DGF Drugfield PHARMACEUTICALS LIMITED

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

Micozol® - Plus Vaginal Tablet

(Miconazole 200mg + Metronidazole 750mg)

1. NAME OF THE MEDICINAL PRODUCT

Micozol® - Plus Vaginal Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains Miconazole nitrate 200mg and Metronidazole 750mg.
(For a full list of excipients, see section 6.1).

3. PHARMACEUTICAL FORM

Vaginal Tablet

4. Clinical particulars

4.1 Therapeutic indications

Micozol®- plus tablet is used in the treatment of candidal vulvovaginitis due to Candida albicans, in bacterial vaginitis due to anaerobic bacteria and Gardnerella vaginalis, in trichomonal vaginitis due to Trichomonas vaginalis and in mixed vaginal infections.

4.2 Posology and method of administration

Do not use without consulting a physician. If it is not advised to the contrary by a physician; To begin with the treatment, one tablet should be inserted high into the vagina at night for 7 days. In recurrent cases, or when the vaginitis has been resistant to other treatments, application of one tablets at night for 14 days is recommended.

Method of Administration: Only for intravaginal use. The tablet should be applied in lying position. Insert the tablet into the vagina using applicator provided in the package. Not to be swallowed or applied by other routes.

Pediatric population: Not to be used in children under 12 years.
Geriatric population: Adult dose should be applied for elderly over 65 years

4.3 Contraindications

Micozol-Plus Vaginal Tablets should not be used - in patients known to be hypersensitive to the active ingredients (Miconazole, Metronidazole) or any component of the formulation.
Avoid in-take of alcohol during treatment or at least 3 days after end of treatment, Avoid disulfiram during treatment or within last 2 weeks
First trimester of pregnancy since found to be carcinogenic in rats. Miconazole was considered to be unsafe in patients with acute porphyria because it has been shown to be porphyrinogenic in animals or invitro systems.

4.4 Special Warnings and Precautions for use

Discontinue if sensitivity or irritation develop.

The basis in miconazole nitrate pessaries may interact with latex product including contraceptive diaphragms.

Use during menstruation is not recommended.

Metronidazole is a nitroimidazole and should be used with care in patients with evidence of a history of blood dyscrasias.

During treatment with Micozol-Plus other vaginal products (e.g. tampon, douche and spermicide) should not be used concurrently.

Sexual partners of patients with Trichomonas vaginalis should be treated at the same time. As with all Vaginal infections, sexual intercourse during the infection and during treatment Micozol-Plus Vaginal Tablet is not recommended.

Dose Adjustment in Renal Impairment

Additional information about special populations: Renal / Liver failure In renal failure, the half-life of metronidazole is not changed. Therefore, there is no need to decrease the dose of metronidazole, however the dose should be adjusted by severe renal function insufficiency requiring hemodialysis. In severe liver function failures metronidazole clearance may be impaired. Metronidazole may increase encephalopathy symptoms due to increased plasma levels and therefore should be used carefully in hepatic encephalopathy patients. The daily dose of metronidazole must be reduced to 1 /3 in patients with hepatic encephalopathy. These features should be taken into account by patients with liver and/or renal function disorders who will use MICOZOL- Plus.

4.5.1 Interaction with other medicinal products and other forms of interaction

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 elongation, torsades de pointes, cardiac arrest)

Astemizole and terfenadine: Metronidazole inhibits the metabolism of these drugs and increases plasma concentrations.

Disulfiram: Central nervous system related effects (e.g. psychotic reactions) may occur.

Phenytoin: Increase in blood levels of phenytoin, decrease in plasma levels of metronidazole

Phenobarbital: Decrease in blood levels of metronidazole.

Fluorouracil: Increase in blood levels of fluorouracil and rise in its toxicity

Carbamazepine: Increase in blood concentration of carbamazepine,

Lithium: Increase in lithium toxicity

Oral anticoagulants: Increase in anticoagulant effect (increase in bleeding risk)

Cyclosporine: Increase in cyclosporine toxicity.

