Product Monograph
Including Patient Medication Information

PrFLAGYSTATIN®

(500 mg metronidazole and 100,000 IU nystatin)

Vaginal Ovules

Trichomonacide – Moniliacide

Sanofi-aventis Canada Inc.

1755 Steeles Avenue West
Toronto ON,
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Date of Authorization:

2025-09-25

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Recent Major Label Changes

7 Warnings and Precautions, Gastrointestinal	2025-03
7 Warnings and Precautions, Neurologic	2025-03
7 Warnings and Precautions, Skin	2025-09
3 Serious Warnings and Precautions Box	2025-09

Table of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Part 1: Healthcare Professional Information

1. INDICATIONS

FLAGYSTATIN (metronidazole and nystatin) is indicated for:

- Mixed vaginal infection due to *Trichomonas vaginalis* and *Candida albicans*.

FLAGYSTATIN has antibacterial and antifungal properties. To reduce the development of drug-resistant bacteria/fungi and maintain the effectiveness of FLAGYSTATIN and other antibacterial/antifungal drugs, FLAGYSTATIN should be used only to treat proven or strongly suspected mixed vaginal infections.

1.1. Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2. 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 6 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.

3. Serious Warnings and Precautions Box

- 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).
- Severe cutaneous adverse reactions (SCAR) have been reported with metronidazole (see 7 Warnings and Precautions, Skin).

4. Dosage and Administration

4.1. Dosing Considerations

Consideration should be given to use FLAGYSTATIN therapy in female patients, only when trichomonal or candida infection has been confirmed by appropriate diagnostic techniques. In the male patient, oral metronidazole is recommended in those who are evidently the source of reinfection in female consorts

and those with demonstrated urogenital infection (see 7 Warnings and Precautions).

4.2. Recommended Dose and Dosage Adjustment

One vaginal ovule daily, inserted deep into the vagina, for 10 consecutive days.

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 b.i.d. should be administered for 10 days.

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

Pediatrics (<18 years of age): The safety and effectiveness of FLAGYSTATIN in children is not known; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics: The safety and effectiveness of FLAGYSTATIN in geriatric patients is not known; therefore, Health Canada has not authorized an indication for geriatric use.

4.5. Missed Dose

If a dose is missed, the missed dose should be skipped, and the regular dosing schedule should be resumed. The patient should be advised **never to insert a double dose.**

5. Overdose

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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

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.

7. Warnings and Precautions

Please see 3 Serious Warnings and Precautions Box***Error! Reference source not found.***.

General

Metronidazole has been shown to be carcinogenic in mice and rats (see 16 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 1 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 10 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 8 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.

Gastrointestinal

Use of metronidazole may increase the risk of subsequent inflammatory bowel disease (IBD).

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 8 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 3 Serious Warnings and Precautions Box).

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 9 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.

Patients treated with metronidazole have been reported to develop posterior reversible encephalopathy syndrome (PRES). If patients taking metronidazole present with symptoms indicating PRES such as headache, altered mental status, seizures, and visual disturbances, a radiological procedure (e.g. MRI) should be performed. If PRES is diagnosed, adequate blood pressure control and immediate discontinuation of metronidazole is advised. Most patients completely recover after appropriate measures are taken.

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

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), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with FLAGYSTATIN treatment (see 8 Adverse Reactions section). Cases of severe bullous skin reactions such as toxic epidermal necrolysis (TEN) have been reported with metronidazole (see 8 Adverse Reactions section). If symptoms or signs of SJS, TEN, AGEP or DRESS are present, FLAGYSTATIN treatment must be immediately discontinued.

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.

7.1. Special Populations

7.1.1. Pregnancy

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.

7.1.2. Breastfeeding

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.

7.1.3. Pediatrics

Pediatrics (≥ 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

Geriatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8. Adverse Reactions

8.1. 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.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

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 10 Clinical Pharmacology section).

8.5. 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.

Skin and subcutaneous tissue disorders:
Drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with metronidazole.

9. Drug Interactions

9.2. 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.

9.3. Drug-Behaviour 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).

9.4. 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.

9.5. Drug-Food Interactions

Interactions with food have not been established.

9.6. Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7. 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 7 Warnings and Precautions section).

10. Clinical Pharmacology

10.1. 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.

10.2. 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.

