For The Use of Registered Medical Practitioner or a Hospital or a Laboratory Only

Metronidazole + Miconazole Nitrate

Trimic™

500 mg / 100 mg Vaginal Suppositories
Antibacterial / Antiprotozoal / Antifungal

℞

COMPOSITION
Each vaginal suppository contains:
Metronidazole BP ..... 500 mg
Miconazole Nitrate BP ..... 100 mg
Excipients ..... q.s.

PHARMACODYNAMICS
TRIMIC (Metronidazole + Miconazole Nitrate) Vaginal Suppository contains metronidazole for antibacterial and antitrichomonal effects and miconazole for antifungal action. Miconazole nitrate has a wide spectrum of activity. It is particularly effective against pathogen fungi including *Candida albicans*, in addition to Gram (+) bacteria. Metronidazole is an antibacterial and antiprotozoal agent that is effective against several infections caused by anaerobic bacteria and protozoa such as *Gardnerella vaginalis, Trichomonas vaginalis* and anaerobic bacteria including *anaerobic streptococci.*

PHARMACOKINETICS
Absorption of miconazole nitrate through the intravaginal route is very low (approximately 1.4% of dose). Bioavailability of metronidazole by this route is 20% compared to the oral route. Steady state level of metronidazole in plasma reaches 1.6-7.2 µg/mL.

Metronidazole is metabolized in the liver. The hydroxyl-metabolite is effective. The half-life of metronidazole is 6-11 hours. Approximately 20% of the dose is excreted unchanged in urine.

INDICATIONS
It is used in the treatment of candidal vulvovaginitis due to *Candida albicans*, in bacterial vaginosis due to anaerobic bacteria and *Gardnerella vaginalis*, in trichomonal vaginitis due to *Trichomonas vaginalis* and in mixed vaginal infections.

DOSAGE AND ADMINISTRATION
In treatment of Vaginitis
Adults and Elderly (>65 years):
Usual dose: Insert 1 vaginal suppository at night and in the morning for 7 days or insert 1 vaginal suppository at night for 14 days.
Vaginitis resistant to other treatments or recurrent vaginitis: Insert 1 vaginal suppository at night and in the morning for 14 days.

Children: Not recommended for children.

CONTRAINDICATIONS
- In patients hypersensitive to Metronidazole, Miconazole Nitrate or any other ingredients of the product.
- First trimester of pregnancy
- Patients with severe liver problems
- Patients with nervous system diseases
- Patients with disturbances in hematopoiesis

WARNINGS & PRECAUTIONS
Caution should be taken while administering TRIMIC (Metronidazole + Miconazole Nitrate) vaginal suppositories to patients with liver impairment including porphyria, diseases of the nervous system and hematopoiesis.
Pessaries may be used after the first trimester of pregnancy in cases considered essential by a physician, but should be used under control. Breastfeeding should be discontinued during Trimic therapy, since metronidazole appears in milk. Breastfeeding can be started again 24-48 hours after the end of therapy. Patients should be warned not to take alcohol during the therapy and for at least 2 days after the end of a course of treatment because of the possibility of disulfiram-like reactions. The base contained in the pessary formulation may interact with certain rubber or latex products, such as those used in vaginal contraceptive diaphragms or condoms, therefore concurrent use is not recommended. Sexual partners of patients with *Trichomonas vaginalis* should be treated at the same time.

PREGNANCY AND LACTATION
There is no data established for the use of Metronidazole and Miconazole in second and third trimester. The active ingredients are found in the breast milk. Hence Metronidazole and Miconazole if used during pregnancy and lactation should be under medical supervision only if the benefits outweigh the risk.

