

NYSTAZOLE

Vaginal Ovules

Composition

Each Ovules contains 500 mg Metronidazole and 100,000 IU Nystatin.

Action

Metronidazole is bactericidal against anaerobic bacteria; it exerts trichomonocidal 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 antiinflammatory 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 antiinflammatory effect. It has been proposed that the reduction in rosacea lesions and erythema is the result of antiinflammatory 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.

Pharmacokinetics

Metronidazole is readily absorbed from the rectal mucosa and widely distributed in body tissues. Maximum concentrations occur in the serum after about 1 hour and traces are detected after 24 hours.

At least half the dose is excreted in the urine as metronidazole and its metabolites, including an acid oxidation product, a hydroxy derivative and glucuronide. Metronidazole diffuses across the placenta, and is found in breast milk of nursing mothers in concentrations equivalent to those in serum.

Nystatin is not absorbed from intact skin or mucous membranes.

Indications

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

Contraindications

Hypersensitivity to NYSTAZOLE (Metronidazole and Nystatin); or any of its constituents, or to imidazoles.

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.

Adverse Reactions

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 NYSTAZOLE local treatment.

In the course of clinical trials with NYSTAZOLE, 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 impaired/hearing loss (including hypoacusis, deafness, deafness neurosensory)
- tinnitus

Gastrointestinal disorders

Metronidazole: Diarrhea, nausea, vomiting, epigastric distress, epigastric pain, dyspepsia, constipation, 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.

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, and aseptic meningitis.

Reports of encephalopathy (e.g. confusion) 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.

Skin and subcutaneous tissue disorders

Metronidazole: Hypersensitivity reactions including flushing, urticaria and pustular eruptions. 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 sensitization have been reported after local application, treatment should be stopped if such reaction occurs. Skin reaction may occur, notably Stevens-Johnson syndrome, 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.

Warnings & Precautions

General

Metronidazole has been shown to be carcinogenic in mice and rats. 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 for.

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

Nystatin is not absorbed from mucous membranes; therefore, no systemic effect is expected.

NYSTAZOLE 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).

Hepatic

NYSTAZOLE, 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.

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, NYSTAZOLE 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 Nystazole.

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 gynecological ovule, therefore their use during NYSTAZOLE treatment is not recommended.

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 NYSTAZOLE .

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

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.

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

NYSTAZOLE 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.

NYSTAZOLE 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 NYSTAZOLE below those usually recommended should be administered and with caution.

Patients should be warned that NYSTAZOLE may darken urine (due to Metronidazole metabolite).

Pregnant Women

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.

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.

Nursing Women

As Metronidazole is excreted in human milk, exposure to the drug should be avoided. No data is available whether Nystatin enters the breast milk.

Occupational Hazards

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

Drug Interactions

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 NYSTAZOLE .

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).

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 cyclosporine and serum creatinine should be closely monitored when co-administration with Metronidazole is necessary.

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

5 Fluorouracil: reduced clearance of 5 fluorouracil resulting in increased toxicity of 5 fluorouracil (co-administration 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 co-administration 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.

Dosage and Administration

One vaginal ovule 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 vagina/is* 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.

Presentation

Box of 10 Ovules with Applicator