10.3. Pharmacokinetics

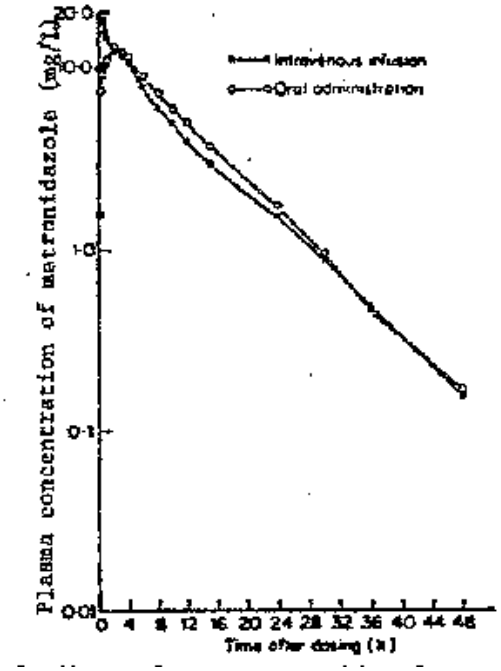
Absorption and Distribution

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.

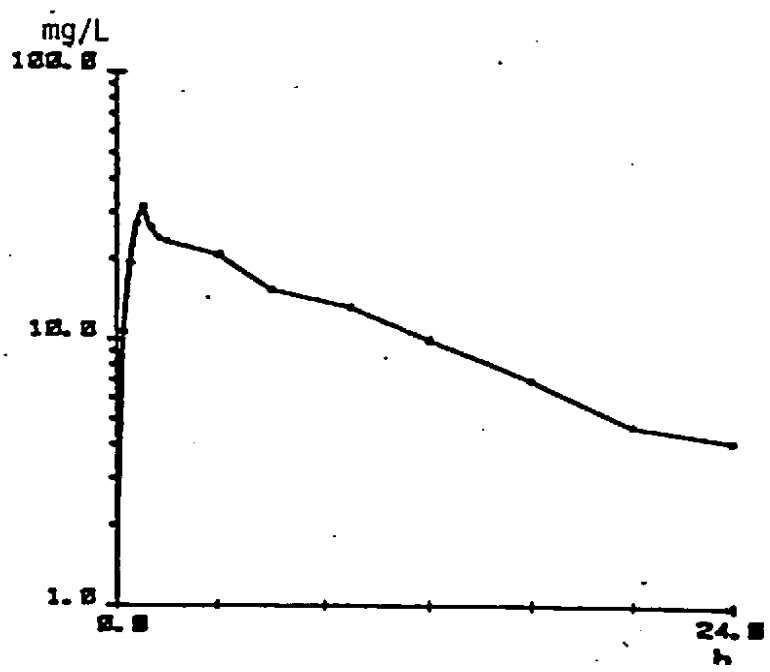
Continuous Ambulatory peritoneal dialysis

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.

11. Storage, Stability and Disposal

Store the vaginal ovules at room temperature between 15 - 25°C and protect from light.

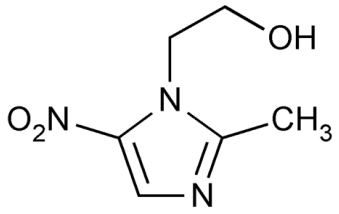
12. Special Handling Instructions

No special handling instructions required.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substances:	a) Metronidazole b) Nystatin
Chemical name:	a) 1H-Imidazole-1-ethanol,2-methyl-5-nitro or 2-Methyl-5 nitroimidazole-1-ethanol. b) nystatin
Molecular formula and molecular mass:	a) $C_6H_9N_3O_3$ & 171.2 b) Not applicable – Nystatin is a mixture of two or more substances
Structural formula:	a)  b) Nystatin is a substance, or a mixture of two or more substances, produced by the growth of Streptomyces noursei.
Physicochemical properties:	Metronidazole is a white to pale yellow, odorless crystals or crystalline powder. It is stable in air, but darkens on exposure to light. Soluble in dilute hydrochloric acid (1 in 2); sparingly soluble in water and in alcohol; slightly soluble in ether and in chloroform. Nystatin is a polyene antifungal antibiotic produced by the growth of Streptomyces noursei. It is a yellow to light tan powder, having an odor suggestive of cereals. Is hygroscopic, and is affected by long exposure to light, heat, and air. Freely soluble in dimethylformamide and in dimethyl sulfoxide; slightly to sparingly soluble in methanol, in n-propyl alcohol, and in n-butyl alcohol; practically insoluble in water and in alcohol; insoluble in chloroform and in ether.

14. Clinical Trials

Clinical trial information is not available.

15. Microbiology

No microbiological information is available.

16. 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

7 Warnings and Precautions section).

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrFLAGYSTATIN®
metronidazole and nystatin ovules

This Patient Medication Information is written for the person who will be taking **Flagystatin**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **Flagystatin**, talk to a healthcare professional.

