pharmaniaga™

Metronidazole

Tablet

DESCRIPTION

Pharmaniaga Metronidazole tablet 200 mg
Yellow, round, biconvex, film-coated tablets with 'RMB' breakline on one side and plain on the other.

Pharmaniaga Metronidazole tablet 400 mg
Yellow, round, biconvex tablet with Pharmaniaga icon on one side and plain on the other.

COMPOSITION

Pharmaniaga Metronidazole tablet 200 mg
Each film-coated tablet contains Metronidazole 200 mg.

Pharmaniaga Metronidazole tablet 400 mg
Each tablet contains Metronidazole 400 mg.

ACTIONS

Metronidazole is active against most obligate anaerobic bacteria and protozoa by undergoing intracellular chemical reduction via mechanisms unique to anaerobic metabolism within the organism. Reduced metronidazole, which is cytotoxic but short-lived, interacts with microorganisms DNA to cause a loss of helical structure, strand breakage and resultant inhibition of nucleic acid synthesis and cell death.

Metronidazole is well absorbed orally with a bioavailability of at least 80%. Peak plasma concentrations of 6, 12 and 40 mcg/mL are achieved within 1 to 2 hours of a 250 mg, 500 mg and 2 g single oral doses respectively. Absorption may be delayed, but is not reduced overall by administration with food.

Metronidazole is widely distributed. It appears in most body tissues and fluids including bile, bone, breast milk, saliva, seminal fluid, liver and liver abscesses, lungs and vaginal secretions. It also crosses the placenta and the blood brain barrier. Not more than 20% is bound to plasma proteins.

Metronidazole is metabolised in the liver by side-chain oxidation and glucuronide conjugation to 2-hydroxymethyl (also active) and other metabolites. The half-life of metronidazole in normal adults is 8 hours and in patients with alcoholic liver disease 18 hours.

Metronidazole and its primarily metabolites are rapidly removed from the blood by haemodialysis but is not significantly removed by peritoneal dialysis.

INDICATIONS

Metronidazole is indicated for the treatment of symptomatic trichomoniasis in females and males when the presence of trichomonad has been confirmed by appropriate laboratory procedures (wet smears and/or cultures).

Metronidazole is indicated in the treatment of asymptomatic females when the organism is associated with endocervicitis, cervicitis or cervical erosion. Since there is evidence that presence of the tricomonad can interfere with accurate assessment of abnormal cytological smears, additional smears should be performed after eradication of the parasite.

T. vaginalis infections is a venereal disease. Therefore, asymptomatic sexual partners of treated patients should be treated, simultaneously if the organism has been found to be present, in order to prevent reinfection of the partner. The decision as to whether to treat an asymptomatic male-partner who has negative culture or one for whom no culture has been attempted is an individual one. In making this decision, it should be noted that there is evidence that a woman may become reinfected if her consort is not treated. Also, since there can be considerable difficulty in isolating the organism from the asymptomatic male carrier, negative smears and cultures cannot be relied upon in this regard. In any event, the consort should be treated with metronidazole in cases of reinfection.

Metronidazole is indicated in the treatment of acute intestinal amoebiasis (amoebic dysentery) and amoebic liver abscess.

In amoebic liver abscess, metronidazole therapy does not obviate the need for aspiration or drainage of pus. Metronidazole is indicated in the treatment of serious infections caused by susceptible anaerobic bacteria. Indicated surgical procedures should be performed in conjunction with metronidazole therapy. In a mixed aerobic and anaerobic infection, antimicrobials appropriate for the treatment of the aerobic infection should be used in addition to metronidazole.

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

Intra-abdominal infections, including peritonitis, intra-abdominal abscess, and liver abscess caused by *Bacteroides* species including the *B. fragilis* group *(B. fragilis, B. distasonis, B. ovatus, B. thetaiotaomicron, B. vulgatus), Clostridium* species, *Eubacterium* species*, Peptococcus niger* or *Peptostreptococcus* species.

