Flagystatin®

Metronidazole & Nystatin

PRESENTATION

Vaginal Ovules: Each ovule contains metronidazole 500 mg and nystatin 100,000 units. Tartrazine-free.

INDICATIONS

Mixed vaginal infection due to *Trichomonas vaginalis* and *C. albicans.*

CONTRAINDICATIONS

Hypersensitivity to FLAGYSTATIN (metronidazole and nystatin), or to imidazoles, or any of its constituents, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

Combined treatment with oral metronidazole should be avoided in cases of active neurological disorders or a history of blood dyscrasia, hypothyroidism or hypoadrenalism unless, in the opinion of the physician, the benefits outweigh the possible hazard to the patient.

SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings 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, FLAGYSTATIN should therefore only be used after careful benefit-risk assessment and only if no alternative treatment is available (see 7 WARNINGS AND PRECAUTIONS).

DOSAGE

One vaginal ovule daily, inserted deep into vagina, before retiring for 10 consecutive days. In order to facilitate disintegration, moisten the vaginal tablet under water for a second or two just before introduction in the vagina.
If after 10 days of treatment a cure has not been achieved, a second 10 day course of treatment should be given. If Trichomonas vaginalis has not been completely eliminated, oral metronidazole 250 mg should be administered twice daily for 10 days.

The applicator should not be used after the 7th month of pregnancy.

OVERDOSAGE

Symptoms

No case of accidental massive ingestion of FLAGYSTATIN has been reported yet. However, 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.

The administration of massive peroral nystatin doses can as well induce gastrointestinal disorders (nausea, vomiting, and diarrhea).

Treatment

There is no specific antidote. Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

For management of a suspected drug overdose, contact your regional poison control centre.

DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Vaginal ovules	500 mg of metronidazole and 100,000 units of nystatin	glycerides of saturated fatty acid (hard fat).

Available in boxes of 10 ovules with applicator.

WARNINGS AND PRECAUTIONS

Please see SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Metronidazole has been shown to be carcinogenic in mice and rats (see NON-CLINICAL TOXICOLOGY section). Unnecessary use of the drug should be avoided and prolonged treatment duration should be carefully weighed. Its use should be reserved for the conditions described in the INDICATIONS section.

Nystatin possesses little or no antibacterial activity while metronidazole is selective against certain anaerobic bacteria; therefore, FLAGYSTATIN may not be effective in bacterial vaginal infections.

Primary resistance to nystatin is rare; cross-resistance with other polyene antibiotics has been reported.

Nystatin is not absorbed from mucous membranes; therefore, no systemic effect is expected (see CLINICAL PHARMACOLOGY section). Local irritation or sensitizations have occasionally been reported after local application. If this occurs, it is recommended to stop the treatment (see ADVERSE REACTIONS section).

FLAGYSTATIN should not be prescribed unless there is direct evidence of trichomonal infestation or candidiasis.

Once candidiasis has been confirmed, care must be taken to investigate the possible factors that could promote fungal growth. To avoid recurrences, it is essential to eradicate or offset these promoting factors.

It is recommended to treat all sites associated with *Candida* concomitantly (e.g. intestinal and vaginal or other infections).

Patients should be warned against consuming alcohol, during FLAGYSTATIN therapy and for at least one day afterward, because of a possible disulfiram-like reaction related to the metronidazole.

Driving and Operating Machinery

Patients should be advised not to drive or operate machinery due to the potential for confusion, dizziness, vertigo, hallucinations, convulsions or eye disorders when treated with metronidazole.

Hematologic

Although no persistent hematologic abnormalities have been observed in clinical studies, total and differential leukocyte counts should be made before and after treatment, especially if a second course of metronidazole therapy is needed.

Hepatic/Biliary/Pancreatic

FLAGYSTATIN, a metronidazole containing preparation, should be used with great caution in patients with a history of hepatic enzyme increase or liver injury associated with previous administration of metronidazole (see ADVERSE REACTIONS section).

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, FLAGYSTATIN should therefore only 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 FLAGYSTATIN (see SERIOUS WARNINGS AND PRECAUTIONS BOX and ADVERSE REACTIONS).

