For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞ Metronidazole Tablets IP 200 mg / 400 mg
metrogyl® 200 / 400

WARNING
Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided.

COMPOSITION
Each film coated tablet contains:
Metronidazole IP ..... 200 mg
Excipients ..... q.s.
Colour: Ponceau 4R

Each film coated tablet contains:
Metronidazole IP ..... 400 mg
Excipients ..... q.s.
Colour: Sunset Yellow FCF

DOSAGE FORM
Film coated Tablets.

THERAPEUTIC INDICATIONS
Metrogyl is indicated in the prophylaxis and treatment of infections in which anaerobic bacteria have been identified or are suspected to be the cause.
Metrogyl is active against a wide range of pathogenic micro-organisms notably species of *Bacteroides, Fusobacteria, Clostridia, Eubacteria, anaerobic cocci and Gardnerella vaginalis.*
It is also active against *Trichomonas, Entamoeba histolytica, Giardia lamblia and Balantidium coli.*
Metrogyl is indicated in adults and children for the following indications:
- The prevention of post-operative infections due to anaerobic bacteria, particularly species of *Bacteroides* and anaerobic streptococci
- The treatment of septicaemia, bacteraemia, peritonitis, brain abscess, necrotising pneumonia, osteomyelitis, puerperal sepsis, pelvic abscess, pelvic cellulitis, and post-operative wound infections from which pathogenic anaerobes have been isolated
- Urogenital trichomoniasis in the female (*Trichomonal vaginitis*) and in the male
- Bacterial vaginosis (also known as non-specific vaginitis, anaerobic vaginosis or *Gardnerella vaginitis*)
- All forms of amoebiasis (intestinal and extra-intestinal disease and that of symptomless cyst passers)
- Giardiasis
- Acute ulcerative gingivitis
- Anaerobically-infected leg ulcers and pressure sores
- Acute dental infections (e.g. acute pericoronitis and acute apical infections)

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

POSOLOGY AND METHOD OF ADMINISTRATION
1. Prophylaxis against anaerobic infection:
Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.
Adults: 400 mg 8 hourly over the 24 hours immediately preceding the operation followed by post-operative intravenous or rectal administration until the patient is able to take tablets.

Paediatric population
Children < 12 years: 20 – 30 mg/kg as a single dose given 1 – 2 hours before surgery.
Newborns with a gestation age < 40 weeks: 10 mg/kg body weight as a single dose before operation.

2. Anaerobic infections:
The duration of a course of Metrogyl treatment is about 7 days but it will depend upon the seriousness of the patient's condition as assessed clinically and bacteriologically.
Treatment of established anaerobic infection:
Adults: 800 mg followed by 400 mg 8 hourly.

Paediatric population:
Children > 8 weeks to 12 years of age: The usual daily dose is 20 – 30 mg/kg/day as a single dose or divided into 7.5 mg/kg every 8 hours. The daily dose may be increased to 40 mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.
Children < 8 weeks of age: 15 mg/kg as a single dose daily or divided into 7.5 mg/kg every 12 hours.
Newborns with a gestation age < 40 weeks: accumulation of metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.

