RANCANGAN LEAFLET

Flagystatin®
Metronidazole & Nystatin

sanofi

Composition
Each ovule contains 500 mg metronidazole and 100,000 I.U. nystatin.
Excipients: semi-synthetic glycerides.

Pharmacological Properties
Fungicide and bactericide, i.e. *Trichomonacide and anti-candidiasis*.

Indications
Mixed vaginal infections due to *Trichomonas vaginalis and Candida albicans*.

Dosage
One ovule daily, inserted deep into the vagina for 7 to 10 days.
Preferably, Flagyl oral tablets 250 mg twice daily should be given together with Flagystatin during the same period. Only in rare case a secondary course of treatment should be necessary.

Warnings and Precautions
- Where there is evidence of trichomonal infection in the male consort, he should be treated concurrently with oral Flagyl tablet to avoid re-infection.
- Should not be given during the first trimester of pregnancy. On second and third trimester, only to be used as paliative therapy.
- Therapy should be discontinued whenever irritation occured.
- As metronidazole is carcinogenic in mouse, it should be used only for the above mentioned indication.
- 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.

- 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, vertigo, convulsive seizures).
- Severe cutaneous adverse reactions (SCARs): Serious skin reactions including Stevens- Johnson syndrome (SJS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with FLAGYSTATIN treatment (see Adverse Reaction section). Cases of severe bullous skin reactions such as toxic epidermal necrolysis (TEN) have been reported with metronidazole (see Adverse Reactions section). Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of skin hypersensitivity.
- For systemic and pessary formulations only
  Cases of suicidal ideation with or without depression have been reported during treatment with Flagystatin. Patients should be advised to discontinue treatment and contact their healthcare provider immediately if they experience psychiatric symptoms during treatment.

Contraindications
No absolute contraindications, but should be used with care for hypersensitivity patients to any of the components.

Driving a Vehicle or Performing Other Hazardous Tasks
Patients should be warned about the potential for confusion, dizziness, vertigo, hallucinations, convulsions or eye disorders (see Section Adverse Reactions) and advised not to drive or operate machinery if these symptoms occur.

Adverse Reactions
Gastrointestinal disorders
- Tongue discoloration/furry tongue (e.g. due to fungal overgrowth).

Nervous system disorders
- Reports of encephalopathy (e.g. confusion, vertigo) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus, and tremor), which may resolve with discontinuation of the drug.
- Headache
- Peripheral sensory neuropathy
- Convulsions
- Dizziness
- Aseptic meningitis
- Frequency not known: vertigo

Eye disorders

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

Blood and lymphatic system disorders
- Cases of agranulocytosis, neutropenia and thrombosytopenia have been reported

Ear and Labyrinth disorders
- Hearing impaired/hearing loss (including sensorineural)
- Tinnitus

Cardiac disorders
- Frequency not known: QT prolongation has been reported, particularly when metronidazole was administered with drugs with the potential for prolonging the QT interval.

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
Metronidazole: Hypersensitivity reactions including flushing, urticaria and pustular eruptions, acute generalized exanthematous pustulosis (AGEP). Rash and pruritus, fixed drug eruption. Cases of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. Many of these case reports revealed the use of concomitant medications known to be associated with SJS or TEN.

Nystatin: Local irritation or sensitizations have been reported after local application, treatment should be stopped if such reaction occurs. Skin reactions may occur; particularly Stevens-Johnson Syndrome (SJS) and acute generalized exanthemous pustulosis (AGEP) have been reported.

Interactions
Applies only to metronidazole:

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): Potentiation 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.

Cyclosporin: Risk of elevation of 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.

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

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

Interferences with Laboratory and Diagnostic Test
Interference with laboratory tests:

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

Storage
Store in a cool place (15° - 25°C)

Presentation
Box of 2 Strips @ 5 Vaginal Ovules
Reg. No. DKL0121201550A1

ON MEDICAL PRESCRIPTION ONLY
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Date of text revisions
As on approval date