FLAGYSTATIN should be administered with caution to patients with hepatic encephalopathy. Patients with severe hepatic disease metabolize metronidazole slowly with resultant accumulation of metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses of FLAGYSTATIN below those usually recommended should be administered and with caution.

Patients should be warned that FLAGYSTATIN may darken urine (due to metronidazole metabolite).

Monitoring and Laboratory Tests

Metronidazole may interfere with certain types of blood test determinations in blood which may lead to false negative or an abnormally low result (see DRUG INTERACTIONS).

Neurologic

Patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paresthesia, ataxia, dizziness, vertigo, and convulsive seizures) related to metronidazole.

FLAGYSTATIN 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 related to metronidazole.

Treatment with metronidazole should be discontinued if ataxia or any other symptom of CNS involvement occurs.

Psychiatric

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.

Reproductive Health: Female and Male Potential

Where there is evidence of trichomonal infestation in the sexual partner, he should be treated concomitantly with oral metronidazole to avoid reinfestation.

The effectiveness of condoms or diaphragms could be impaired by some of the fatty constituents contained in nystatin and metronidazole gynaecological ovule, therefore their use during FLAGYSTATIN treatment is not recommended.

Treatment should not be stopped during menstruation.

Vaginal injection, menstrual tampons and soaps with an acid pH (for personal hygiene use) should not be used during treatment because they may promote fungal replication.

It is possible that adverse effects normally associated with oral administration of metronidazole or nystatin may occur following the vaginal administration of FLAGYSTATIN.

Sensitivity/Resistance

Development of Drug-Resistant Organisms

Prescribing FLAGYSTATIN in the absence of a proven or strongly suspected mixed vaginal infection is unlikely to provide benefit to the patient and risks the development of resistant organisms.

Potential for Microbial Overgrowth

Prolonged use of FLAGYSTATIN may result in overgrowth of non-susceptible bacteria and fungi. If the infection is not improved following 2 treatment courses of 10 days, cultures should be obtained to guide further treatment. If such infections occur, discontinue use and institute alternate therapy.

Skin

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 REACTIONS 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.

Special Populations

Pregnant Women

Metronidazole: Metronidazole passes the placental barrier. Although it has been given to pregnant women without apparent complication, its effects on human fetal organogenesis are not known; it is advisable that its use be avoided in pregnant patients and the drug be withheld during the first trimester of pregnancy.

Nystatin: No reliable teratogenicity data related to nystatin administration from animal studies is available. Use of nystatin should be avoided unless the benefits to the mother outweigh the potential risks to the fetus or baby.

The applicator should not be used after the 7th month of pregnancy.

Breast-feeding

Metronidazole: As metronidazole is excreted in human milk, exposure to the drug should be avoided.

Nystatin: No data is available whether nystatin enters the breast milk.

ADVERSE REACTIONS

Adverse reaction overview

They are infrequent and minor: vaginal burning and granular sensation. Bitter taste, nausea and vomiting, already known to occur with metronidazole, were mainly seen when oral metronidazole was administered concomitantly with FLAGYSTATIN local treatment.

Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In the course of clinical trials with FLAGYSTATIN, reactions, not necessarily related to the product, were observed: spots on the skin around the knees, welts all over the body, aching and swelling of wrists and ankles, pruritis, headache, coated tongue and fatigue.

Other adverse events related to metronidazole, usually observed after oral or I.V. administration of metronidazole, and to nystatin include:

Blood and lymphatic system disorders

Metronidazole: Transient eosinophilia, neutropenia, cases of agranulocytosis and thrombocytopenia have been reported.

Cardiac disorders

Metronidazole: Palpitation and chest pain

Eye disorders

Metronidazole: Transient vision disorders such as diplopia, myopia, blurred vision, decreased visual acuity, changes in color vision. Optic neuropathy/neuritis has been reported.