Skin and skin structure infections caused by *Bacteroides* species including the *B. fragilis* group. *Clostridium* species, *Peptococcus niger, Peptostreptococcus* species or *Fusobacterium* species.

Gynaecologic infections including endometritis, endomyometritis, tubo-ovarian abscess, and postsurgical vaginal cuff infection, caused by *Bacteroides* species including the *B. fragilis* group. *Clostridium* species, *Peptococcus niger* or *Peptostreptococcus* species.

Bacterial septicaemia caused by *Bacteroides* species including the *B. fragilis* group or *Clostridium* species.

Bone and joint infections (as adjunctive therapy) caused by *Bacteroides* species including the *B.fragilis* group.

Central nervous system (CNS) infections, including meningitis and brain abscess, caused by *Bacteroides* species including the *B.fragilis* group.

Endocarditis caused by *Bacteroides* species including the *B. fragilis* group.

CONTRAINDICATIONS

Metronidazole is contraindicated in patients with a prior history of hypersensitivity to metronidazole or other nitroimidazole derivations; in patients with trichomoniasis, during the first trimester of pregnancy.

ADVERSE REACTIONS

The following reactions have also been reported during treatment with metronidazole.

Central Nervous System: Two serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterised mainly by numbness or paraesthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, patients should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur. In addition, patients have reported dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness and insomnia.

Gastro-intestinal: The most common adverse reactions reported have been referable to the gastro-intestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache, anorexia and occasionally vomiting, diarrhoea, epigastric distress; and abdominal cramping. Constipation has also been reported.

A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with sudden overgrowth of Candida which may occur during therapy. Rare cases of pancreatitis, which generally abated on withdrawal of the drug, have been reported.

Haematopoietic: Reversible neutropenia (leucopenia); rarely, reversible thrombocytopenia.

Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.

Hypersensitivity: 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.

Other: Proliferation of Candida in the vagina, dyspareunia, decrease of libido, proctitis and fleeting joint pains sometimes resembling "serum sickness". If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing or headache. A modification of the taste of alcoholic beverages has also been reported.

Patients with Crohn's disease are known to have an increased incidence of gastro-intestinal and certain extra-intestinal 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 metronidazole.

WARNING AND PRECAUTIONS

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 should therefore 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.

WARNING

Convulsive seizures and peripheral neuropathy: Convulsive seizures and peripheral neuropathy, the latter characterised mainly by numbness or paraesthesia of an extremity, have been reported in patients treated with metronidazole.

The appearance of abnormal neurologic signs demands the prompt discontinuation of metronidazole therapy. Metronidazole should be administered with caution to patient with central nervous system disease.

PRECAUTION

Patients with severe hepatic disease metabolise metronidazole slowly, with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Known or previously unrecognised candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.

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Caution is also adviced in patients with active organism CNS disease including epilepsy and in patients with a history of blood dyscrasias.

Pregnancy
Metronidazole crosses the placenta and enters the foetal circulation rapidly. Adequate and well-controlled studies in humans have not been done. Studies in rats, given doses of up to 5 times the human dose, have not shown that metronidazole causes impaired fertility or birth defects in the foetus. Metronidazole, administered intraperitoneally to pregnant mice at approximately the human dose, has been shown to cause foetotoxicity. When administered orally, no foetotoxicity was seen in pregnant mice (FDA Pregnancy Category B). However, the use of metronidazole in the treatment of trichomoniasis is contraindicated during the first trimester. If metronidazole is used during the second and third trimester for trichomoniasis, it is recommended that its use be limited to those patients whose symptoms are not controlled by local palliative treatment. Also, the 1-day course of therapy should not be used since this results in higher maternal and foetal serum concentrations.

Breast-feeding
Metronidazole is distributed into breast milk; concentrations are similar to those found in the maternal plasma. Use is not recommended in nursing mothers since some studies in rats and mice have shown that metronidazole is carcinogenic and may cause adverse effects in the infant. However, use in the treatment of anaerobic bacterial infections or a short course of treatment with metronidazole for amoebiasis, severe periodontal infections, or trichomoniasis may be necessary in nursing mothers. During treatment with metronidazole the breast milk should be expressed and discarded. Breast-feeding may be resumed 24 and 48 hours after treatment is completed.

