Winthrop

Metronidazole 500mg

500 mg Tablet

Antiprotozoal

FORMULATION
Each tablet contains
Metronidazole ........................................... 500 mg

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES
Metronidazole is an anti-infective agent belonging to the 5-nitroimidazole group. The antibacterial spectrum of metronidazole concerns exclusively anaerobic microorganisms.

Susceptible species
More than 90% of the species are susceptible
Peptostreptococcus, C. perfringens, C. difficile, Bacteroides fragilis, Bacteroides sp., Fusobacterium, Clostridium sp., Prevotella, Veillonella.

Species with inconstant susceptibility
The susceptibility of the pathogens should be tested by an antibiogram: Bifidobacterium, Eubacterium.

Normally resistant species
More than 50% of the species are resistant:
Propionibacterium, Actinomycetes, Mobilunicus.

The antiparasitic activity concerns: Trichomonas vaginalis, Giardia intestinalis, Entamoeba histolytica.

PHARMACOKINETIC PROPERTIES

Absorption:
Metronidazole is rapidly absorbed following oral administration, at least 80% in less than one hour.
The peak serum concentration achieved following oral administration are similar to those obtained following intravenous administration of equivalent doses.
The oral bioavailability is 100% and is not modified by simultaneous ingestion of food.

Distribution:
Approximately one hour after a single dose administration of 500 mg of metronidazole, the peak serum concentration is, on average, 10 μg/mL.
The plasma half-life is between 8 to 10 hours.
The protein binding is low: <20%.
The volume of distribution is large, on average 40 L (i.e. 0.69 L/kg).
Diffusion of the drug is rapid and extensive with concentrations close to serum levels in the lungs, kidneys, liver, skin, bile, CSF, saliva, seminal fluid and vaginal secretions.
Metronidazole crosses the placental barrier and is excreted in breast milk.

Metabolism:
Metronidazole is primarily metabolized in the liver. Oxidation yields two main metabolites:
• the alcoholic metabolite, the primary metabolite, with a bactericidal activity against anaerobic bacteria equal to approximately 30% of that of metronidazole, and with an elimination half-life of 11 hours.
• the acid metabolite, in small amounts, and with a bactericidal activity approximately equal to 5% of that of metronidazole.

Elimination:
High liver and biliary concentration. Low concentration in the colon.
Little fecal elimination.
Excretion is primarily urinary, shown by the fact that the metronidazole and its oxidation metabolites excreted in the urine account for approximately 35 to 65% of the administered dose.

THERAPEUTIC INDICATIONS
The indications are based on the anti-parasitic and antibacterial activity, and on the pharmacokinetic characteristics of metronidazole.
They are restricted to infections caused by the microorganisms defined above as susceptible to metronidazole:
• Amebiasis
• Urogenital trichomoniasis
• Non specific vaginitis
• Giardiasis
• Curative treatment of medico-surgical infections due to susceptible anaerobic pathogens.
• Prophylaxis against infections caused by susceptible anaerobic pathogens in high risk surgical contexts.
• Conversion from prophylactic or curative injectable treatment of infections due to susceptible anaerobic pathogens.

DOSEAGE AND METHOD OF ADMINISTRATION

Amebiasis
The duration of treatment is 7 consecutive days.
Adults : 1.50 g daily, in 3 divided doses.
Children : 30 to 40 mg/kg/day, in 3 divided doses.
In hepatic amebiasis, at the abscess stage, the abscess must be evacuated concomitantly with metronidazole treatment.

Giardiasis
The duration of treatment is 5 consecutive days.
Adults : 0.750 to 1 g daily.
Children : From 2 to 5 years: 250 mg/day.
From 5 to 10 years: 375 mg/day.
From 10 to 15 years: 500 mg/day.

Trichomoniasis
• In women (urethritis and vaginitis due to trichomonas): single dose of 2 g or 500 mg/day by oral route in two divided doses for 10 days.
Whether or not the partner presents clinical signs of infection with trichomonas vaginalis, he must be treated concurrently, even in the absence of positive laboratory tests.
• In men (urethritis due to trichomonas): 2 g in a single dose or 500 mg by oral route in 2 divided doses for 10 days.