3. Protozoal and other infections:

Dosage is given in terms of metronidazole or metronidazole equivalent					
	Duration of dosage in days	***Adults and children over 10 years***	***Children***		
			7 – 10 years	***3 – 7 years***	***1 – 3 years***
Urogenital trichomoniasis *(*Where re-infection is likely, in adults the consort should receive a similar course of treatment concurrently)					
	7 Or 5 – 7	2000 mg as a single dose Or 200 mg three times daily or 400 mg twice daily	40 mg/kg orally as a single dose Or 15 – 30 mg/kg/day divided in 2 – 3 doses; not to exceed 2000 mg/kg dose		
Bacterial vaginosis					
	5 – 7 Or 1	400 mg twice daily Or 2000 mg as a single dose	N/A		
Amoebiasis					
(a) Invasive intestinal disease in susceptible subjects	5	800 mg three times daily	400 mg three times daily	200 mg four times daily	200 mg three times daily
(b) Intestinal disease in less susceptible subjects and chronic amoebic hepatitis	5 – 10	400 mg three times daily	200 mg three times daily	100 mg four times daily	100 mg three times daily
(c) Amoebic liver abscess also other forms of extra-intestinal amoebiasis	5				
(d) Symptomless cyst passers	5 – 10	400 – 800 mg three times daily	200 – 400 mg three times daily	100 – 200 mg four times daily	100 – 200 mg three times daily
	Alternatively, doses may be expressed by body weight: 35 – 50 mg/kg daily in 3 divided doses for 5 – 10 days, not to exceed 2400 mg/day				
Giardiasis					
	3 Or 5 Or 7 – 10	2000mg once daily Or 400 mg three times daily Or 500 mg twice daily	1000 mg once daily	600 – 800 mg once daily	500 mg once daily
	Alternatively, as expressed in mg per kg of body weight: 15 – 40 mg/kg/day divided in 2 – 3 doses.				
Acute ulcerative gingivitis					
	3	200 mg three times daily	100 mg three times daily	100 mg twice daily	50 mg three times daily
Acute dental infections					
	3 – 7	200 mg three times daily	N/A		
Leg ulcers and pressure sores					
	7	400 mg three times daily	N/A		
Children and infants <10 kg should receive proportionally smaller dosages. *Elderly:* Metronidazole is well tolerated by the elderly but a pharmacokinetic study suggests cautious use of high dosage regimens in this age group.					

4. Eradication of Helicobacter pylori in paediatric patients:
As a part of a combination therapy, 20 mg/kg/day not to exceed 500 mg twice daily for 7 – 14 days. Official guidelines should be consulted before initiating therapy.

Renal impairment:
The elimination half-life of metronidazole remains unchanged in the presence of renal failure. Therefore, the dosage of metronidazole needs no reduction. However, such patients retain the metabolites of metronidazole. The clinical significance of this is not known at present.
In patients undergoing haemodialysis metronidazole and metabolites are efficiently removed during an eight-hour period of dialysis. Therefore, metronidazole should be re-administered immediately after haemodialysis.
No routine adjustment in the dosage of metronidazole need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).

Hepatic impairment:
Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Significant accumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Therefore, metronidazole should be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

Method of administration
Oral administration, Metrogyl tablets should be swallowed with water (not chewed). It is recommended that the tablets be taken during or after a meal.

CONTRAINDICATIONS
Hypersensitivity
Metrogyl Tablets is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.
In patients with trichomoniasis, Metrogyl Tablets is contraindicated during the first trimester of pregnancy.

Psychotic Reaction with Disulfiram
Use of oral metronidazole is associated with psychotic reactions in alcoholic patients who were using disulfiram concurrently. Do not administer metronidazole to patients who have taken disulfiram within the last two weeks.

Interaction with Alcohol
Use of oral metronidazole is associated with a disulfiram-like reaction to alcohol, including abdominal cramps, nausea, vomiting, headaches, and flushing. Discontinue consumption of alcohol or products containing propylene glycol during and for at least three days after therapy with metronidazole.

Cockayne Syndrome
Metrogyl Tablets are contraindicated in patients with Cockayne syndrome. Severe irreversible hepatotoxicity/acute liver failure with fatal outcomes have been reported after initiation of metronidazole in patients with Cockayne syndrome.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Hypersensitivity Reactions
Hypersensitivity reactions including severe cutaneous adverse reactions (SCARs) can be serious and potentially life threatening.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported with the use of metronidazole. Symptoms can be serious and potentially life threatening. If symptoms or signs of SCARs develop, discontinue Metrogyl tablets immediately and institute appropriate therapy.

