

PRODUCT MONOGRAPH

Pr METRONIDAZOLE 5MG/ML INJECTION

Metronidazole

Solution, 5mg/ml

USP

Antibacterial-Antiprotozoan

Baxter Corporation
7125 Mississauga Road
Mississauga
Ontario
Canada L5N 0C2

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METRONIDAZOLE 5MG/ML INJECTION

Metronidazole

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	Solution, 5mg/ml	Citric Acid Anhydrous, USP Nitrogen, NF Sodium Chloride, USP Dibasic Sodium Phosphate Anhydrous, USP Water for Injection, USP <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

METRONIDAZOLE 5MG/ML INJECTION is indicated for:

- **TREATMENT OF BACTERIAL INFECTIONS.**

The treatment of serious anaerobic intra-abdominal infections due to susceptible anaerobic bacteria, such as *Bacteroides fragilis* (and other species of Bacteroides), *Clostridium*, *Fusobacterium*, *Peptococcus*, and *Peptostreptococcus species*. 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, modifications 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 **WARNINGS** section).

Treatment of a small number of cases of brain and lung infections (some with abscesses) caused by anaerobic bacteria.

- **PREVENTION OF BACTERIAL INFECTIONS.**

The prevention of the incidence of post-operative infections in patients undergoing elective colorectal surgery. 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of METRONIDAZOLE 5MG/ML INJECTION and other antibacterial drugs, METRONIDAZOLE 5MG/ML INJECTION should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Pediatrics:

Safety and effectiveness in pediatrics have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to Metronidazole or other nitroimidazole derivatives or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Metronidazole should not be administered to patients with active neurological disorders, a history of blood dyscrasia, hypothyroidism or hypoadrenalism.

WARNINGS AND PRECAUTIONS

General

Metronidazole Injection 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.

Some adverse reactions to metronidazole such as seizure, dizziness, optic neuropathy, may impair the ability to drive or operate machines (see **ADVERSE REACTIONS**).

Genitourinary/ Respiratory/ Skin

Known or previously unrecognized moniliasis may present more prominent symptoms after treatment with Metronidazole.

Studies in rats and mice have provided some evidence that Metronidazole may cause tumors in these species when administered orally for a long period at high doses. The relevance of these findings in humans is not known. However, it is therefore 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

Agranulocytosis, transient eosinophilia, leukopenia and neutropenia have been observed during treatment with Metronidazole. 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.

Central and Peripheral Nervous System Effects

Severe neurological disturbances (including seizures and peripheral and optic neuropathies) have been reported in patients treated with Metronidazole (administered orally or intravenously). . Stop metronidazole treatment if any abnormal neurologic symptoms occur such as ataxia, dizziness, confusion or any other CNS adverse 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 (see **ADVERSE REACTIONS**).

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 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.

Patients with Cockayne Syndrome

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 5 MG/ ML INJECTION should therefore only be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking METRONIDAZOLE 5 MG/ ML INJECTION.

Hepatic Impairment

Patients with severe hepatic disease especially those with hepatic encephalopathy, metabolize metronidazole slowly with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses of Metronidazole Injection should be reduced below those usually recommended administer-with caution.

Renal Impairment

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.

Sodium Content

This medicinal product contains 12.8 – 14.2 mmol sodium per 100 mL. To be taken into consideration by patients on a controlled sodium diet.

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

Disulfiram

Concurrent use of metronidazole and disulfiram may result in psychotic reactions and confusion in patients drinking alcohol or taking alcohol-containing products. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks (see **DRUG INTERACTIONS**)

Alcohol

Discontinue consumption of alcoholic beverages or alcohol-containing products before, during, and up to 72 hours after taking metronidazole because abdominal cramps, nausea, vomiting, flushing, headaches, and tachycardia may occur (see **DRUG INTERACTIONS**).

Risk of Air Embolism

Do not connect flexible plastic containers in series in order to avoid air embolism due to possible residual air contained in the primary container.

Pressurizing intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.

Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing METRONIDAZOLE 5MG/ML INJECTION in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Special Populations

Pregnant Women:

Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. There are no adequate data from the use of metronidazole in pregnant or lactating women. In serious anaerobic infections, if the administration of Metronidazole Injection 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.

Nursing Women:

Metronidazole is secreted in breast milk in concentrations similar to those found in plasma. During lactation either breastfeeding or metronidazole should be discontinued.

Pediatrics (< 12 years of age):

There have been no studies performed by Baxter Healthcare Corporation in the pediatric population.

Geriatrics

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

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 AST (SGOT), AL T (SGPT), LDH, triglycerides and hexokinase glucose determinations 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.

ADVERSE REACTIONS

Post-Market Adverse Drug Reactions

The following adverse reactions have been reported the use of metronidazole. These reactions are listed by MedDRA System Organ Class (SOC).

BLOOD AND LYMPHATIC SYSTEM DISORDERS: agranulocytosis, leukopenia, neutropenia, thrombocytopenia, eosinophilia

IMMUNE SYSTEM DISORDERS: anaphylactic reaction, hypersensitivity

METABOLISM AND NUTRITION DISORDERS: decreased appetite. an antithyroid effect has been reported by some investigators but three different clinical studies failed to confirm this.

PSYCHIATRIC DISORDERS: confusional state, depression, insomnia

NERVOUS SYSTEM DISORDERS: encephalopathy, seizure, neuropathy peripheral, ataxia, dizziness, hypoesthesia, paresthesia, dysgeusia, headache, meningitis aseptic, somnolence, dysarthria

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.

EYE DISORDERS: optic neuropathy

CARDIAC DISORDERS: tachycardia, palpitation, chest pain, dyspnea

GASTROINTESTINAL DISORDERS: pancreatitis, abdominal pain, diarrhea, nausea, anorexia, vomiting, dry mouth, constipation, tongue discoloration, glossitis, dyspepsia, rare cases of pseudomembranous colitis

SKIN AND SUBCUTANEOUS DISORDERS: toxic epidermal necrolysis, swelling face, pruritus, urticaria, hyperhidrosis, erythema, rash, Stevens-Johnson syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS: muscle spasms, arthralgia, myalgia

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

HEPATOBIILIARY DISORDERS: jaundice

RENAL AND URINARY DISORDERS: chromaturia, dysuria

Darkening of the urine has been reported. This is probably due to a metabolite of metronidazole and seems to have no clinical significance. Reversible lowering of serum lipids has been reported.

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.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: injection site reaction, malaise, face edema, edema peripheral, chills, asthenia

INVESTIGATIONS: hepatic enzyme increased, reversible lowering of serum lipids has been reported.

DRUG INTERACTIONS

Drug-Drug Interactions

Disulfiram: Concurrent use of metronidazole and disulfiram has been associated with psychotic reactions and confusion in patients drinking alcohol. A possible mechanism of the interaction is an additive effect of inhibition of aldehyde dehydrogenase (ALDH). (See **WARNINGS AND PRECAUTIONS**).

Alcohol: Administration of metronidazole in patients drinking alcohol was associated with nausea, vomiting, flushing, headache, and/or tachycardia. A possible mechanism is inhibition of aldehyde dehydrogenase (ALDH) by metronidazole, resulting in accumulation of acetaldehyde, a toxic metabolite of alcohol. (See **WARNINGS AND PRECAUTIONS**).

Oral Anticoagulant therapy (Warfarin type): Metronidazole has been reported to potentiate the anticoagulant effect of warfarin and other oral coumarin anticoagulants resulting in a prolongation of prothrombin time and increased risk of hemorrhages. Patients taking metronidazole and warfarin or other oral coumarins concomitantly should have their prothrombin time and international normalized ratio (INR) carefully monitored, and their anticoagulant dose adjusted accordingly. Monitor patients for signs and symptoms of bleeding.

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

Lithium: Concomitant use of lithium and Metronidazole may result in lithium toxicity due to decreased renal clearance of lithium. Persistent renal damage may develop. When Metronidazole Injection must be administered to patients on lithium therapy, it may be prudent to consider tapering or discontinuing lithium temporarily when feasible.