Ear and labyrinth disorders

- hearing impairment/hearing loss (including hypoacusis, deafness, deafness neurosensory)
- tinnitus

Gastrointestinal disorders

Metronidazole: Diarrhea, nausea, vomiting, epigastric distress, epigastric pain, dyspepsia, constipation, tongue discoloration/coated tongue, dry mouth, taste disorders including metallic taste, oral mucositis. Reversible cases of pancreatitis have been reported.

General disorders and administration site conditions

Metronidazole: Thrombophlebitis has occurred with I.V. administration. Fever has been reported.

Hepatobiliary disorders

Metronidazole: 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.

Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome, in patients with Cockayne syndrome have been reported with products containing metronidazole.

Immune system disorders

Metronidazole: Angioedema, anaphylactic shock.

Nystatin: Hypersensitivity reactions may occur. Local irritation or sensitizations have been reported after local application. Skin reactions may occur; particularly, Stevens-Johnson Syndrome has been reported

Infections and infestations

Metronidazole: Cases of pseudomembranous colitis have been reported.

Metabolism and nutrition disorders

Metronidazole: Anorexia has been reported.

Nervous system disorders

Metronidazole: Convulsive seizures, peripheral sensory neuropathy, transient ataxia, dizziness, drowsiness, insomnia, headache, aseptic meningitis.

Reports of encephalopathy (e.g. confusion, vertigo) and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait impairment, nystagmus, and tremor) have been reported, which may resolve with discontinuation of the drug.

Psychiatric disorders

Metronidazole: Psychotic disorders including confusion, hallucinations. Depressed mood.

Reproductive system disorders

Vaginal burning sensation.

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 exanthematous pustulosis (AGEP) have been reported.

Other

Metronidazole: Proliferation of *Candida albicans* in the vagina, vaginal dryness and burning; dysuria; and headaches. Reversible lowering of serum lipids has been reported. A case of gynecomastia has been reported which resolved on discontinuing metronidazole administration.

Nystatin: Nystatin is not absorbed from mucous membranes; therefore, no systemic manifestations are observed after local application of the product (see CLINICAL PHARMACOLOGY section).

Post-Market Adverse Reactions

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

Nervous system disorders
Metronidazole: Vertigo.

DRUG INTERACTIONS

Drug Interactions Overview

The drugs listed are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Precautions must be borne in mind, as it is possible that drug interactions usually associated with oral administration of metronidazole or nystatin may occur following the vaginal administration of FLAGYSTATIN.

Drug-Behavioural Interactions

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).

Drug-Drug Interactions

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

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

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

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.

5 Fluorouracil: reduced clearance of 5 fluorouracil resulting in increased toxicity of 5 fluorouracil (coadministration 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.

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

Phenytoin or phenobarbital: increased elimination of metronidazole resulting in reduced plasma levels. Patients maintained on phenytoin were found to have toxic blood levels after oral metronidazole administration. Phenytoin concentration returned to therapeutic blood level after discontinuance of metronidazole.

Vecuronium: A slight potentiation of the neuromuscular blocking activity of vecuronium has been reported in patients administered metronidazole at a dose of 15 mg/kg.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Test Interactions

Interference with laboratory tests:

Metronidazole may interfere with certain types of blood test determinations in blood (alanine 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. (See WARNINGS AND PRECAUTIONS section).

CLINICAL PHARMACOLOGY

Mechanism of Action

Metronidazole is bactericidal against anaerobic bacteria; it exerts trichomonacidal activity and is also active against Giardia lamblia and Entamoeba histolytica. Its exact mechanism of action has not been entirely determined as yet. It has been proposed that an

intermediate in the reduction of metronidazole, produced only in anaerobic bacteria and protozoa is bound to deoxyribonucleic acid and electron-transport proteins, inhibits subsequent nucleic acid synthesis.

At present, the mechanism by which topical metronidazole reduces the lesions and erythema associated with acne rosacea is not precisely known. Despite the established antimicrobial effects of metronidazole, there is no evidence that the suppression of bacteria or parasitic mites harbored in the skin is directly responsible for its beneficial effects in rosacea. In vitro and in vivo studies indicate that metronidazole has direct anti-inflammatory activity and affects neutrophil chemotaxis and cell-mediated immunity. An antioxidant action via inhibition of neutrophil-generated reactive oxygen species has also been demonstrated; this action is believed to underlie its anti-inflammatory effect. It has been proposed that the reduction in rosacea lesions and erythema is the result of anti-inflammatory or immunosuppressive actions of metronidazole.

