PRODUCT MONOGRAPH

PrAPO-METRONIDAZOLE

Metronidazole Capsules

500 mg

Apotex Standard

Antibacterial - Antiprotozoal

APOTEX INC.
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500 mg
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THERAPEUTIC CLASSIFICATION

Antibacterial - Antiprotozoal

ACTION AND CLINICAL PHARMACOLOGY

APO-METRONIDAZOLE (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.

Comparative Bioavailability

A comparative bioavailability study was performed using healthy male volunteers. The rate and extent of absorption of metronidazole was measured, and compared following oral administration of a single 1 x 500 mg dose of APO-METRONIDAZOLE (Metronidazole Capsules), and FLAGYL® (metronidazole) capsules, under fasting conditions. The results from measured data are summarized below.

Summary Table of the Comparative Bioavailability Data APO-METRONIDAZOLE (Dose: 1 x 500 mg) From Measured Data - Under Fasting Conditions Based on Metronidazole				
	Geometric Mean Arithmetic Mean (CV%)		Ratio of Geometric Means (%)**	90% Confidence interval (%)**
Parameter	APO-METRONIDAZOLE	FLAGYL®†		
AUC_T (ng.h/mL)	120859 121913 (14)	121439 122428 (13)	99.5	97.5 – 101.6
AUC_I (ng.h/mL)	123300 124503 (15)	123863 125005 (14)	99.5	97.5 – 101.6
C_{MAX} (ng/mL)	10950 11148 (22)	11187 11403 (22)	97.9	93.2 – 102.8
T_{MAX}^{*} (h)	1.27 (56)	1.41 (64)		
$T_{½}^{*}$ (h)	8.37 (13)	8.27 (15)		
* Arithmetic means (CV%). ** Based on the least squares estimate. † FLAGYL® by Rhône-Poulenc Rorer, purchased in Canada.				

INDICATIONS AND CLINICAL USES

PROTOZOAL INFECTIONS

- Trichomonal infections in men as well as in women.
- Hepatic and intestinal amebiasis.
- Giardiasis.

BACTERIAL VAGINOSIS

The "1988 Canadian Guidelines for the Treatment of Sexually Transmitted Diseases in Neonates, Children, Adolescents and Adults" recommends metronidazole for the treatment of this condition.

BACTERIAL INFECTIONS

Treatment:

Metronidazole is indicated in 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*. In the treatment of most serious anaerobic infections, intravenous metronidazole is usually administered initially. This may be followed by oral therapy with APO-METRONIDAZOLE capsules at the discretion of the physician.

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 **WARNINGS** section).

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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of APO-METRONIDAZOLE and other antibacterial drugs, APO-METRONIDAZOLE 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.

CONTRAINDICATIONS

APO-METRONIDAZOLE (metronidazole) is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.

APO-METRONIDAZOLE should not be administered to patients with active neurological disorders or a history of blood dyscrasia, hypothyroidism or hypoadrenalism.

WARNINGS

General

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

APO-METRONIDAZOLE (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.

Known or previously unrecognized moniliasis may present more prominent symptoms after treatment with APO-METRONIDAZOLE.

Neurologic

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

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

APO-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.

Patients should be advised not to take alcohol or alcohol-containing medicines during APO-METRONIDAZOLE therapy and for at least one day afterwards because of the possibility of a disulfiram-like (Antabuse effect) reaction.

Hepatic

APO-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 **ADVERSE REACTIONS** section).

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, APO-METRONIDAZOLE 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 APO-METRONIDAZOLE.

Susceptibility/Resistance

Development of Drug Resistant Bacteria

Prescribing APO-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 drug-resistant bacteria.

PRECAUTIONS

General

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

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 APO-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 APO-METRONIDAZOLE therapy and, when severe, immediate medical attention. Activated charcoal may be administered to aid in the removal of unabsorbed drug, if no more than two or three hours have elapsed since administration of the drug.

If for compelling reasons, APO-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, convulsive seizures).