Otherwise frequent monitoring of serum lithium, creatinine and electrolyte levels and urine osmolality should be done.

Busulfan: Plasma concentrations of busulfan may increase during concomitant treatment with metronidazole, which may result in an increased risk for serious busulfan toxicity such as sinusoidal obstruction syndrome, gastrointestinal mucositis, and hepatic veno-occlusive disease.

Cytochrome P450 inhibitors: 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 inducers: Concomitant administration of drugs that induce microsomal liver enzyme activity, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole and therefore decrease its efficacy. Phenytoin clearance may be impaired. 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.

Cytochrome P450 3A4 (CYP3A4) substrates: 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.

5-Fluorouracil: Metronidazole decreases the clearance of 5-fluorouracil and may therefore cause 5-fluorouracil toxicity.

DOSAGE AND ADMINISTRATION

Metronidazole is for intravenous infusion.

Dosage, rate, and duration of administration are to be individualized and depend upon the indication for use, the patient's age, weight, clinical condition and concomitant treatment, and on the patient's clinical and laboratory response to the treatment.

Metronidazole has a theoretical calculated osmolality of 297 mOsmol/L.

Recommended Dose and Dosage Adjustment

Treatment of Anaerobic infections:

I.V. Administration:

a) 100 mL (500 mg) by slow intravenous infusion (i.e. at the rate of 5 mL/min) every 8 hours, or

b) 300 mL (1500 mg) by slow intravenous infusion (i.e. at the rate of 6 mL/min) every 24 hours.

Metronidazole Injection has been used with success at a dosage of 1.5 g once per day in a limited number of patients. The decision to employ the once-a-day dosing schedule should be determined by careful evaluation of the risk chances for infection.

Prevention in Colorectal Surgery:

The recommended dosage schedule is: 1g I.V. infused (over 40 minutes) just prior to surgery and a second and third 500 mg dose administered at 8-hour intervals after the initial dose.

Although Metronidazole Injection has been employed alone, serious consideration should be given to the concomitant administration of an antibiotic with activity against aerobic bacteria in order to minimize the possibilities of post-operative infection.

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 lack of pharmacokinetic information, specific dosage recommendations cannot be given for these patients. Therefore, close monitoring of blood metronidazole levels and of patients for signs of toxicity are recommended (see **Warnings** and **Precautions**).

Severe Impairment of Renal Function and Anuria:

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. Patients with severe impairment of renal function who are not undergoing hemodialysis should be monitored closely for signs of toxicity.

Administration

Treatment should be initiated by the I.V. route. Oral medication may be substituted when it is feasible and/or practical.

Consideration should be given to official guidance on the appropriate use of antibacterial agents to reduce the development of drug resistance and maintain the effectiveness of metronidazole and other antibacterial drugs. In a mixed aerobic and anaerobic infection, antibiotics appropriate for the treatment of the aerobic infection may be used in combination with metronidazole.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact.

Visually inspect the container. If the administration port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired.

Additives known or determined to be incompatible should not be used.

Before adding a substance or medication, verify that it is soluble and stable in metronidazole, and that the pH range of metronidazole is appropriate (pH of solution is 4.50 - 7.00). Additives may be incompatible. When introducing additives, the instructions for use of the medication to be added and other relevant literature must be consulted (see **DRUG INTERACTIONS**).

Mix the solution thoroughly when additives have been introduced.

After addition, if there is a color change and/or the appearance of precipitates, insoluble complexes or crystals, do not use.

Do not store solutions containing additives.

Discard any unused portion.

For single use only.

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.

Metronidazole Injection is ready-to-use solutions which require no further dilution.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Symptom:

Massive ingestion may result in an overdose. Signs and symptoms may include: nausea, vomiting, and neurotoxic effects, including ataxia, confusion, disorientation, seizures, and peripheral neuropathy. 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:

The effects of an overdose may require immediate medical attention and treatment. There is no specific antidote. Symptomatic treatment is recommended. Discontinue metronidazole administration in the event of an overdose.

