands, difficulty in breathing or swallowing, wheezing; drop in blood pressure, feeling sick to your stomach and throwing up itching, rash, red spots and blisters			√
Pseudomembranous colitis (bowel inflammation)**:** severe or persistent diarrhea, abdominal pain, nausea and vomiting, fever	√		
Drug reaction with eosinophilia and systemic symptoms (DRESS) (serious skin reaction that may affect more than one or more organs): fever, severe rash, peeling skin, swollen lymph glands, flu-like feeling, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feel thirsty, urinating less often, less urine			√
Hearing loss			√
Heart Problems: very fast or uneven heartbeat, chest pain, dizziness, weakness, blurred vision, fainting. This may also happen when METRONIDAZOLE is taken with drugs that can cause QT prolongation (a heart rhythm condition).			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Leukopenia / Neutropenia (decreased white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms		√	
Liver problems: including cases of liver failure with symptoms such as intense fatigue, yellowing of the skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, abdominal pain, unusual tiredness.			√
Meningitis (inflammation of the thin tissue that surrounds the brain and spinal cord): fever, nausea, vomiting, headache, stiff neck, extreme sensitivity to bright light, confusion, seizures, sleepiness or difficulty waking, no appetite or thirst			√
Mental health problems: irrational thoughts, feeling confused or feeling depressed and seeing hearing things that are not there (hallucinations), thoughts or actions of self-harm or suicide			√
Muscular Disorders: muscle spasms, muscle aches and pain, joint stiffness		√	
Nervous system problems: inability to coordinate voluntary movements, problems using your arms and legs, problems with speaking or feeling confused, convulsions, tingling sensation on the skin, stiff neck associated with headache, extreme sensitivity to bright light, have spinning sensations (vertigo).			√

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Eye sight problems: pain when moving the eye, blurred vision, double vision, vision loss		√	
Pancreatitis (inflammation of the pancreas): severe abdominal pain which may reach through to your back, especially associated with nausea, vomiting and fatigue.			√
Peripheral neuropathy: Numbness, tingling, pain, or a feeling of weakness, in the arms or legs, sensitivity to touch		√	
Seizures (fit)**:** uncontrollable shaking with or without loss of consciousness			√
Stevens-Johnson syndrome (SJS) (severe skin rash): redness, blistering and/or peeling of the skin and/or inside of the lips, eyes, mouth, nasal passages or genitals, accompanied by fever, chills, headache, cough, body aches or swollen glands.			√
Thrombophlebitis (blood clot in the vein of the leg or arm): swelling and redness along the vein which is extremely tender or painful when you touch the area		√	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		√	
Toxic Epidermal Necrolysis (TEN) (severe skin reaction): redness, blistering and/or peeling of large areas of the body			√
Vaginal Yeast Infection: vaginal dryness, burning and discharge		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

METRONIDAZOLE should be stored at 15° C to 25°C.

Keep out of reach and sight of children.

If you want more information about METRONIDAZOLE:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (http://www.aapharma.ca/en/), or by calling 1877-998-9097.

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Last Revised: JUN 1, 2023