Serious warnings and precautions box

- Cases of severe liver failure (including cases leading to death) in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. If you have Cockayne syndrome, your doctor should check your liver function many times during and after your treatment.
- Cases of severe skin reactions (**Severe Cutaneous Adverse Reactions (SCAR)**) have been reported with metronidazole. Stop using FLAGYSTATIN at the first sign of rash, sores or other skin reactions. For more information read the "Serious side effects and what to do about them" table, below.

What Flagystatin is used for:

- **Flagystatin** treats and reduces two infections in your vagina at the same time.
- These infections are caused by the following microorganisms or "germs": *Trichomonas vaginalis* and *Candida albicans*.

Antibacterial and antifungal drugs, like **Flagystatin**, treat only bacterial and fungal infections. They do not treat viral infections. Although you may feel better early in your treatment, **Flagystatin** should be used exactly as directed. Misuse or overuse of **Flagystatin** could lead to the growth of bacteria/fungi that will not be killed by **Flagystatin** (resistance). This means that **Flagystatin** may not work for you in the future. Do not share your medicine.

How Flagystatin works:
Flagystatin kills the microorganisms causing the vaginal infection.

The ingredients in Flagystatin are:
Medicinal ingredients: Metronidazole, nystatin.
Non-medicinal ingredients: Glycerides of saturated fatty acid (hard fat).

Flagystatin comes in the following dosage form:

- **Flagystatin** comes in vaginal ovules. Each ovule contains metronidazole (500 mg) and nystatin (100,000 IU).

Do not use Flagystatin if:

- you are allergic to metronidazole or nystatin, or any of the other ingredients in **Flagystatin**. (Read also "**The ingredients in Flagystatin are:**" above).
- you are allergic to medications in the imidazole group of drugs. This group includes clotrimazole and miconazole. These drugs are used to treat fungal and yeast infections.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Flagystatin. Talk about any health conditions or problems you may have, including if you:

- are pregnant, think you may be pregnant, or plan to get pregnant.
- are breastfeeding or plan to breastfeed. Metronidazole passes into breast milk and may affect your baby.
- have liver problems.
- have a disease of the nervous system.
- have a blood problem (like leukemia or hemophilia).
- have a thyroid problem.
- have hypoadrenalism (underactive adrenal glands).

Other warnings you should know about:

Reproductive Health:

- Condoms or diaphragms may not work well when you are using **Flagystatin**. Please talk to your healthcare professional about choosing a different form of birth control while you are using this medicine.
- Do NOT use other vaginal injection or irrigation products, menstrual tampons, and soaps, douches and washes for your vagina while you are using **Flagystatin**. Your infection may be harder to treat if you use these products.
- If a sexual partner thinks they may be infected, they should go to the healthcare professional for treatment too.

Liver Problems:

- Cases of severe liver toxicity/acute liver failure, including deaths, in patients with Cockayne syndrome have been reported with products containing metronidazole.
- If you are affected by Cockayne syndrome, your doctor should also monitor your liver function frequently while you are being treated with metronidazole and afterwards.
- Tell your doctor immediately and stop taking metronidazole if you develop stomach pain, loss of appetite, nausea, vomiting, fever, malaise, fatigue, jaundice (e.g. yellowing of skin and eyes), putty or mastic (yellowish to greenish) colored stools or itching.
- Do NOT drink alcohol (beer, wine or liquor) while you are using **Flagystatin**. Do NOT drink alcohol until one day after you finish your treatment. You could have a reaction that could make you throw up (vomit), feel flushed (become red in the face or other part of the body) and have a fast heartbeat.

Mental Health Problems:

- Some people being treated with metronidazole can experience mental health problems such as irrational thoughts, hallucinations, feeling confused or feeling depressed, including thoughts of

self-harm or suicide. These symptoms can occur even in people who have never had similar problems before.

Flagystatin may make your urine darker. You do not need to worry about this.

Do NOT drive any type of vehicle or use any tools or machinery if:

- you feel confused, dizzy or experience vertigo (spinning sensation).
- you see or hear things that are not there (hallucinations).
- you have a seizure.
- you have an eye problem, like blurred or double vision.