ACTION AND CLINICAL PHARMACOLOGY

Metronidazole is bactericidal against anaerobic bacteria; it exerts trichomonocidal 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.

STORAGE AND STABILITY

Metronidazole Injection should be stored at room temperature (15 - 25°C).

Do not use equipment containing aluminum (e.g., needles, cannulae) that would come in contact with the drug solution as precipitates may form.

Metronidazole is incompatible with (includes but is not limited to):

- Aztreonam
- Cefamandole nafate
- Cefoxitin
- Penicillin G
- sodium lactate 5% w/v and dextrose 10% w/v injection

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products (see **DOSAGE AND ADMINISTRATION**).

SPECIAL HANDLING INSTRUCTIONS

N/A

DOSAGE FORMS, COMPOSITION AND PACKAGING

Metronidazole Injection is a sterile, non-pyrogenic, pale yellow solution for I.V. infusion. These are ready-to-use solutions which require no further dilution.

Injection 0.5% w/v: Each Vialflex® plastic bag of 100 mL contains metronidazole 500 mg for I.V. infusion.
Boxes of 48.

Injection 0.5% w/v: Each Vialflex® plastic bag of 300 mL contains metronidazole 1500 mg for I.V. infusion.
Boxes of 12.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

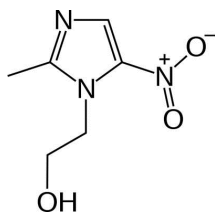
Drug Substance

Proper name: Metronidazole

Chemical name: 1-(2-Hydroxyethyl)-2-methyl-5-nitroimidazole

Molecular formula and molecular mass: $C_6H_9O_3N_3$; 171.15

Structural formula:



Physicochemical properties: White crystalline powder with slight yellow tint. Slightly soluble in water, alcohol, chloroform and ether.

DETAILED PHARMACOLOGY

Animal Pharmacology

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.

Human Pharmacology and Pharmacokinetics

Pharmacokinetics:

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.

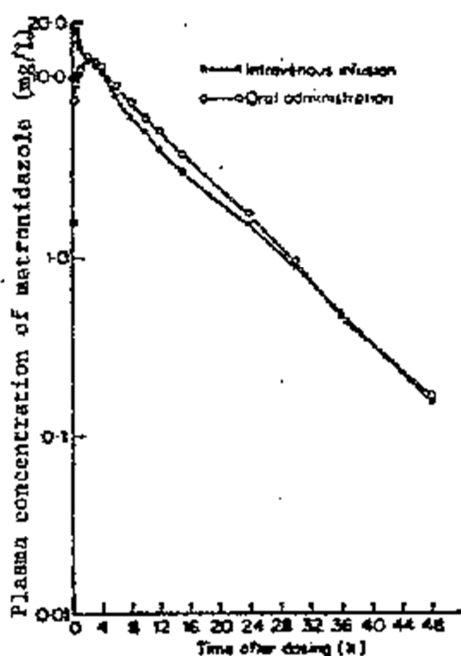


Figure 1. Mean plasma metronidazole concentrations following a single oral or intravenous dose of metronidazole (500 mg) (n= 9 females).

In two kinetic studies in which a single Metronidazole 1.5 g dose was infused intravenously over a 50-60 minute period in volunteers, a peak level of 30-40 mg/L was obtained 1 hour after the start of infusion and fell to 10 mg/L at 12 h and 4 mg/L at 24 hours.