Treatment with APO-METRONIDAZOLE should be discontinued if ataxia or any other symptom of central nervous system (CNS) involvement occurs.

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 APO-METRONIDAZOLE should be discontinued should pancreatitis occur once other causes of this disease are excluded.

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

Patients should be warned that APO-METRONIDAZOLE may darken urine. This is probably due to a metabolite of metronidazole and seems to have no clinical significance (see **ADVERSE REACTIONS** section).

Hematologic

Transient eosinophilia and leukopenia have been observed during treatment with metronidazole. Haematological 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

The use of APO-METRONIDAZOLE for longer treatment than usually required should be carefully weighed since it has been shown to be carcinogenic in mice and rats (see **WARNINGS** section).

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

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; it is advisable that administration of APO-METRONIDAZOLE be avoided in pregnant patients and be withheld during the first trimester of pregnancy. In serious anaerobic infections, if the administration of APO-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.

Nursing Mothers

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

Children

Clinical experience in children is very limited. The monitoring of this group of patients is particularly important.

Laboratory Test Interferences

Metronidazole interferes with serum AST, ALT, 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.

DRUG INTERACTIONS

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

Busulfan: Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

Cyclosporin: risk of elevation of cyclosporin serum levels. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Disulfiram: Administration of disulfiram and metronidazole has been associated with acute psychoses and confusion in some patients; therefore, these drugs should not be used concomitantly.

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

Lithium: Concomitant use of lithium and metronidazole may result in lithium intoxication due to decreased renal clearance of lithium. Persistent renal damage may develop. When APO-METRONIDAZOLE 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 lithium, creatinine and electrolyte levels and urine osmolality should be done.

Oral anticoagulant therapy (Warfarin type): Metronidazole has been reported to potentiate the anticoagulant effect of warfarin resulting in a prolongation of prothrombin time and increased hemorrhagic risk caused by decreased hepatic catabolism. This possible drug interaction should be considered when APO-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 APO-METRONIDAZOLE.

Phenytoin or Phenobarbital: In single dose studies, metronidazole injection did not interfere with the biotransformation of diazepam, antipyrine or phenytoin in man. However, 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.

The metabolism of metronidazole has been reported to be increased by concurrent administration of phenobarbital or phenytoin.

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.

ADVERSE REACTIONS

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

Cardiac disorders: palpitation and chest pain.

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

Ear and labyrinth disorders:

- hearing impaired/hearing loss (including hypoacusis, deafness, and deafness neurosensory)
- tinnitus

Gastrointestinal disorders: diarrhea, nausea, vomiting, epigastric distress, epigastric pain, dyspepsia, constipation, coated tongue, tongue discoloration/furry tongue (e.g. due to fungal overgrowth), dry mouth, taste disorders including metallic taste, and oral mucositis. Reversible cases of pancreatitis have been reported infrequently.

General disorders and administration site conditions: Thrombophlebitis has occurred with I.V. administration. 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, and anaphylactic shock.

Infections and infestations: rare cases of pseudomembranous colitis have 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, and aseptic meningitis.

Very rare reports of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus, and tremor) have been reported, which may resolve with discontinuation of the drug.

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.

Other: Proliferation of *Candida albicans* in the vagina, vaginal dryness and burning; dysuria; occasional flushing and headaches, especially with concomitant ingestion of alcohol; altered taste of alcoholic beverages.

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

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

Reproductive system and breast disorders: 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, and fixed drug eruption. Cases of Stevens – Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Many of these case reports revealed the use of concomitant medications known to be associated with SJS or TEN.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptom

Single oral doses of metronidazole, up to 12 g have been reported in suicide attempts and 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. Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

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

DOSAGE AND ADMINISTRATION

TREATMENT OF TRICHOMONIASIS

Note: The 250 mg metronidazole tablet is not marketed by Apotex Inc.