Do not use the applicator after the seventh month of pregnancy.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

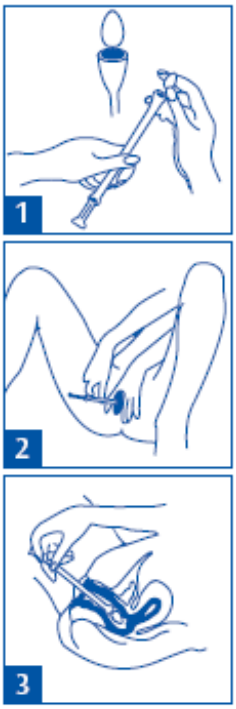
The following may interact with Flagystatin:

- alcohol (e.g., beer, wine or liquor).
- drugs containing alcohol.
- anticoagulants (blood thinners), like warfarin.
- busulfan, a drug used to treat cancer.
- cyclosporine, a drug used to suppress the immune system.
- disulfiram, a drug used to treat drinking problems.
- 5-fluorouracil, a drug used to treat cancer.
- lithium, a drug used to treat bipolar disorder.
- phenobarbital, a drug used to treat anxiety or to control seizures.
- phenytoin, a drug used to control seizures.
- medications that may cause heart rhythm changes (QT prolongation), like certain anti-arrhythmics (medicines for heart rhythm disorders), certain antibiotics, and psychotropic medicines.

Flagystatin may interact with some blood tests. Tell your healthcare professional if you have any upcoming blood tests while you are taking **Flagystatin**.

How to take Flagystatin:

Insert one vaginal ovule deep into your vagina. Do this at bedtime.



Flagystatin ovule applicator

1. The applicator in this package is especially designed to be used with **Flagystatin** ovules.
2. The applicator will help you to properly insert **Flagystatin** ovules into your vagina.

How to use the Flagystatin ovule applicator

1. Pull back the applicator plunger about 2.5 centimetres (1 inch).
2. Remove an ovule from its plastic wrapping by pulling the tabs apart. Insert the ovule into the cup at the end of the hollow tube (applicator).
3. Lie on your back with your knees drawn up. Insert the applicator into your vagina as far as it will comfortably go. Do NOT try to force it to go further.
4. ***BE SURE*** the applicator is in the correct position in your vagina ***BEFORE*** you push the plunger.
5. Then, push the plunger to place the ovule in your vagina.
6. Remove the applicator. Wash with mild soap and warm water. Rinse thoroughly and dry.

Usual dose:

Insert one vaginal ovule deep into your vagina at bedtime each day. Do this for 10 days in a row, or as prescribed by your doctor.

Further general directions:

- Tell your healthcare professional if you still have the infections after you finish the 10 days of treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much **Flagystatin**, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you miss a dose of **Flagystatin**, ask your healthcare professional for advice. Do NOT insert two doses at the same time. Do NOT make up for a missed dose.

Possible side effects from using Flagystatin:

These are not all the possible side effects you may have when taking **Flagystatin**. If you experience any side effects not listed here, tell your healthcare professional.

- slight burning or grainy feeling in your vagina
- darker urine
- constipation
- dry mouth

- bitter or metallic taste in your mouth
- indigestion (stomach upset)
- loss of appetite
- nausea
- vomiting
- depression
- headache
- trouble sleeping
- hearing loss
- noise such as buzzing, ringing, or whistling heard in the ear.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Diarrhea	✓		
Irritation in or around your vagina		✓	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual tiredness.			✓
Nervous system problems: trouble moving, seizures, tingling feeling on the skin.			✓
Posterior Reversible Encephalopathy Syndrome (brain swelling): headache, confusion, visual disturbances, seizures.			✓
Mental health problems: irrational thoughts, hallucinations, feeling confused or feeling depressed.			✓
Thoughts or actions of self-harm or suicide.			✓
Vertigo (spinning sensation)		✓	
Decrease in some blood cells: fever, other sign of infection such as chills, body aches, sore throat; or extreme tiredness.		✓	
Allergic reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Severe Cutaneous Adverse Reactions (SCAR) (severe skin reactions that may also affect other organs): - Skin peeling, scaling, or blistering (with or without pus) which may also affect your eyes, mouth, nose, or genitals, itching, severe rash, bumps under the skin, skin pain, skin color changes (redness, yellowing, purplish). - Swelling and redness of the eyes or face. - Flu-like feeling, rash, fever, shills, body aches, swollen glands, cough. - Shortness of breath, chest pain, or discomfort.			✓
Meningitis (inflammation of the thin tissue that surrounds the brain and spinal cord): sudden, high fever, severe headache, stiff neck, confusion, nausea and vomiting.			✓
Heart problems: very fast or uneven heartbeat, chest pain, dizziness, weakness, blurred vision, fainting. This may also happen when **Flagystatin** is taken with drugs that can cause QT prolongation (a heart rhythm condition).			✓
Gastrointestinal problems: abdominal pain, cramps, diarrhea with possible bloody stools.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store the vaginal ovules at room temperature, between 15°C and 25°C.

Protect them from light.

Keep out of the reach and sight of children.

If you want more information about Flagystatin:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website (https://www.sanofi.com/en/canada/), or by calling 1-800-265-7927.

This leaflet was prepared by sanofi-aventis Canada Inc.

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