Flagyl®

Metronidazole

500mg

COMPOSITION :

Flagyl® Forte 500 mg film coated tablets : each contains 500 mg metronidazole.

PHARMACOLOGICAL PROPERTIES :

Pharmacodynamic properties :

Trichomoniacide, anaerobicide

Disposition of Metronidazole given orally or by intravenous injection remains constant, with average elimination time of 8 hours in healthy man. Metronidazole was detected in cerebrospinal fluid, saliva and breast milk in same concentration as in plasma. Metronidazole was also detected in the pus of hepatic abscess.

INDICATION :

- Urethritis and vaginitis due to *Trichomonas vaginalis.*
- Amoebiasis (*Intestinal and hepatic amoebiasis*)
- Prevention of post-operative anaerobic infection.
- Giardiasis due to *Giardia lamblia*

DOSAGE AND ADMINISTRATION :

It is recommended to take tablet during or after meal. Suspension should be taken 1 hour before meal.

Amoebiasis :

- Adults, intestinal amoebiasis : 750 mg, three times daily for 5 to 10 days.
- Adults, hepatic amoebiasis : 750 mg, three times daily for 5 to 10 days.
- Children : 35-50 mg/kg/24 hours, divided into three doses, for 10 days.

Trichomoniasis :

To prevent reinfection, spouse of a patients should be given the same dosage regimen.

- **Adults :** 2 gram, given either as a single dose in one day or 500 mg, two times daily or 250 mg, three times daily for 7 consecutive days.
- **Children :** 15 mg/kg bodyweight daily, divided into three doses, for 7 to 10 days.

Giardiasis :

- **Adults :** 250 mg to 500 mg, three times daily for 5 to 7 days or 2 gram daily as a single dose for 3 days.
- **Children :** 5 mg/kg bodyweight three times daily for 5 to 7 days.

Anaerobic bacterial infections :

In serious infection, metronidazole intravenous has to be given as an initial treatment.

Adults : 7.5 mg/kg every 6 hours (approximately 500 mg for a 70 kg adult), maximum 4 gram daily for 7 to 10 days.

WARNINGS AND PRECAUTIONS :

- Used with caution in nursing mothers as metronidazole is excreted in breast milk, during first and second trimesters of pregnancy as metronidazole crosses the placental barrier.
- 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. Disturbances of central nervous system has been reported in some cases but disappeared if therapy is discontinued or dose decreased.
- 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.
- Patients with Cockayne Syndrome

  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 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.
- The use of Flagyl® for prolonged treatment duration should be carefully weighed.
- If for compelling reasons, metronidazole must be administered longer than the usually recommended duration, it is recommended that hematological 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).
- Dosage should be reduced and administered with caution to patients with hepatic diseases.
- Flagyl® should be administered with caution to patients with hepatic encephalopathy
- Safety and effectiveness in pediatric patients have not been established, except in the treatment of amoebiasis.

- Patients should be warned that metronidazole may darken urine (due to metronidazole metabolite).
- 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, Flagyl treatment must be immediately discontinued.
- Central nervous system

  If symptoms suggestive of encephalopathy or cerebellar syndrome occur (for example, ataxia, dysarthria, gait disturbance, nystagmus, tremor, vertigo, confusion, convulsions, peripheral sensory neuropathy, headache (see section **ADVERSE REACTIONS**), the patient's treatment must be immediately reassessed, and therapy with metronidazole must be discontinued.
- Interference with paraclinical examinations and laboratory tests

  Metronidazole may interfere with certain types of blood tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH], triglycerides, glucose), which may lead to a false negative or an abnormally low result. These analytical methods are based on a decrease in ultraviolet absorbance, which occurs when hydrogenated nicotinamide adenine dinucleotide (NADH) is oxidised to nicotinamide adenine dinucleotide (NAD). This interference is due to the similarity of the absorption peaks of NADH (340 nm) and metronidazole (322 nm) at pH 7.

ADVERSE REACTIONS :

Gastrointestinal disorders
- epigastric pain, nausea, vomiting, diarrhea.
- oral mucositis, taste disorders, anorexia.
- reversible cases of pancreatitis.
- tongue discoloration/furry tongue (e.g. due to fungal overgrowth).

Immune system disorders
- angioedema, anaphylactic shock.

Nervous system disorders
- peripheral sensory neuropathy.
- headache, convulsions, dizziness.
- reports of encephalopathy (e.g. confusion) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus, and tremor), which may resolve with discontinuation of the drug.
- aseptic meningitis.

Psychiatric disorders
- psychotic disorders including confusion, hallucinations.
- depressed mood

Eye disorders

- transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision.
- optic neuropathy/ neuritis.

Ear and Labyrinth disorders

- hearing impaired/hearing loss (including sensorineural)
- tinnitus

Blood and lymphatic system disorders

- cases of agranulocytosis, neutropenia and thrombocytopenia have been reported.
- Mild reversible leucopenia in some patients 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.

Skin and subcutaneous tissue disorders

- rash, pruritus, flushing, urticaria.
- pustular eruptions, acute generalized exanthematous pustulosis
- fixed drug eruption
- Stevens-Johnson syndrome, toxic epidermal necrolysis.

General disorders and administration site conditions

- Fever

Cardiac disorders

- Not known: Cases of QT interval prolongation have been reported, particularly when metronidazole is administered with medicinal products that may prolong the QT interval.

OVERDOSAGE :

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. There is no specific antidote for metronidazole overdosages. In case of suspected massive overdosages, a symptomatic and supportive treatment should be instituted.

CONTRAINDICATIONS :

- Hypersensitivity to imidazoles
- During the first trimester of pregnancy

DRUG INTERACTIONS :

- It is recommended to use metronidazole as single drug. In combination with other antibiotic, both should be given in a full dose for normal therapy
- **Cimetidine** might prolonged metronidazole plasma clearance which lead to toxic concentration of metronidazole.
- Psychotic reaction has been reported when concomitant metronidazole, disulfiram and alcohol was taken simultaneously.
- **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 therapy and for at least one day afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction (flushing, vomiting, tachycardia).
- **Oral anticoagulant therapy** (warfarin type) : potention of the anticoagulant effect and increased hemorrhagic risk caused by decreased hepatic catabolism. In case of coadministration, 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.
- **Ciclosporin :** risk of elevation of ciclosporin serum levels. Serum ciclosporin and serum creatine 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.
- **Busulfan :** Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.
- **Drug causing QT interval prolongation**
  Cases of QT interval prolongation have been reported, particularly when metronidazole is administered with medicinal products that may prolong the QT interval.

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.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDAUS TASKS :

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

CARCINOGENICITY :
Metronidazole has been shown to be carcinogenic in the mouse and in the rat. However similar studies in the hamster have given negative results and extensive human epidemiological studies in humans have provided no evidence of an increased carcinogenic risk in humans. Therefore, the use of Flagyl® for longer treatment than usually required prolonged treatment duration should be carefully weighed.

MUTAGENICITY :
Metronidazole has been shown to be mutagenic in bacteria *in vitro*. In studies conducted in mammalian cells *in vitro* as well as in rodent or humans *in vivo*, there was inadequate evidence of a mutagenic effect of metronidazole, with some studies reporting mutagenic effects, while other studies were negative. Therefore, the use of Flagyl® for longer treatment than usually required prolonged treatment duration should be carefully weighed.

Shelf life
3 years

Storage :
Store below 30°C
Protected from light

PRESENTATIONS :
FLAGYL FORTE 500 mg tablet
Box of 10 blisters @ 10 film coated tablets.
Reg.No.DKL0121200717A1

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:
PT Aventis Pharma, Jakarta,Indonesia