Consideration should be given to use APO-METRONIDAZOLE therapy (oral) in female patients, only when trichomonal infection has been confirmed by appropriate diagnostic techniques. In the male patient, oral APO-METRONIDAZOLE is recommended in those who are evidently the source of reinfection in female consorts and those with demonstrated urogenital trichomoniasis (see **WARNINGS** section).

Oral Administration:

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.

TREATMENT OF AMEBIASIS

Adults:

Intestinal Amebiasis – Three 250 mg tablets three times daily for 5 to 7 days.

Amebic abscesses of the liver – Two to three 250 mg tablets three times daily for 5 to 7 days.

Children:

Administer 35 to 50 mg/kg/day in three divided doses for 5 to 7 days.

TREATMENT OF GIARDIASIS

Adults:

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

Children:

Administer 25 to 35 mg/kg/day in two divided doses for 5 to 7 days.

Note – 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.

TREATMENT OF BACTERIAL VAGINOSIS

Adults:

500 mg orally twice a day for 7 days.

Concurrent treatment of sexual partners is not usually indicated.

ANAEROBIC INFECTIONS

Adults:

Treatment

In the treatment of most serious anaerobic infections, intravenous metronidazole is usually administered initially. This may be followed by oral therapy with APO-METRONIDAZOLE capsules at the discretion of the physician.

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.

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 **WARNINGS** and **PRECAUTIONS** sections).

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 APO-METRONIDAZOLE does not need to 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.

Children:

The safety and effectiveness of metronidazole in children is not known. Due to lack of pharmacokinetic data, no dosage recommendations can be made (see **PRECAUTIONS** section).

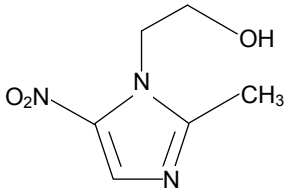
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Metronidazole

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

Structural Formula:



Molecular Formula: $C_6H_9O_3N_3$

Molecular Weight: 171.15 g/mol

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°C to 163°C

COMPOSITION

Capsules: In addition to the active ingredient (metronidazole) each APO-METRONIDAZOLE (Metronidazole Capsule), 500 mg contains the non-medicinal ingredients: colloidal silicon dioxide, croscarmellose sodium and stearic acid. The capsule shell contains the following non-medicinal

ingredients: D&C red #33, D&C yellow #10, FD&C blue #1, FD&C green #3, gelatin, talc (antistatic agent) and titanium dioxide. The edible ink used to imprint the capsule shells contains the following non-medicinal ingredients: FD&C blue #2, FD&C red #40, iron oxide black, propylene glycol and shellac glaze.

STABILITY AND STORAGE RECOMMENDATIONS

APO-METRONIDAZOLE (Metronidazole Capsules) should be stored between 15°C to 25°C.

AVAILABILITY OF DOSAGE FORMS

APO-METRONIDAZOLE (Metronidazole Capsules), 500 mg: Each pale green and light grey capsule, printed "500" contains 500 mg of metronidazole. Available in bottles of 100 capsules.

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 1: ACTIVITY* OF METRONIDAZOLE AGAINST ANAEROBIC BACTERIA

BACTERIA	No. of strains tested	CUMULATIVE 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			
Bacteroids 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, Megasphaera, 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 *trichomonas* 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 trichomonas in the control group and normal sub-cutaneous tissue free of *trichomonas* 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.

PHARMACOLOGY

ANIMAL PHARMACOLOGY

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

Metronidazole at doses of 40 to 50 mg/kg administered by intravenous infusion to 4 anaesthetised 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 KINETICS

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.

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.