Cimetidine: The blood level of metronidazole and the risk of neurologic side effects may increase. Interference with blood levels of liver enzymes, glucose (hexokinase method), theophylline, and procainamide may be observed during treatment with metronidazole.

Due to miconazole nitrate absorption, the following interactions can be seen if used concomitantly with the drugs below: Acenocoumarol, Anisindione, Dicoumarol, Phenindione, Phenprocoumon,

Warfarin: Increase in bleeding risk,

Astemizole, cisapride and terfenadine: Miconazole inhibits metabolism of these drugs and increases plasma concentrations.

Phenytoin and fosphenitoin: Increase in phenytoin toxicity risk (ataxia, hyperreflexia, nystagmus, tremor)

Fentanyl: Increase or prolongation of opioid effects (central neural system depression, respiratory depression),

Glimepiride: Hypoglycemia,

Carbamazepine: Decrease in carbamazepine metabolism,

Oxybutynin: Exposure to oxybutynin due to inhibition of oxybutynin metabolism or increase in plasma concentration (dry mouth, constipation, headache),

Oxycodone: Increase in oxycodone plasma concentration and decrease in clearance.

Pimozide: Increase in cardiotoxicity risk (QT elongation, torsades de pointes, cardiac arrest)

Cyclosporine: Increase in cyclosporine toxicity risk (renal disfunction, cholestasis, paraesthesia).

Tolterodine: Increase in tolterodine bioavailability in individuals with weak cytochrome P450 2D6 activity,

Trimetrexate: Increase in trimetrexate toxicity (bone marrow depression, renal and hepatic dysfunction and gastrointestinal ulceration).

KEEP OUT OF REACH OF CHILDREN

4.6 Pregnancy and Lactation

Pregnancy category is C

Pregnancy

In animals, miconazole nitrate has shown no teratogenic effects but is foetotoxic

at high oral doses. The significance of this man is unknown as there is no evidence of increased risk when taken in human pregnancy. Data on a large number of exposed pregnancies indicate no significance adverse effects of metronidazole on the foetus / newborn child. Therefore Micozol -Plus may be used after first trimester of pregnancy in cases considered essential by a physician but should be used under control. There have been no studies on the use of topical or vaginal metronidazole in breastfeeding mothers, although metronidazole administration by these routes during breastfeeding is considered unlikely to be of concern.

Lactation

There have been no studies on the use of topical or vaginal metronidazole in breastfeeding mothers, although metronidazole administration by these routes during breastfeeding is considered unlikely to be of concern.

Pediatric Use

No interaction studies have been performed on children.

4.7 Effects on ability to drive and use machines

Systemic use of metronidazole may have influence on the ability to drive and use machines. Compared with systemic application, metronidazole is absorbed less through vaginal route.

4.8 Undesirable effects

The incidence of systemic side effects is very rare since after intravaginal administration of metronidazole, very low plasma levels are observed (2% - 12% compared to oral route).

Miconazole nitrate can cause vaginal irritation (burning, itching) as all other imidazole derivative antifungal drugs applied intravaginally (2-6%).

More Common: Vaginal irritation (burning, itching)

Less Common: Vulvar swelling, Menstrual discomfort /irregularities, vaginal spotting/ bleeding.

4.9 Overdose

Micozol – Plus Vaginal Tablets is for intravaginal use only. In unlikely event of oral ingestion, an appropriate method of Gastric emptying or haemodialysis maybe used. Symptomatic and supporting treatment is applied on overdose. There exists no antidote for metronidazole. Cure can be provided in persons who ingested a dose of 12 g of metronidazole. Symptoms due to metronidazole overdosage are nausea, vomiting, abdominal pain, diarrhea, itching, metallic taste, ataxia, vertigo, paraesthesia, convulsion, leukopenia, darkening of urine; symptoms due to miconazole nitrate overdosage are sore throat and mouth, anorexia, nausea, vomiting, headache, diarrhea.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: : Antibacterial, antiprotozoal, antifungal, ATC code: G01AF20

Micozol®-Plus contains miconazole nitrate for antifungal, metronidazole for antibacterial and antitrichomonal effects.