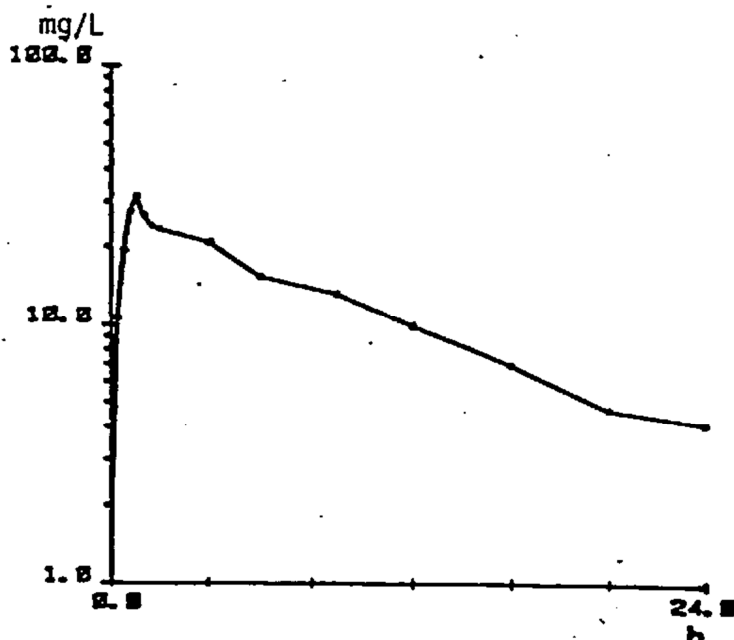


Figure 2. Mean plasma metronidazole concentration following a single intravenous dose of metronidazole (1.5 g) (n= 10).

Excretion and Metabolism:

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose) with fecal excretion accounting for 6 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.

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 2: 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.	26 mg/L (on day 5)	N/A*
	p.o. x 10 days	20 mg/L (on day 15)	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 - 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.	35 mg/L inflamed meninges	N/A
	600 mg i.v. t.i.d.	43 mg/L	N/A
Pus (Pulmonary Empyema)	400 mg, p.o. q.i.d.	24.2 mg/L	N/A

*Not applicable

Decreased renal function:

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 3: 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- ylacetic 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.

Impaired liver function:

In patients with impaired liver function, the plasma clearance of metronidazole is decreased and accumulation can therefore result.

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:

ACTIVITY* OF METRONIDAZOLE AGAINST ANAEROBIC BACTERIA

		0.1	0.5	1.0	2.0	4.0	8.0	16.0	32.0	64.0	128.0	256
<i>Bacteroides fragilis</i> group	77	1	12	27	56	84	97	99	100			
<i>Bacteroides melaninogenicus</i>	69	15	81	93	99	100						
Other <i>Bacteroides</i>	72	6	42	68	85	93	96	96	99			100
<i>Fusobacterium nucleatum</i>	19	58	95			100						
Other <i>Fusobacterium</i>	46	15	76	100								
<i>Peptococcus</i> and <i>Gaffkya</i>	73	3	69	88	96						96	100
<i>Peptostreptococcus</i>	41	29	66	76	81	83	88	90				100
Microaerophilic and Anaerobic streptococci	11		27			36					46	100
Gram-negative cocci (<i>Acidaminococcus</i> , <i>Megasphaera</i> , <i>Veillonella</i>)	28	4	57	89	96	100						
<i>Eubacterium</i>	59	7	44	61	66		71		75	80	86	100
<i>Arachnia</i>	3		33									100
<i>Propionibacterium</i>	12		8			17						100
<i>Actinomyces</i>	16					13		19	50	56	63	100
<i>Bifidobacterium</i>	8					36		66	75	87		100

<i>Lactobacillus</i>	20	10	35	55		65	75			80	90	100
<i>Clostridium perfringens</i>	12		25	67	100							
Other <i>Clostridium</i>	164	32	54	65	74	84	93	98	100			

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

With rare exceptions, anaerobic gram-negative non-spore forming bacilli and cocci as all 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 liter 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* 10³ 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.

TOXICOLOGY

Acute Toxicity

The LD₅₀ values for metronidazole are given in the following Table:

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 21/2 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.

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 as 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).

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 - 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 5-17 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.

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.

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 CF₁ 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 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 28-80 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.