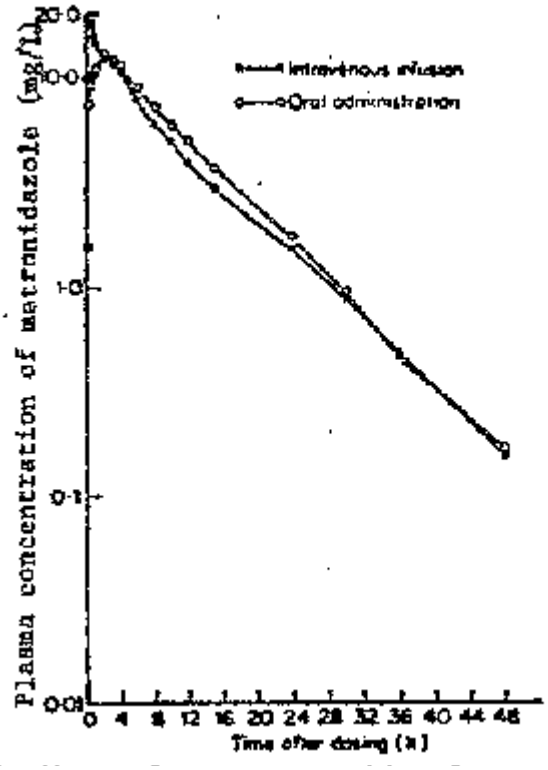


Figure 1. Mean plasma metronidazole concentrations following a single oral or intravenous dose of metronidazole (500 mg) (n= 9 females).

In two kinetic studies in which a single Metronidazole 1.5 g dose was infused intravenously over a 50-60 minutes 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 hour and 4 mg/L at 24 hour.

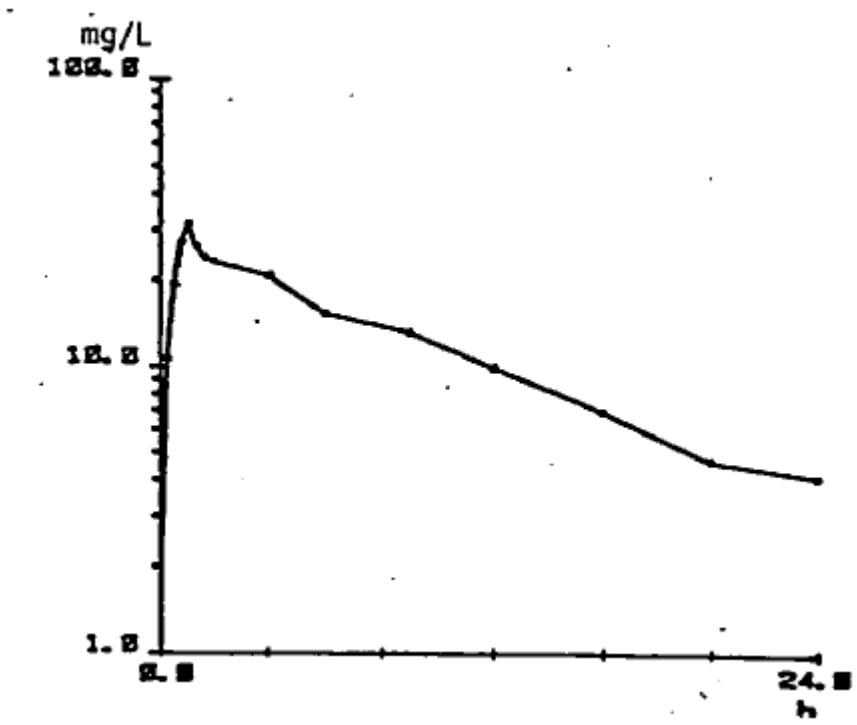


Figure 2. Mean plasma metronidazole concentration following a single intravenous dose of metronidazole (1.5 g) (n=10).

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-(ß-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 ADMINISTERED	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 i.v. 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

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).

Compound	ELIMINATION HALF LIFE (hours)		
	Patients		
	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.

Impaired Liver Function:

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

TOXICOLOGY

Acute Toxicity

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

Table 4: 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 initial 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).

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 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 28-80 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.

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38. Product Monograph ^{Pr}FLAGYL®- (Metronidazole Capsule) 500 mg. ODAN LABORATORIES LTD. Date of Revision: January 29, 2018, Control No. 209684.

