

PRODUCT MONOGRAPH

FLAGYSTATIN
(metronidazole and nystatin)

Vaginal Ovules
Vaginal Cream

Trichomonacide - Moniliacide

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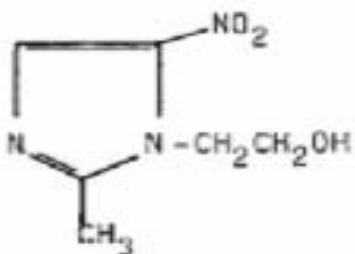
FORMULA AND CHEMISTRY

FLAGYSTATIN is a preparation delivering 500 mg of metronidazole a) and 100,000 units of nystatin b) per vaginal application.

Structural Formula

a)

b) Not completely elucidated



Molecular Formula: a) C₆H₉N₃O₃
b) C₄₆H₇₇NO₁₉

Molecular Weight: a) 171.2
b) 948.1

Chemical Name: a) 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole
b) nystatin

Description: Metronidazole is a white crystalline powder with a light yellow tint, sparingly soluble in water, alcohol and chloroform; slightly soluble in ether.

Nystatin is a polyene antifungal antibiotic produced by Streptomyces noursei, Streptomyces aureus and other Streptomyces species. It is a light yellow powder, practically insoluble in water, soluble in dimethylformamide, sparingly soluble in methanol, ethanol and propylene glycol.

INDICATIONS

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

CONTRAINDICATIONS

Hypersensitivity to one of the components.

Combined treatment with oral Flagyl 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.

WARNINGS

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.

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

PRECAUTIONS

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

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

When administering oral Flagyl (see Flagyl Product Monograph) the following precautions must be borne in mind.

Patients should be warned against consuming alcohol, because of a possible disulfiram-like reaction. 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 oral Flagyl therapy is needed.

Metronidazole passes the placental barrier. Although it has been given to pregnant women without apparent complication, it is advisable that oral use be avoided in pregnant patients and the drug be withheld during the first trimester of pregnancy.

Oral treatment should be discontinued if ataxia or any other symptom of CNS involvement occurs.

ADVERSE REACTIONS

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

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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

No case of accidental massive ingestion of FLAGYSTATIN has been reported yet. However, should this occur, symptoms such as nausea, vomiting, diarrhea and slight disorientation may be observed.

Treatment

There is no specific antidote. Treatment should be symptomatic after gastric lavage.

PHARMACOLOGY

Flagyl 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 37°C. 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.

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

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

In vivo, rabbits were infested by the oral route with 2.5×10^8 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 μ g of metronidazole to 1 unit of Nystatin as in FLAGYSTATIN vaginal inserts) Nystatin does not alter the antitrichomonal activity of Flagyl and that Flagyl 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 FLAGYSTATIN cream exert antitrichomonal and anticandidal activities comparable to those of the individual components.

TOXICOLOGY

Acute Toxicity

The acute toxicity of Flagyl 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 Flagyl 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.

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.

DOSAGE AND ADMINISTRATION

One vaginal ovule, or one applicatorful of FLAGYSTATIN cream 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 Flagyl 250 mg b.i.d. should be administered for 10 days.

SUPPLY

Vaginal ovules containing 500 mg metronidazole and 100,000 U. nystatin; boxes of 10 with applicator.

Vaginal Cream delivering 500 mg metronidazole and 100,000 U. nystatin per applicatorful; tubes of 55 g with applicator. Non-medicinal ingredients: methylparaben 0.12%, propylparaben 0.04%.

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