Paediatrics
When used for the treatment of anaerobic infections and amoebiasis, metronidazole has not demonstrated any paediatrics-specific problems that would limit its usefulness in children.

Geriatrics
No information is available on the relationship of age to the effects of metronidazole in geriatric patients. However, elderly patients are more likely to have an age-related decrease in hepatic function, which may require an adjustment in dosage in patients receiving metronidazole.

DRUG INTERACTIONS
Alcohol
It is recommended that metronidazole not be used concurrently with or for at least 1 day following ingestion of alcohol; accumulation of acetaldehyde by interference with the oxidation of alcohol may occur, resulting in disulfiram-like effect such as abdominal cramps, nausea, vomiting, headache or flushing; in addition, modifications in the taste of alcoholic beverages have been reported during concurrent use.

Anticoagulants, coumarin or indandione-derivative
Effects may be potentiated when these agents are used concurrently with metronidazole, because of inhibition of enzymatic metabolism of anticoagulants; periodic prothrombin time determinations may be required during therapy to determine if dosage adjustments of anti-coagulants are necessary.

Disulfiram
It is recommended that metronidazole not be used concurrently with, or for 2 weeks following disulfiram in alcoholic patients; such use may result in confusion and psychotic reactions because of combined toxicity.

Cimetidine
Hepatic metabolism of metronidazole may be decreased when metronidazole and cimetidine are used concurrently, possibly resulting in delayed elimination and increased serum metronidazole concentrations; monitoring of serum concentrations as a guide to dosage is recommended since dosage adjustment of metronidazole may be necessary during and after cimetidine therapy.

Phenobarbital
Phenobarbital may induce microsomal liver enzymes, increasing metronidazole's metabolism and resulting in a decrease in half-life plasma concentration.

Phenytoin
Metronidazole may impair the clearance of phenytoin, increasing phenytoin's plasma concentration.

Lithium
Concomitant administration may impair clearance of lithium.

DOSAGE AND ADMINISTRATION
Tablets are to be taken with or after food.

Amoebiasis, Balantidiasis, *Blastocystis hominis* infection
Adults : 400 to 800 mg three times daily for 5-10 days.
Children : 35 to 50 mg per kg body-weight daily in divided doses.

Giardiasis
Adults : 2 g daily as a single dose for 3 successive days.
Children : 15 mg per kg body-weight daily in divided doses.

Trichomoniasis
Adults : Single 2 g dose or a 7 day course of 200 mg three times daily or 400 mg twice daily or 2 day course of 800 mg in the morning and 1.2 g in the evening. Sexual partners should be treated concomitantly.

Children : 15 mg per kg body-weight daily in divided doses for 7 days.

Bacterial vaginosis
Adults : Single 2 g dose or 7 day course of 400 mg twice daily.

Acute necrotising ulcerative gingivitis, acute dental infections
200 mg three times daily for 3 days.

Anaerobic bacterial infections
Adults : Initial dose of 800 mg followed by 400 mg every 8 hours for 7 days.
Children : 7.5 mg per kg body-weight every 8 hours.

OVERDOSAGE
Symptoms:
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 sensitiser in the treatment of malignant tumours. 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:
There is no specific antidote for metronidazole overdose, therefore, management of the patient should consist of symptomatic and supportive therapy.

ROUTE OF ADMINISTRATION
Oral

STORAGE CONDITIONS
Store below 30°C.
Keep container tightly closed.
Protect from light.

SHELF LIFE
Product should not be used beyond the expiry date imprinted on the product packaging.

PRESENTATION
Pharmaniaga Metronidazole tablet 200 mg
In bottle of 1000 tablets (for export only).
In blisters of 100 and 500 tablets.

Pharmaniaga Metronidazole tablet 400 mg
In blisters of 500 tablets.

Date of revision: 31st October 2018

PRODUCT REGISTRATION HOLDER/MANUFACTURER:
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