Nystatin is an antifungal antibiotic, produced by a strain of Streptomyces noursei, active against yeasts and yeast like fungi, including Candida albicans. The antifungal activity is probably due to the binding of sterols in the cell membrane of the fungus with a resultant change in membrane permeability allowing leakage of intracellular components. Nystatin has no appreciable activity against bacteria.

Pharmacodynamics

Metronidazole shows little or no effect on the cardiovascular, respiratory or autonomic nervous systems of dogs, rats and mice.

In vitro, activity was studied using decreasing concentrations of metronidazole which were added to a series of Trichomonas vaginalis cultures maintained at 37ºC. A 1:400,000 dilution of metronidazole kills up to 99% of the trichomonads in 24 hours.

In vivo, 0.5 mL of a 48-hour culture of Trichomonas vaginalis injected under the dorsal skin in a control and a test group of mice revealed, seven days later, extensive abscess-like lesions swarming with trichomonads in the control group and normal subcutaneous tissue free of trichomonads in the animals which had received oral metronidazole in a daily dosage of 12.5 mg/kg of body weight.

In vitro, nystatin is fungistatic against Candida albicans at a concentration of 3.12 mcg/mL (4.4-6.2 U/mL) in liquid medium. A fungicidal activity is observed after a 5-hour contact with 1000 mcg/mL (1400-2000 U/mL) or after 24 hours with 100 mcg/mL (140-200 U/mL).

In vivo, rabbits were infested by the oral route with 2.5 x 108 cells of C. albicans. The administration of 50 mg/kg (100,000 U/kg) per os for 3 days reduced the number of organisms found in the feces from a few millions to less than 20 yeast cells per g.

Mortality in rabbits infested with C. albicans by the I.V. route is usually 100%. It is reduced to 62.5% when 20 mg (40,000 I.U.) is administered twice daily by the S.C. route for 4 days.

Metronidazole and nystatin do not show antagonism in vitro. It was demonstrated that, when used in combination, (in the proportion of 5 mcg of metronidazole to 1 unit of nystatin as in FLAGYSTATIN vaginal inserts) nystatin does not alter the antitrichomonal activity of metronidazole and that metronidazole does not affect the anticandidal activity of

nystatin. Furthermore, the presence of excessive amounts of either product failed to alter the specific effectiveness of the other.

It was also shown that both FLAGYSTATIN vaginal inserts and ovules and metronidazole/nystatin cream exert antitrichomonal and anticandidal activities comparable to those of the individual components.

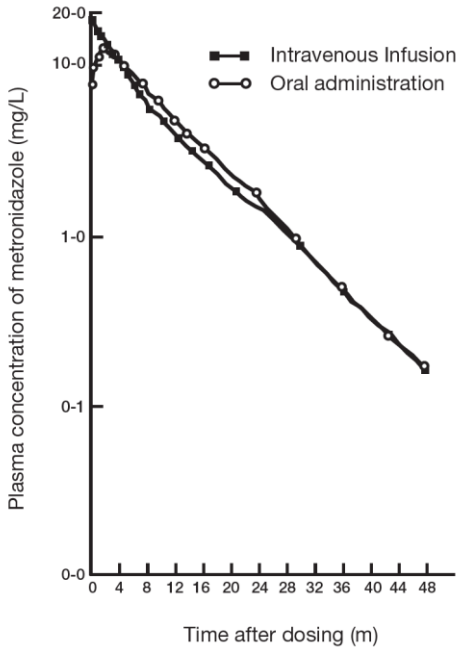
Pharmacokinetics

Absorption and Distribution

Following oral administration, metronidazole is completely absorbed with plasma concentration usually reaching a peak within 1 to 2 hours. After single oral 500 mg doses, peak plasma levels of approximately 13 mg/L were obtained. On a regimen of 500mg t.i.d. administered by the i.v. route, a steady state was achieved after approximately three days. The mean peak and trough concentrations measured at that time were 26 and 12 mg/L respectively, and the elimination half-life was approximately 7 to 8 hours. Comparison of the pharmacokinetics of oral and i.v. metronidazole revealed that the area under the plasma metronidazole concentration against time curves were essentially identical.