CONSUMER INFORMATION

PrAPO-METRONIDAZOLE
(Metronidazole Capsules, 500 mg)
Apotex Standard

This leaflet is published and designed specifically for Consumers. This leaflet is a summary and will not tell you everything about APO-METRONIDAZOLE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

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

APO-METRONIDAZOLE belongs to a group of medicines called antibacterial - antiprotozoal. It can be used to treat:

- infections of the genital tract (such as trichomoniasis: a sexually transmitted infection, bacterial vaginosis);
- stomach, liver and intestinal infections (amebiasis, giardiasis);
- infections (such as intra-abdominal, brain or lung infections), caused by anaerobic bacteria (bacteria that are able to survive in the absence of oxygen).

What it does:

APO-METRONIDAZOLE works by killing bacteria and parasites that cause infections in your body.

When it should not be used:

Do not take APO-METRONIDAZOLE and tell your doctor if:

- You are allergic (hypersensitive) to metronidazole, nitroimidazoles (e.g. tinidazole) or any of the ingredients in APO-METRONIDAZOLE (see **What the nonmedicinal ingredients are**).
- You have a disease of the nervous system.
- You have a history of blood disease, hypothyroidism (underactive thyroid gland) or hypoadrenalism (underactive adrenal glands).

Do not take APO-METRONIDAZOLE if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking APO-METRONIDAZOLE.

What the medicinal ingredients are:

Each APO-METRONIDAZOLE capsule contains metronidazole.

What the nonmedicinal ingredients are:

Capsules:
Colloidal silicon dioxide, croscarmellose sodium and stearic acid. The capsule shell contains the following non-medicinal ingredients: D&C red #33, D&C yellow #10, FD&C blue #1, FD&C green #3, gelatin, talc (antistatic agent) and titanium dioxide. The edible ink used to imprint the capsule shells contains the following non-medicinal ingredients: FD&C blue #2, FD&C red #40, iron oxide black, propylene glycol and shellac glaze.

What dosage forms it comes in:

APO-METRONIDAZOLE is available as:

- Oral capsules containing 500 mg metronidazole. Each pale green and light grey capsule, printed "500" contains 500 mg of metronidazole. Available in bottles of 100 capsules.

WARNINGS AND PRECAUTIONS

BEFORE you use APO-METRONIDAZOLE talk to your doctor or pharmacist if you:

- are pregnant, think you are, or plan to get pregnant.
- are breastfeeding, or planning to breastfeed, as metronidazole is excreted in human breast milk.
- have liver problems.
- have any allergies to this drug or its ingredients (see **What the nonmedicinal ingredients are**) or a known allergy to nitroimidazoles (e.g. tinidazole).
- have an active or chronic severe disease of the nervous system.

- have any blood disorder (e.g. leukemia, hemophilia, or other). Your doctor may order periodic blood tests.
- have a thyroid condition or hypoadrenalism (underactive adrenal glands).

Contact your doctor if the following occurs while taking APO-METRONIDAZOLE:

- You feel sleepy, dizzy, confused, see or hear things that are not there (hallucinations), have fits (convulsions), have temporary eyesight problems (e.g. blurred or double vision). If this happens do not drive or use machinery or tools
- You feel tingling, pain, numbness or weakness in the arms or legs (peripheral neuropathy)

Unnecessary use of APO-METRONIDAZOLE should be avoided and prolonged treatment duration should be carefully weighed by your doctor. Its use should be reserved for the conditions described in the **"What the medication is used for"** section.

Avoid alcohol during APO-METRONIDAZOLE treatment and for at least one day following treatment to avoid an adverse reaction.

If a sexual partner shows signs of infection, the partner should be examined and treated by the doctor too.

If you have liver problems, your doctor may tell you to use a lower dose or to use the medicine less often. APO-METRONIDAZOLE may darken your urine and this is not considered a concern.

Cases of severe liver toxicity/acute liver failure, including deaths, in patients with Cockayne syndrome have been reported with products containing metronidazole.

If you are affected by Cockayne syndrome your doctor should also monitor your liver function frequently while you are being treated with APO-METRONIDAZOLE and afterwards.