Central and Peripheral Nervous System Effects
Encephalopathy and peripheral neuropathy: Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole.
Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, and dysarthria. CNS lesions seen on MRI have been described in reports of encephalopathy. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible.
Peripheral neuropathy, mainly of sensory type has been reported and is characterized by numbness or paresthesia of an extremity.
Convulsive seizures have been reported in patients treated with metronidazole.
Aseptic meningitis: Cases of aseptic meningitis have been reported with metronidazole. Symptoms can occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.
The appearance of abnormal neurologic signs and symptoms demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy.

Precautions
General

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

Renal Impairment
Patients with end-stage renal disease may excrete metronidazole and metabolites slowly in the urine, resulting in significant accumulation of metronidazole metabolites. Monitoring for metronidazole associated adverse events is recommended.

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

Use in Patients with Blood Dyscrasias
Metronidazole is a nitroimidazole and should be used with caution in patients with evidence of or history of blood dyscrasia. A mild leukopenia has been observed during its administration; however, no persistent hematologic abnormalities attributable to metronidazole have been observed in clinical studies. Total and differential leukocyte counts are recommended before and after therapy.

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

Information for Patients

Interaction with Alcohol
Discontinue consumption of alcoholic beverages or products containing propylene glycol while taking Metrogyl and for at least three days afterward because abdominal cramps, nausea, vomiting, headaches, and flushing may occur.

Treatment of Bacterial and Parasitic Infections
Patients should be counseled that Metrogyl should only be used to treat bacterial and parasitic infections. Metrogyl does not treat viral infections (e.g., the common cold). When Metrogyl is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Metrogyl in the future.

Severe Cutaneous Adverse Reactions
Advise patients that Metrogyl tablets may increase the risk of serious and sometimes fatal dermatologic reactions, including TEN, SJS, and DRESS. Instruct the patient to be alert for skin rash, blisters, fever or other signs and symptoms of these hypersensitivity reactions. Advise patients to stop Metrogyl tablets immediately if they develop any type of rash and seek medical attention.

DRUG INTERACTIONS
Disulfiram
Psychotic reactions have been reported in alcoholic patients who are using metronidazole and disulfiram concurrently. Metronidazole should not be given to patients who have taken disulfiram within the last two weeks.

Alcoholic Beverages
Abdominal cramps, nausea, vomiting, headaches, and flushing may occur if alcoholic beverages or products containing propylene glycol are consumed during or following metronidazole therapy.

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

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

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

Drugs that Inhibit CYP450 Enzymes
The simultaneous administration of drugs that decrease microsomal liver enzyme activity, such as cimetidine, may prolong the half-life and decrease plasma clearance of metronidazole.

Drugs that Induce CYP450 Enzymes
The simultaneous administration of drugs that induce microsomal liver enzymes, such as phenytoin or phenobarbital, may accelerate the elimination of metronidazole, resulting in reduced plasma levels; impaired clearance of phenytoin has also been reported.

Drugs that Prolong the QT interval
QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

Drug/Laboratory Test Interactions
Metronidazole may interfere with certain types of determinations of serum chemistry values, such as aspartate aminotransferase (AST, SGOT), alanine aminotransferase (ALT, SGPT), lactate dehydrogenase (LDH), triglycerides, and glucose hexokinase. Values of zero may be observed. All of the assays in which interference has been reported involve enzymatic coupling of the assay to oxidation-reduction of nicotinamide adenine dinucleotide ($NAD^+ \leftrightarrow NADH$). Interference is due to the similarity in absorbance peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

USE IN SPECIFIC POPULATIONS
Pregnancy:

Teratogenic Effects:
There are no adequate and well controlled studies of Metrogyl in pregnant women. There are published data from case-control studies, cohort studies, and 2 meta-analyses that include more than 5000 pregnant women who used metronidazole during pregnancy. Many studies included first trimester exposures. One study showed an increased risk of cleft lip, with or without cleft palate, in infants exposed to metronidazole in-utero; however, these findings were not confirmed. In addition, more than ten randomized placebo-controlled clinical trials enrolled more than 5000 pregnant women to assess the use of antibiotic treatment (including metronidazole) for bacterial vaginosis on the incidence of preterm delivery. Most studies did not show an increased risk for congenital anomalies or other adverse fetal outcomes following metronidazole exposure during pregnancy. Three studies conducted to assess the risk of infant cancer following metronidazole exposure during pregnancy did not show an increased risk; however, the ability of these studies to detect such a signal was limited.
Metronidazole crosses the placental barrier and its effects on the human fetal organogenesis are not known. Reproduction studies have been performed in rats, rabbits, and mice at doses similar to the maximum recommended human dose based on body surface area comparisons. There was no evidence of harm to the fetus due to metronidazole.