There is negligible percutaneous absorption following topical application of metronidazole 1% cream. In healthy volunteers who applied a single 100 mg dose of 14C-labelled metronidazole 2% cream to intact skin, no metronidazole could be detected in plasma after 12 hours. Only about 1% and 0.1% of the applied dose could be found in urine and feces, respectively. After once-daily application of the 1% cream for 1 month, only traces (about 1% of the C_{max} of a 200 mg oral dose) could be detected in 25% of patients. In the rest of the patients, no detectable plasma levels were found.

Figure 1 – Mean plasma metronidazole concentrations following a single oral or intravenous dose of metronidazole (500 mg) (n= 9 females)



In two kinetic studies in which a single metronidazole 1.5 g dose was infused intravenously over a 50-60 minutes period in volunteers, a peak level of 30-40 mg/L was

obtained 1 hour after the start of infusion and fell to 10 mg/L at 12 h and 4 mg/L at 24 hour.

Metabolism and Elimination

The major route of elimination of metronidazole and its metabolites is via the urine (60-80% of the dose) with fecal excretion accounting for 6 to 15% of the dose. The metabolites that appear in the urine result primarily from side chain oxidation (i.e. 1-(ß-hydroxyethyl)-2-hydroxymethyl-5- nitroimidazole and 2-methyl-5 nitroimidazole-1-yl-acetic acid) and glucuronide conjugation, with unchanged metronidazole accounting for approximately 20% of the total.

Metronidazole is the major component appearing in the plasma with lesser quantities of the 2-hydroxymethyl metabolite also being present. The ratio of these components varies with time but the maximum concentration of the metabolite (C_{max}) is approximately 20% of the C_{max} of metronidazole for the oral route of administration.

Protein Binding:

Less than 20% of the circulating metronidazole is bound to plasma proteins.

Tissue Distribution:

The concentrations of metronidazole found in various tissues and body fluids are given in the following Table 2.

Table 2 – Concentrations of metronidazole in various tissues and body fluids

TISSUE OR FLUID	DOSE ADMINISTERED	TISSUE OR FLUID LEVEL	PLASMA LEVEL
Bile	500 mg q.i.d. p.o. x 10 days	26 mg/L (on day 5) 20 mg/L (on day 15)	N/A* N/A
Saliva	500 mg p.o. single dose	7 mg/L (at 2-3 hour)	N/A
Placenta	250 mg p.o. single dose	0 to 1.4 mg/kg (at 4-5 hour)	3.0 - 6.9 mg/L (maternal)
Embryo	250 mg p.o. single dose	0 - 1.0 mg/kg	3.0 - 6.9 mg/L (maternal)
Breast milk	200 mg p.o.	1.3 to 3.4 mg/L	1.8 - 3.9 mg/L
Cerebrospinal fluid	500 mg p.o. b.i.d.	11.0 to 13.9 mg/L	8.3 - 15.4 mg/L
Pus (brain abscess)	400 mg p.o. t.i.d. 600 mg i.v. t.i.d.	35 mg/L inflamed meninges 43 mg/L	N/A N/A
Pus (pulmonary empyema)	400 mg, p.o. q.i.d.	24.2 mg/L	N/A

* Not available

Decreased Renal Function:

Decreased renal function does not appear to alter the single dose pharmacokinetics of metronidazole, although the elimination half-life of the metabolites is prolonged.

Haemodialysis

During haemodialysis, the hydroxy metabolite is removed from the plasma about three times more rapidly than in normal subjects. Comparison of the elimination half-lives of metronidazole and two metabolites are given in the following Table 3.