Non-specific vaginitis
500 mg, twice daily for 7 days.
The partner must be treated simultaneously.

Treatment of anaerobic infections
As first line treatment or substitute treatment:
Adults : 1 to 1.5 g/day.
Children : 20 to 30 mg/kg/day.

Surgical chemoprophylaxis
The studies published in the literature do not make it possible to define the ideal protocol for surgical chemoprophylaxis.
Metronidazole must be combined with a product active against Enterobacteria.
One 500 mg dose every 8 hours, the treatment being
begun approximately 48 hours before surgery, appears to be effective. The last dose must be administered at the latest 12 hours before surgery. The goal of chemoprophylaxis is to reduce the bacterial inoculum in the gastro-intestinal tract at the time of surgery; it is therefore useless to continue the antibiotic in the post-operative period, at least by the oral route.

Children: same protocol at a dosage of 20 mg to 30 mg/kg/day.

CONTRAINDICATIONS
Hypersensitivity to imidazoles.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

WARNINGS
- 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 during metronidazole therapy and for at least one day afterwards because of the possibility of a disulfiram-like (Antabuse effect) reaction.

PRECAUTIONS FOR USE
- If for compelling reasons, metronidazole must be administered longer than the usually recommended duration, it is recommended that hemotological tests, especially leucocyte count should be carried out regularly and that patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paresthesia, ataxia, dizziness, convulsive seizures).
- Metronidazole should be administered with caution to patients with hepatic encephalopathy.

**Warnings**
Metronidazole, like any other imidazole derivative, has been shown to be carcinogenic in rodents. Unnecessary use of the drug should therefore be avoided.

**DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS**
Patients should be warned about the potential for confusion, dizziness, hallucinations, or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

**DRUG INTERACTIONS**
Disulfiram: psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.

Alcohol: alcoholic beverages and drugs containing alcohol should not be consumed during metronidazole therapy and for at least one day afterwards because of the possibility of disulfiram-like antabuse effect reaction (flushing, vomiting, tachycardia).

Oral anticoagulant therapy (warfarin type): potentiation of the anticoagulant effect and increased hemorrhagic risk caused by decreased hepatic catabolism. In case of concomitant administration, prothrombin time should be more frequently monitored and anticoagulant therapy adjusted during treatment with metronidazole.

Lithium: Plasma levels of lithium may be increased by metronidazole. Plasma concentration of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

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

Phenytoin or phenobarbital: increased elimination of metronidazole resulting in reduced plasma levels.

5-fluorouracil: reduced clearance of 5-fluorouracil resulting in increased toxicity of 5-fluorouracil.

**PREGNANCY AND LACTATION**

**PREGNANCY**
As metronidazole crosses the placental barrier and as its effects on human fetal organogenesis are not known, its use in pregnancy should be carefully evaluated.

**LACTATION**
As metronidazole is excreted in human milk, unnecessary exposure to the drug should be avoided.

**ADVERSE REACTIONS**
- Gastrointestinal effects
  - epigastric pain, nausea, vomiting, diarrhea.
  - oral mucositis, taste disorders, anorexia.
  - exceptional and reversible cases of pancreatitis
- Hypersensitivity reactions
  - rash, pruritus, flushing, urticaria
  - fever, angioedema, exceptional anaphylactic shocks
  - very rare pustular eruptions
- Peripheral and central nervous system
  - peripheral sensory neuropathy.
  - headaches, convulsions, dizziness, ataxia
- Psychiatric disorders
  - psychotic disorders including confusion, hallucinations
- Visions disorders
  - transient vision disorders such as diplopia, myopia
- Hematology
  - very rare cases of agranulocytosis, neutropenia and thrombocytopenia have been reported.
- Liver
  - very rare cases of reversible abnormal liver function tests and cholestatic hepatitis have been reported.

**CAUTION**
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

**STORAGE**
Store at temperatures not exceeding 30°C.

**PRESENTATION**
Tablets: each containing 500 mg of metronidazole, boxes of 100's

**Manufactured by:**
PT Aventis Pharma, Jakarta, Indonesia
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![Sanofi Aventis Logo]