Nursing Mothers
Metronidazole is present in human milk at concentrations similar to maternal serum levels, and infant serum levels can be close to or comparable to infant therapeutic levels. There are no data on the effects of metronidazole on milk production. Animal studies have shown the potential for tumorigenicity after oral metronidazole was administered chronically to rats and mice. This drug is not intended to be administered chronically; therefore, the clinical relevance of the findings of the animal studies is unclear. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Metrogyl and any potential adverse effects on the breastfed infant from Metrogyl or from the underlying maternal condition. Alternatively, a nursing mother may choose to pump and discard human milk for the duration of Metrogyl therapy, and for 48 hours after the last dose and feed her infant stored human milk or formula.

Geriatric Use
In elderly geriatric patients, monitoring for metronidazole associated adverse events is recommended. Decreased liver function in geriatric patients can result in increased concentrations of metronidazole that may necessitate adjustment of metronidazole dosage.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established, except for the treatment of amebiasis.

UNDESIRABLE EFFECTS
The following reactions have been reported during treatment with metronidazole:
Central Nervous System: The most serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures, encephalopathy, aseptic meningitis, optic and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur. In addition, patients have reported headache, syncope, dizziness, vertigo, incoordination, ataxia, tinnitus, hearing impairment, hearing loss, confusion, dysarthria, irritability, depression, weakness, and insomnia.
Gastrointestinal: The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping and constipation.
Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of Candida which may occur during therapy.
Dermatologic: Dermatitis bullous, fixed drug eruption, erythematous rash and pruritus.
Hematopoietic: Reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.
Cardiovascular: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval. Flattening of the T-wave may be seen in electrocardiographic tracings.
Hypersensitivity: Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SJS), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.
Renal: Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.
Hepatic: Cases of severe irreversible hepatotoxicity/acute liver failure, including cases with fatal outcomes with very rapid onset after initiation of systemic use of metronidazole, have been reported in patients with Cockayne syndrome (latency from drug start to signs of liver failure as short as 2 days).
Other: Proliferation of Candida in the vagina, dyspareunia, decrease of libido, proctitis, and fleeting joint pains sometimes resembling "serum sickness." Rare cases of pancreatitis, which generally abated on withdrawal of the drug, have been reported.
Patients with Crohn's disease are known to have an increased incidence of gastrointestinal and certain extraintestinal cancers. There have been some reports in the medical literature of breast and colon cancer in Crohn's disease patients who have been treated with metronidazole at high doses for extended periods of time. A cause and effect relationship has not been established. Crohn's disease is not an approved indication for Metrogyl tablets.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

OVERDOSE
Single oral doses of metronidazole, up to 15 g, have been reported in suicide attempts and accidental overdoses. Symptoms reported include nausea, vomiting, and ataxia.
Oral metronidazole has been studied as a radiation sensitizer in the treatment of malignant tumors. Neurotoxic effects, including seizures and peripheral neuropathy, have been reported after 5 to 7 days of doses of 6 to 10.4 g every other day.
Treatment of Overdosage: There is no specific antidote for metronidazole overdose; therefore, management of the patient should consist of symptomatic and supportive therapy.