REFERENCES

1. AUGER P, BOURGOUIN J, BAGOT C Intravenous metronidazole in the treatment of abdominal sepsis: once vs three times daily administration. *Curr Ther Res* 1988; 43: 494 – 502
2. AUGER P, LEGROS G, GIRARD R, LAVERDIERE M, BERGERON M, BOURGOUIN J, Le MORVAN P Intravenous metronidazole vs oral erythromycin base plus neomycin in the prevention of infection following elective colorectal surgery. *Curr Ther Res* 1987; 42: 922 - 931
3. BRASS C, RICHARD GK, RUEDY J, PRENTIS J, HINCHEY EJ The Effect of Metronidazole on the Incidence of Post-operative Wound Infection in Elective Colon Surgery. *Am J Surg* 1978; 135: 91-96
4. BROGDEN RN, HEEL RC, SPEIGHT TM, AVERY GS Metronidazole in Anaerobic Infections: A Review of its Activity, Pharmacokinetics and Therapeutic Use. *Drugs* 1978; 16: 386-417
5. COSAR C, GANTER P, JULOU L Etude experimentale du metronidazole (8823 R.P.). Activites trichomonacide et amoebicide. Toxicite et proprietes pharmacologiques generales. *Presse Med* 1961; 69: 1069
6. DAVIS JL, SCHULTZ TA, MOSELEY CA Metronidazole lowers serum lipids. *Am Int Med* 1983; 99: 43- 44
7. FAGAN TC, JOHNSON DG, GROSSO DS Metronidazole-induced gynecomastia. *JAMA* 1985; 254: 3217
8. GIAMARELLOU H, KANELLAKOPOULOU K, PRAGASTIS D, TAGARIS N, DAIKOS GK Treatment with metronidazole of 48 patients with serious anaerobic infections. *J Antimicrobial Chemother* 1977; 3: 347-353.
9. Gulbis A.M., Culotta K.S., Jones R.B., Andersson B.S., Busulfan and metronidazole: An often forgotten but significant drug interaction, *Annals of Pharmacotherapy*. 45 (7-8), 2011.
10. JENSEN JC, GUGLAR R Interaction between metronidazole and drugs eliminated by oxidative metabolism. *Clin Pharmacol Ther* 1985; ,3 7: 407- 410.
11. HOUGHTON GW, THORNE PS, SMITH J, TEMPLETON R, COLLIER J Comparison of the Pharmacokinetics of Metronidazole in Healthy Female Volunteers Following either a Single Oral or Intravenous Dose. *Br J Clin. Pharmacol* 1979; 8: 337-341
12. JENNISON RF, STENTON P, EATT L Laboratory studies with the systemic trichomonacide, metronidazole. *J Clin Path* 1961; 14: 431.

13. PETERSON WF, STAUCH JE, RYDER CD Metronidazole in pregnancy. *Am J Obstet Gynecol* 1966; 94: 243 -249.
14. RALPH ED, AMATNIEKS YE Relative susceptibilities of Gardnerella vaginalis (Haemophilus vaginalis), Neisseria gonorrhoeae and Bacteroides fragilis to Metronidazole and its two major metabolites. *Sex Transm Dis* 1980; 7: 157-160.
15. TEICHER MH, AL TESMAN RI, COLE JO, SCHATZBERG AF Possible nephrotoxic interaction of lithium and metronidazole. *JAMA* 1987; **257**: 3365-3366.

PART III: CONSUMER INFORMATION**METRONIDAZOLE 5MG/ML INJECTION
(Metronidazole)**

This leaflet is part III of a three-part "Product Monograph" published when METRONIDAZOLE 5MG/ML INJECTION was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about METRONIDAZOLE 5MG/ML INJECTION. Contact your doctor, nurse or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION**What the medication is used for:**

Metronidazole 5mg/ml Injection is used to:

- treat infections of the abdominal cavity, brain or lung.
- prevent infections in patients having colorectal surgery.

Antibacterial drugs like METRONIDAZOLE 5MG/ML INJECTION treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, METRONIDAZOLE 5MG/ML INJECTION should be used exactly as directed. Misuse or overuse of METRONIDAZOLE 5MG/ML INJECTION could lead to the growth of bacteria that will not be killed by METRONIDAZOLE 5MG/ML INJECTION (resistance). This means that METRONIDAZOLE 5MG/ML INJECTION may not work for you in the future. Do not share your medicine.

