Axcel®

METRONIDAZOLE - 200
TABLET

MAL20032263AZ

COMPOSITION:
Each tablet contains
Metronidazole 200mg

PRESENTATION:
White biconvex, round tablet, with a single score line on one side and marked KOTRA logo on the other, 9.8mm in diameter.

INDICATIONS:
Treatment of protozoal infection, intestinal and extra-intestinal amoebiasis, lambliasis, acute ulcerative gingivitis, urogenital trichomoniasis, giardiasis, and Vincent's infection.

PHARMACOLOGY:
Mechanism of Action:
Metronidazole is a systemic trichomonocide and an effective amoebicide. It is exceedingly active against a wide range of pathogenic micro-organisms, notably *Trichomonas vaginalis* and other species of trichomonas, *Entamoeba histolytica*, *Giardia lamblia*, *Belantidium coli* and the causative organisms of acute ulcerative gingivitis.

Pharmacokinetics:
Metronidazole is usually well absorbed from the gastrointestinal tract after oral administration and widely distributed in body tissues.The biological half-life of Metronidazole is 6.2 hours after administration and the maximum concentrations occur in the serum after 1 to 2 hours and traces are detected after 24 hours. Pharmacologically, Metronidazole appears to be practically inert. Large doses in experimental animals affect neither the cardiovascular system nor respiration. Both unchanged metronidazole and several metabolites including an acid oxidation product and a glucuronide are excreted in the urine. Metronidazole diffuses across the placenta, and is found in the breast milk of nursing mothers in concentrations equivalent to those in the serum.

DOSAGE AND ADMINISTRATION:
To be taken orally.
Children under 12 years and infants should be treated with Axcel Metronidazole-200 Tablets.

For treatment of urogenital trichomoniasis:
For adults and children over 12 years: 200mg thrice daily for 7 days or 800mg in the morning and 1200mg in the evening for 2 days (To prevent re-infection the consort should receive a course of treatment concurrently). Children 7 - 12 years; 100mg 3 times daily; 3 - 7 years: 100mg 2 times daily; 1 - 3 years: 50mg 3 times daily. The dosage of children aged 1 - 12 should be repeated for 7 days.

In amoebiasis of:
a) Invasive intestinal disease in susceptible subjects - For adults and children over 12 years: 800mg 3 times daily for 5 days or 2000mg once daily for 3 days. Children 7 - 12 years : 400mg 3 times daily; 3 - 7 years: 200mg 4 times daily; 1 - 3 years: 200mg 3 times daily. All dosage to be repeated for 5 days in children.

b) Intestinal disease in less susceptible subjects and "chronic amoebic hepatitis" - For adults and children over 12 years: 400mg 3 times daily for 5 days or 2000mg once daily for 2 days. Children 7 - 12 years: 200mg 3 times daily; 3 - 7 years: 100mg 4 times daily; 1 - 3 years: 100mg 3 times daily. All dosage to be repeated for 5 - 10 days in children.

c) Amoebic liver abscess and other forms of extra-intestinal amoebiasis - For adults and children over 12 years: 400mg 3 times daily for 5 days or 2000mg once daily for 2 days. Children 7 - 12 years: 200mg 3 times daily; 3 - 7 years: 100mg 4 times daily; 1 - 3 years: 100mg 3 times daily. All dosage to be repeated for 5 days in children.

d) Symptomless cyst passers - For adults and children over 12 years: 400-800mg 3 times daily. Children 7 - 12 years: 200-400mg 3 times daily; 3 - 7 years: 100-200mg 4 times daily: 1 - 3 years; 100-200mg 3 times daily. All dosage to be repeated for 5 - 10 days.

For Giardiasis:
For adults and children over 12 years: 2000mg. Children 7 - 12 years: 1000mg; 3 - 7 years: 600mg; 1 - 3 years: 400mg. All dosage to be given once daily for 3 days.

For acute ulcerative gingivitis or Vincent's disease:
For adults and children over 12 years: 200mg 3 times daily or 400mg 2 times daily. Children 7 - 12 years: 100mg 3 times daily: 3 - 7 years: 100mg 2 times daily; 1 - 3 years: 50mg 3 times daily. All dosage to be repeated for 3 days.