INTERACTIONS
Due to metronidazole absorption, the following interactions can be seen if used concomitantly with the drugs below:
Alcohol: Alcohol intolerance (disulfiram-like reaction)
Amiodaron: Increase in risk of cardiotoxicity (QT prolongation, *torsades de pointes*, cardiac arrest)
Astemizole and terfenadine: Metronidazole inhibits the metabolism of these drugs and increases their plasma concentrations
Disulfiram: Central nervous system related effects (e.g. psychotic reactions)
Phenytoin: Increase in blood levels of phenytoin, decreases in blood levels of metronidazole
Phenobarbital: Decrease in blood levels of metronidazole
Fluorouracil: Increase in blood levels and toxicity of fluorouracil
Carbamazepine: Increase in blood concentration of carbamazepine
Lithium: Increase in blood levels and lithium toxicity
Oral anticoagulants: Increase in anticoagulant effect
Cyclosporine: Increase in cyclosporine toxicity risk
Cimetidine: Increase in blood levels of metronidazole and the risk of neurologic side effects
Interference with blood levels of liver enzymes, glucose (hexokinase method), theophylline and procainamide have been observed during the treatment with metronidazole.

Due to miconazole nitrate absorption, the following interactions can be seen if used concomitantly with the drugs below:
Acenocoumarol, Anisindione, Dicumarol, Phenindione, Phenprocoumon, Warfarin: Increase in bleeding risk
Astemizole, cisapride and terfenadine: Miconazole inhibits the metabolism of these drugs and increases their plasma concentrations.
Phenytoin and Fosphenytoin: Increase in phenytoin toxicity risk (ataxy, hyperlexia, nystagmus, tremor)
Fentanyl: Increase or prolonged effects of opioid (CNS depression, respiratory depression),
Glimepiride: Increase of hypoglycemic action
Carbamazepine: Decrease in carbamazepine metabolism
Oxybutinin: Increase in plasma concentration or exposure to oxybutinin
Oxycodone: Increase in oxycodone plasma concentration and reduction in clearence.
Pimozide: Increase in cardiotoxicity risk (QT prolongation, *torsades de pointes*, cardiac arrest)
Cyclosporine: Increase in cyclosporine risk toxicity (renal dysfunction, cholestasis, parasthesias)
Tolterodine: Increase in tolterodine bioavalaibility in individuals with deficient cyctochrome P450 2D6 activity
Trimetrexate: Increase in trimetrexate toxicity (bone marrow suppression, renal and hepatic dysfunction and gastrointestinal ulceration).

Do not use barrier contraceptives like condoms with the use of Vaginal Suppositories since it may lead to breaking of rubber.

ADVERSE REACTIONS

Gastrointestinal system	Abdominal pain or cramp, metallic taste, constipation, dry mouth, seldom diarrhea, lack of appetite, vomiting, nausea
Haematopoietic system	Decrease of white blood cells
Musculoskeletal system	Cramps
Nervous system	Headache, movement disorders, dizziness, mental changes, peripheral neuropathy after overdose or long period of usage
Reproductive system	Vaginal irritation (burning, itching)
Skin	Rash

OVERDOSAGE
There is no human experience with overdose of Metronidazole and Miconazole nitrate vaginal suppositories. If large quantities of the product are accidentally taken, an appropriate method of emptying your stomach may be considered necessary. Symptoms of Metronidazole overdose are nausea, vomiting, abdominal pain, diarrhea, itching, metallic taste, movement disorders (ataxia), vertigo, unusual sensations on the skin (paresthesia), cramps, decrease of white blood cells, and darkening of urine.

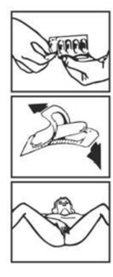
Symptoms of Miconazole nitrate overdose are nausea, vomiting, sore throat and mouth, decrease appetite, headache and diarrhea.

STORAGE
Store at temperatures not exceeding 25°C.
Do not freeze.
Protect from light.
Keep out of the reach and sight of children.

PRESENTATION
Two blister of 7 Vaginal Suppositories packed in a carton along with an insert.

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How to use Vaginal Suppositories
1. Wash your hands.
2. Do not open vaginal suppositories if it seems soft, hold the foil wrapper under cold water or place it in refrigerator for few minutes to harden it before removing the wrapper.
3. Remove one vaginal suppository from the strip and hold it in fingertips.
4. Remove any foil or plastic wrapping stuck to the vaginal suppository.
5. Sit or lie down with your knees bent and legs apart.
6. Gently insert the suppository into the vagina as far as comfortably possible using your fingers.
7. Wash your hands again.



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