What it does:

Metronidazole 5mg/ml Injection kills the bacteria that cause the infection.

When it should not be used:

Do not use Metronidazole 5mg/ml Injection and tell your doctor if you:

- are allergic (hypersensitive) to metronidazole
- are allergic (hypersensitive) to any of the nonmedicinal ingredients in the formulation (see "What the nonmedicinal ingredients are) or components of the VIAFLEX plastic container
- have a disease of the nervous system
- have a history of blood-disorders, hypothyroidism (underactive thyroid gland) or hypoadrenalism (underactive adrenal gland)

What the medicinal ingredient is:

Metronidazole

What the nonmedicinal ingredients are:

Citric Acid
Nitrogen
Sodium Chloride
Sodium Phosphate
Water for Injection

What dosage forms it comes in:

Metronidazole 5mg/ml Injection, solution

WARNINGS AND PRECAUTIONS

BEFORE receiving Metronidazole 5mg/ml Injection talk to your doctor, pharmacist or nurse if you:

- have other infections
- have Cockayne Syndrome
- have been consuming alcohol
- have kidney problems
- have liver problems
- have an active or chronic severe disease of the nervous system
- have any blood disorder (e.g., transient eosinophilia, leukopenia or other)
- have a history of edema (swelling of the legs, ankles and/or feet)
- are pregnant or plan to get pregnant
- are breastfeeding, or plan to breastfeed, as metronidazole is excreted in human breast milk.
- are less than 18 years of age

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with Metronidazole 5mg/ml Injection:

- Disulfiram
- Medicines used to thin the blood such as warfarin (Coumadin)
- Phenobarbital or Phenytoin (Dilantin)
- Vecuronium
- Lithium
- Busulfan (Myleran®)
- 5-Fluorouracil

If you are not sure, talk to your doctor or pharmacist before using metronidazole.

Do not drink any alcohol while you are receiving Metronidazole 5mg/ml Injection. Consumption of alcohol with metronidazole may cause headaches and flushing.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:

The appropriate dose is selected by the Health Care Professional and is administered through a vein.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your scheduled infusion, contact your doctor or nurse as soon as possible to schedule your next treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Side effects may include:

- Nausea, diarrhea, vomiting, constipation
- Indigestion, loss of appetite
- abdominal pain
- dry mouth, furred tongue
- unpleasant metallic taste
- dark urine
- painful urination
- flushing
- headaches
- trouble sleeping, feeling
- skin rash and itching

Metronidazole 5mg/ml Injection can cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
Allergic Reaction: rash, blisters, mouth sores, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, fever			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
Cardiac Disorders: Chest pain, unusually rapid, strong, or irregular heartbeat. Difficulty breathing (Dyspnea).		√	
Eye disorders: blurred vision, vision loss		√	
Gastrointestinal disorders: Pancreatitis (inflammation of the pancreas) with symptoms such as severe abdominal pain which may reach through to your back, especially associated with nausea, vomiting and fatigue. Stomach pain, diarrhea which can be bloody, fever		√	
Nervous System Disorders: inability to coordinate voluntary movements, problems using your arms and legs, feel confused, seizures, stiff neck associated with headache, dizziness, drowsiness and insomnia			√
Skin Disorders: Numbness, burning, tingling, pain in the hands and/or feet, sensitivity to touch		√	
Vaginal Yeast Infection: vaginal dryness, burning and discharge		√	
Muscular Disorders: Muscle spasms		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor, nurse, or pharmacist		Stop taking drug and seek immediate medical help
	Only if severe	In all cases	
General Disorders and Administration Site Conditions: Injection site reaction, Malaise, Face edema, Edema peripheral, Chills, Pain, burning, or swelling at the injection site			√

This is not a complete list of side effects. For any unexpected side effects while taking Metronidazole 5mg/ml Injection, contact your doctor, nurse or pharmacist.

HOW TO STORE IT

Store at room temperature (15° to 25° C).

Keep out of reach and sight of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: **Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9**

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Baxter Corporation, at:

1-800-387-8399

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