CONTRAINDICATION:
Known hypersensitivity to nitroimidazoles, metronidazole or any of the excipients.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE:
There is a possibility that after Trichomonas vaginalis has been eliminated a gonococcal infection might persist.

The elimination half-life of metronidazole remains unchanged in the presence of renal failure. The dosage of metronidazole therefore needs no reduction.

Such patients however 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. Metronidazole should therefore 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 (IPD) or continuous ambulatory peritoneal dialysis (CAPD).

Metronidazole is mainly metabolised by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency.

Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of metronidazole for more than 10 days is considered to be necessary and patients should be monitored for adverse reactions, such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, vertigo, convulsive seizures).

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

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 therefore be used after careful benefit-risk assessment and only if no alternative treatment is available.

Liver functions 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.

Cases of severe bullous skin reactions such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalized exanthematous pustulosis (AGEP) have been reported with metronidazole. If symptoms or signs of SJS, TEN or AGEP are present, treatment must be immediately discontinued.

Significant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Metronidazole should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

Use in Pregnancy and Lactation:
Use of metronidazole should be avoided during pregnancy, especially the first trimester and especially high dose regimens. Women taking metronidazole should not breast feed their babies.

SIDE EFFECTS:
The frequency of adverse events listed below is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

Serious adverse reactions occur rarely with standard recommended regimens. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.

Blood and lymphatic system disorders:
Very rare: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
Not known: leucopenia.

Immune system disorders:
Rare: anaphylaxis
Not known: angiodema, urticaria, fever.

Metabolism and nutrition disorders:
Not known: anorexia.

Psychiatric disorders:
Very rare: psychotic disorders, including confusion and hallucinations.
Not known: depressed mood

Nervous system disorders:
Very rare:
- encephalopathy (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug.
- drowsiness, dizziness, convulsions, headaches

Not known:
- during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced.
- septic meningitis

Eye disorders:
Very rare: vision disorders such as diplopia and myopia, which, in most cases, is transient.
Not Known: optic neuropathy/neuritis

Ear and labyrinth disorders:
Not known: hearing impaired/hearing loss (including sensorineural), tinnitus

Gastrointestinal disorders:
Not known: taste disorders, oral mucositis, tongue discolouration/furred tongue (e.g. due to fungal overgrowth), nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea.

Hepatobiliary disorders:
Very rare:
- increase in liver enzymes (AST, ALT, alkaline phosphatase), cholestatic or mixed hepatitis, and hepatocellular injury, sometimes with jaundice and pancreatitis which is reversible on drug withdrawal.
- cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders:
Very rare: skin rashes, pustular eruptions, pruritis, flushing, fixed drug eruption, acute generalized exanthematous pustulosis

Not known: erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Musculoskeletal, connective tissue and bone disorders:
Very rare: myalgia, arthralgia.

Renal and urinary disorders:
Very rare: darkening of urine (due to metronidazole metabolite).

DRUG INTERACTIONS:
Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction.

Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.

Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and metronidazole.

Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Patients receiving phenobarbitone metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.

Metronidazole reduces the clearance of 5-fluorouracil and can therefore result in increased toxicity of 5-fluorouracil.

Patients receiving cyclosporin are at risk of elevated cyclosporin serum levels.Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.

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

OVERDOSAGE AND TREATMENT:
Symptoms of overdosage are as in side effects. Treatment is symptomatic and there is no specific treatment for gross overdosage of the drug. Uneventful recovery has followed attemps at suicide with quantities of 6000mg and 12000mg of metronidazole.

STORAGE:
Keep container well closed. Store below 30^{o}C. Protect from light.

LIST OF EXCIPIENTS:
Lactose, Microcrystalline Cellulose, Sodium Starch Glycolate, Dioctyl Sodium Sulphosuccinate, Povidone K90, Magnesium Stearate, Corn Starch, Aerosil, Isopropyl Alcohol, Purified Water, Opadry II White

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

PACK QUANTITIES:
Available in blister pack of 10 x 10's.

Further information can be obtained from pharmacist, physician or the manufacturer.

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