CLINICAL PHARMACOLOGY
PHARMACOLOGICAL PROPERTIES
Pharmacotherapeutic group: Anti-bacterials for systemic use
ATC code: J01X D01

Pharmacodynamic properties:
Metronidazole, a nitroimidazole, exerts antibacterial effects in an anaerobic environment against most obligate anaerobes. Once metronidazole enters the organism by passive diffusion and activated in the cytoplasm of susceptible anaerobic bacteria, it is reduced; this process includes intracellular electron transport proteins such as ferredoxin, transfer of an electron to the nitro group of the metronidazole, and formation of a short-lived nitroso free radical. Because of this alteration of the metronidazole molecule, a concentration gradient is created and maintained which promotes the drug's intracellular transport. The reduced form of metronidazole and free radicals can interact with DNA leading to inhibition of DNA synthesis and DNA degradation leading to death of the bacteria. The precise mechanism of action of metronidazole is unclear.
Resistance
A potential for development of resistance exists against metronidazole.
Resistance may be due to multiple mechanisms that include decreased uptake of the drug, altered reduction efficiency, overexpression of the efflux pumps, inactivation of the drug, and/or increased DNA damage repair.
Metronidazole does not possess any clinically relevant activity against facultative anaerobes or obligate aerobes.
Antimicrobial Activity
Metronidazole has been shown to be active against most isolates of the following bacteria both in vitro and in clinical infections.

Gram-positive anaerobes
Clostridium species
Eubacterium species
Peptococcus species
Peptostreptococcus species

Gram-negative anaerobes
Bacteroides fragilis group *(B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B.vulgatus)*
Fusobacterium species

Protozoal parasites
Entamoeba histolytica
Trichomonas vaginalis
The following in vitro data are available, **but their clinical significance is unknown:**
Metronidazole exhibits *in vitro* minimal inhibitory concentrations (MIC's) of 8 mcg/mL or less against most (≥90%) isolates of the following bacteria; however, the safety and effectiveness of metronidazole in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-negative anaerobes
Bacteroides fragilis group *(B. caccae, B. uniformis)*
Prevotella species *(P. bivia, P. buccae, P. disiens)*