- Tell your doctor immediately and stop taking APO-METRONIDAZOLE if you develop stomach pain, loss of appetite, nausea, vomiting, fever, malaise, fatigue, jaundice (e.g. yellowing of skin and eyes), dark urine putty or mastic colored stools or itching.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines. This is because APO-METRONIDAZOLE can affect the way some other medicines work. Also, some other medicines can affect the way APO-METRONIDAZOLE works.

In particular tell your doctor if you are taking any of the following medicines:

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

If you are not sure, talk to your doctor or pharmacist before taking APO-METRONIDAZOLE.

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

PROPER USE OF THIS MEDICATION

Note: The 250 mg metronidazole tablet is not marketed by Apotex Inc.

Usual adult dose:

TREATMENT OF TRICHOMONIASIS

Oral Administration:

Single-Dose Treatment
For both women and men, 2 g (4 capsules) 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.

TREATMENT OF AMEBIASIS

Adults:
Intestinal amebiasis – Three 250 mg tablets three times daily for 5 to 7 days.

Amebic abscesses of the liver – Two to three 250 mg tablets three times daily for 5 to 7 days.

Children:
Administer 35 to 50 mg/kg/day in three divided doses for 5 to 7 days.

TREATMENT OF GIARDIASIS

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

Children:
Administer 25 to 35 mg/kg/day in two divided doses for 5 to 7 days.

TREATMENT OF BACTERIAL VAGINOSIS

Adults:
500 mg orally twice a day for 7 days.

Concurrent treatment of sexual partners is not usually indicated.

ANAEROBIC INFECTIONS

Adults:
In the treatment of most serious anaerobic infections, intravenous metronidazole is usually administered initially. This may be followed by oral therapy with APO-METRONIDAZOLE capsules.

Oral Administration:
500 mg every 8 hours. Treatment for seven days should be satisfactory for most patients.

Overdose:

If you think you have taken too much APO-METRONIDAZOLE, contact your health care professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you forget to take APO-METRONIDAZOLE, take it 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

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

These side effects may include:
- Unpleasant taste in the mouth
- Furred tongue or tongue
- Feeling sick (nausea), being sick (vomiting), upset stomach, stomach pain or diarrhea
- Hearing loss
- Noise such as buzzing, ringing, or whistling heard in the ear
- Loss of appetite
- Feeling sleepy or dizzy

This is not a complete list of side effects. For any unexpected side effects while taking APO-METRONIDAZOLE, contact your doctor or pharmacist.

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
Allergic reaction with symptoms such as swelling of the mouth, throat, hands, difficulty in breathing or swallowing, itching, rash, red spots and blisters			✓
Diarrhea	✓		
Liver problems including cases of liver failure with symptoms such as intense fatigue, yellowing of the skin and eyes, dark urine, abdominal pain.			✓
Nervous system problems with symptoms such as inability to coordinate voluntary movements, problems using			✓

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

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
	Only if severe	In all cases	
your arms and legs, problems with speaking or feel confused, convulsions, tingling sensation on the skin,; stiff neck associated with headache, extreme sensitivity to bright light			
Fever, unexpected infections, mouth ulcers, bruising, bleeding gums, or extreme tiredness.		✓	
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.			✓
Problems with your eyesight such as blurred or double vision		✓	
Feeling depressed		✓	
Pain in your eyes		✓	
Mental problems such as feeling confused and seeing or hearing things that are not there (hallucinations)	✓		
Numbness, tingling, pain, or a feeling of weakness, in the arms or legs		✓	

HOW TO STORE IT

Keep out of reach and sight of children.

APO-METRONIDAZOLE (Metronidazole Capsules) should be stored between 15°C to 25°C.

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

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting DISpedia, Apotex's Drug Information Service at:

1-800-667-4708

This leaflet can also be found at:
http://www.apotex.ca/products.

This leaflet was prepared by Apotex Inc., Toronto, Ontario, M9L 1T9.

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