The bactericidal action of cefixime is due to the inhibition of cell wall synthesis. It binds to one of the penicillin binding proteins (PBPs) which inhibits the final transpeptidation step of the peptidoglycan synthesis in the bacterial cell wall, thus inhibiting biosynthesis and arresting cell wall assembly resulting in bacterial cell death.

5.2 Pharmacokinetic properties

Absorption:

Miconazole nitrate: Absorption of miconazole nitrate by the intravaginal route is very low (approximately 1.4% of dose).

Metronidazole: Bioavailability of metronidazole by the intravaginal route is app. 20 % compared to oral administration. Steady state levels of metronidazole in plasma ranged 1.1 - 5.0 µg/ml after application of NEO-PENOTRAN® FORTE L.

Distribution

Miconazole nitrate: Protein binding ratio is about 90-93%. It shows weak distribution to cerebrospinal fluid while it distributes widely to other tissues. Volume of distribution is 1400 L.

Metronidazole: Metronidazole distributes to body tissues and fluids like gall, bone, breast, milk, cerebral abscess, cerebrospinal fluid, liver and liver abscess, saliva, seminal and vaginal fluids widely and in nearly same concentrations as plasma. It passes beyond placenta and enters fetal circulation rapidly. Plasma protein binding ratio is not more than 20%. Distribution volume is 0.25-0.85 L/kg.

Metabolism

Miconazole nitrate: It is metabolized in liver. Has two metabolites that are inactive. (2,4- dichlorophenyl-1 H imidazole ethanole and 2,4-dichloromandelic acid)

Metronidazole: It is metabolized in the liver by oxidation. Its hydroxy metabolite is active. Major metabolites of metronidazole, hydroxy and acetic acid metabolites, are excreted in urine. The hydroxy metabolite has a 30% of biologic activity of metronidazole. Lidocaine: Metabolized in the liver. Has active metabolites monoethylglicinexylidide (MEGX) and glicinexylidide (GX).

Elimination: Miconazole nitrate: Half life is 24 hours. Less than 1% of it is excreted by kidneys. 50% of it is excreted unchanged with faeces.

Metronidazole: Half life is 6-11 hours. By systemic or topical application 6-15% of metronidazole dose is excreted by faecal route, 60-80% unchanged and as metabolites in the urine. The ratio of the drug excreted unchanged in the urine is 20%.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for human based on conventional studied of safety, pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

In a microbiological in vitro study, among the active ingredients comprised by the combination, none of the constituents showed any obvious synergistic or antagonistic effect against candida albicans, Streptococcus (Lancefield's Group B), Gardnerella vaginalis and Trichomonas vaginalis.

In a study to evaluate acute toxicity on female rats where 750 mg metronidazole and 200 mg miconazole nitrate combination is used intravaginally, none of the active ingredients showed any potentiation or synergism, furthermore they had no letal or toxic effect.

In a vaginal mucosa irritation study where metronidazole and miconazole nitrate combination is applied to beagle female dogs and it was concluded that it does not cause vaginal mucous irritation in the experimental used animals, as well as nor clinical, biochemical and haematology general alterations. In the same study it was determined that local or systemic toxic effect were not detected.

6.0 PHARMACEUTICALPARTICULARs

6.1 List of Excipients

Microcrystalline Cellulose
Starch
Calcium Hydrogen Phosphate dehydrate (Diabasic Calcium Phosphate)
Magnesium Stearate

6.2 Incompatibilities

None have been reported or are known

6.3 Shelf life

48 Months

6.3.1 Special precautions for storage

Keep out of reach of children. Protect from light and moisture. Store below 30^{o}C

6.4 Nature and contents of container and special equipment for use, administration or implantation

Micozol-Plus is available in a grey foil blister pack containing 7 vaginal tablets with applicator

6.5 Special precautions for disposal and other handling

Empty blisters may be disposed of in household waste. Return unused drug to the pharmacy for disposal. Do not dispose of unused drug in household waste or flush it down the toilet.

7.0 APPLICANT/MANUFACTURER

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