Pharmacokinetic properties
Absorption
Disposition of metronidazole in the body is similar for both oral and intravenous dosage forms. Following oral administration, metronidazole is well absorbed, with peak plasma concentrations occurring between one and two hours after administration.
Plasma concentrations of metronidazole are proportional to the administered dose. Oral administration of 250 mg, 500 mg, or 2,000 mg produced peak plasma concentrations of 6 mcg/mL, 12 mcg/mL, and 40 mcg/mL, respectively. Studies reveal no significant bioavailability differences between males and females; however, because of weight differences, the resulting plasma levels in males are generally lower.
Distribution
Metronidazole is the major component appearing in the plasma, with lesser quantities of metabolites also being present. Less than 20% of the circulating metronidazole is bound to plasma proteins. Metronidazole appears in cerebrospinal fluid, saliva, and breast milk in concentrations similar to those found in plasma. Bactericidal concentrations of metronidazole have also been detected in pus from hepatic abscesses.
Metabolism/Excretion
The major route of elimination of metronidazole and its metabolites is via the urine (60% to 80% of the dose), with fecal excretion accounting for 6% to 15% of the dose. The metabolites that appear in the urine result primarily from side-chain oxidation [1-(ßhydroxyethyl)-2-hydroxymethyl-5-nitroimidazole and 2-methyl-5-nitroimidazole-1-ylacetic acid] and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total. Both the parent compound and the hydroxyl metabolite possess in vitro antimicrobial activity. Renal clearance of metronidazole is approximately 10 mL/min/1.73 m^2. The average elimination half-life of metronidazole in healthy subjects is eight hours.
Renal Impairment
Decreased renal function does not alter the single-dose pharmacokinetics of metronidazole.
Subjects with end-stage renal disease (ESRD; CL_{cR}= 8.1±9.1 mL/min) and who received a single intravenous infusion of metronidazole 500 mg had no significant change in metronidazole pharmacokinetics but had 2-fold higher C_{max} of hydroxy-metronidazole and 5-fold higher C_{max} of metronidazole acetate, compared to healthy subjects with normal renal function (CL_{cR}= 126±16 mL/min). Thus, on account of the potential accumulation of metronidazole metabolites in ESRD patients, monitoring for metronidazole associated adverse events is recommended.
Effect of Dialysis
Following a single intravenous infusion or oral dose of metronidazole 500 mg, the clearance of metronidazole was investigated in ESRD subjects undergoing hemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A hemodialysis session lasting for 4 to 8 hours removed 40% to 65% of the administered metronidazole dose, depending on the type of dialyzer membrane used and the duration of the dialysis session. If the administration of metronidazole cannot be separated from the dialysis session, supplementation of metronidazole dose following hemodialysis should be considered. A peritoneal dialysis session lasting for 7.5 hours removed approximately 10% of the administered metronidazole dose. No adjustment in metronidazole dose is needed in ESRD patients undergoing CAPD.
Hepatic Impairment
Following a single intravenous infusion of 500 mg metronidazole, the mean AUC_{24} of metronidazole was higher by 114% in patients with severe (Child-Pugh C) hepatic impairment, and by 54% and 53% in patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, respectively, compared to healthy control subjects. There were no significant changes in the AUC_{24} of hydroxyl-metronidazole in these hepatically impaired patients. A reduction in metronidazole dosage by 50% is recommended in patients with severe (Child-Pugh C) hepatic impairment. No dosage adjustment is needed for patients with mild to moderate hepatic impairment. Patients with mild to moderate hepatic impairment should be monitored for metronidazole associated adverse events.
Geriatric Patients
Following a single 500 mg oral or IV dose of metronidazole, subjects >70 years old with no apparent renal or hepatic dysfunction had a 40% to 80% higher mean AUC of hydroxy-metronidazole (active metabolite), with no apparent increase in the mean AUC of metronidazole (parent compound), compared to young healthy controls < 40 years old. In geriatric patients, monitoring for metronidazole associated adverse events is recommended.
Pediatric Patients
In one study, newborn infants appeared to demonstrate diminished capacity to eliminate metronidazole. The elimination half-life, measured during the first 3 days of life, was inversely related to gestational age. In infants whose gestational ages were between 28 and 40 weeks, the corresponding elimination half-lives ranged from 109 to 22.5 hours.

NONCLINICAL TOXICOLOGY
Tumors affecting the liver, lungs, mammary, and lymphatic tissues have been detected in several studies of metronidazole in rats and mice, but not hamsters.
Pulmonary tumors have been observed in all six reported studies in the mouse, including one study in which the animals were dosed on an intermittent schedule (administration during every fourth week only). Malignant liver tumors were increased in male mice treated at approximately 1500 mg/m^2 (similar to the maximum recommended daily dose, based on body surface area comparisons). Malignant lymphomas and pulmonary neoplasms were also increased with lifetime feeding of the drug to mice. Mammary and hepatic tumors were increased among female rats administered oral metronidazole compared to concurrent controls. Two lifetime tumorigenicity studies in hamsters have been performed and reported to be negative.
Metronidazole has shown mutagenic activity in in vitro assay systems including the Ames test. Studies in mammals in vivo have failed to demonstrate a potential for genetic damage.
Metronidazole failed to produce any adverse effects on fertility or testicular function in male rats at doses up at 400 mg/kg/day (similar to the maximum recommended clinical dose, based on body surface area comparisons) for 28 days. However, rats treated at the same dose for 6 weeks or longer were infertile and showed severe degeneration of the seminiferous epithelium in the testes as well as marked decreases in testicular spermatid counts and epididymal sperm counts. Fertility was restored in most rats after an eight-week, drug-free recovery period.

INCOMPATABILITIES
Not applicable.

STORAGE AND HANDLING INSTRUCTIONS:
Protect from light & moisture.

PACKAGING INFORMATION:
Blister of 10 tablets and 20 tablets

Marketed by & ® Regd. Trade Mark of:
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai - 400 030, India.

Note: This prescribing information is applicable for India Market only

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