Table 3 – Metronidazole elimination in normal subjects and in patients with renal insufficiency following a single intravenous dose of metronidazole (500 mg)

	ELIMINATION HALF LIFE (hours)		
	Patients		
Compound	**Normal Subjects**	**on dialysis**	**between dialysis**
Metronidazole	7.3 ± 1.0	2.6 ± 0.7	7.2 ± 2.4
1-(β-hydroxyethyl) 2-hydroxymethyl-5 nitroimidazole	9.8 ± 1.3	7.8 ± 4.1	34± 43
2-methyl-5-nitroimidazole-1-yl-acetic acid	--	7.9 ± 4.1	138 ± 82

Therefore, no accumulation should occur in anuric patients undergoing regular dialysis.

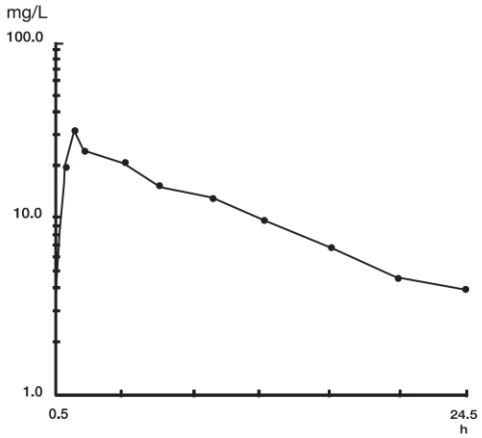
Continuous Ambulatory peritoneal dialysis

Metronidazole was given I.V. at 750 mg to five patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Insignificant changes were noted in the pharmacokinetic parameters of metronidazole (apparent volume of distribution, elimination half-life, total body clearance). Peritoneal dialysis does not appear to reduce the serum levels of metronidazole metabolites.

Impaired Liver Function:

In patients with impaired liver function, the plasma clearance of metronidazole is decreased and accumulation can therefore result.

Figure 2 – Mean plasma metronidazole concentration following a single intravenous dose of metronidazole (1.5 g) (n=10)



Nystatin is not absorbed from mucous membranes; therefore, no systemic manifestations are observed after local application of the product.

NON-CLINICAL TOXICOLOGY

General Toxicology:

Local Tolerance
FLAGYSTATIN vaginal inserts were administered daily to six female Rhesus monkeys for thirty days. As compared with a control group given a placebo insert, no significant compound-related effects were observed with respect to appearance, behavior, signs of toxicity, hematological or biochemical values. No distinctive consistent gross or microscopic alterations in the vagina or cervix of treated animals were seen.

Acute Toxicity
The acute toxicity of metronidazole by the oral route is 4.35 g/kg of body weight in the mouse and 5 g/kg in the rat.

Orally, doses of 7.68 million units/kg of nystatin in rats and of 8.1 to 12.5 million units/kg in mice were still non-toxic. By the I.P. route, the LD50's were in the range of 29,430 to 50,040 units/kg in mice and 85,068 to 93,440 units/kg in rats.

Subacute Toxicity
In rats, doses of up to 1,000 mg/kg per os of metronidazole for thirty days were well tolerated. Dogs given up to 50 mg/kg for a period of one month showed no sign of toxicity while others given up to 225 mg/kg for a period of 6 months developed signs of ataxia, muscular rigidity and tremor. This might be due to species difference in addition to high dosage over a prolonged time.

In the rat given daily oral doses of 121,000 to 810,000 units/kg of nystatin for a period of three months, no effects on red or white blood cells were noted. With the lower dosages, diarrhea, depression of growth and nasal discharge could be observed. In the animals given 810,000 units/kg per day, gastro-intestinal irritation, diarrhea, emaciation, dehydration and death occurred. In dogs, daily oral doses of up to 450,000 units/kg for periods of 185 to 217 days produced no histological changes in the organs.

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. 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.

Therefore, the use of FLAGYSTATIN for prolonged treatment duration should be carefully weighed (see WARNINGS AND PRECAUTIONS section).

STORAGE
Store between 15°C to 25°C away from humidity.

Manufactured by
PT Aventis Pharma, Jakarta,
Indonesia.

SG/FLA/1222/CCDSV7

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Dec 2022
(CCDS V7)