Lithosan	
Firma Adı	Exeltis İlaç
Ürün Adı	Neo-Penotran Malezya-Singapur Prospektüs
Artwork Kodu	251713
Ebadı	155 x 185 mm
Farmakod	
Hammadde	60 gr I.Hamur K.
Renk	Siyah
TARİH	10/07/2020
ONAY:	
O.TARİHİ	
İlgili Kişi	Aysel KALELİ
Versiyon No	V00

P04/F08/04.04.2017/Rev.05

Tüm ölçüler aynıdır.

15 mm 8 mm

Exeltis eurodrug LABORATORIES

NEO-PENOTRAN®
Vaginal Ovule

Name Of The Medicinal Product
Neo-Penotran Vaginal Ovule

Qualitative And Quantitative Composition
1 vaginal ovule contains:
500 mg metronidazole
100 mg miconazole nitrate

Pharmaceutical Form
Vaginal Ovule
White or creamy coloured ellipsoid shaped ovule.

Clinical Particulars

Therapeutic 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.

Posology and method of administration Posology
Do not use without consulting a physician. If it is not advised otherwise by a physician; One ovule should be inserted at night and in the morning for 7 days. In recurrent cases, application of one ovule in the morning and one ovule at night for 14 days is recommended. It is not recommended that the administration of NEO-PENOTRAN® in the menstrual period because of the impaired efficacy of the product or facing some difficulties during administration.

Method of administration
Only for intravaginal use.

NEO-PENOTRAN® should be applied in lying position, high into the vagina. Not to be swallowed or applied by other routes.

Additional information on special populations:

Renal/Liver failure:
In renal failure, the half-life of metronidazole is not changed.

In serious liver function failures metronidazole clearence may be impaired. Metronidazole may increase encephalopathy symptoms due to increased plasma levels and therefore should be used carefully in hepatic encephalopathy patients.

Paediatric population:
Not recommended for children.

Geriatric population:
Same dose as for adults is administered in elderly over 65 years.

Contraindications
NEO-PENOTRAN® should not be used;
- In patients known to be hypersensitive to the active ingredients or their derivatives,
- In patients using alcohol during the treatment or at least 3 days after the treatment,
- In patients using disulfiram during the treatment or within 2 weeks,
- During the first trimester of pregnancy,
- In pregnant women who have trichomonal vaginitis in the first trimester,
- In cases of porphyria, epilepsy, and serious liver function disorders.

Special warnings and precautions for use

Patients should be warned not to take alcohol during the therapy and for 3 days after the end of the treatment, because of the possibility of disulfiram-like reactions.

High doses and long term metronidazole may cause peripheral neuropathy and convulsion due to systemic usage.

Should not be used in virgins and in young people (girls) who are not sexually mature.

The ovules must not be used with contraceptive diaphragms and preservatives since the ovule base may react with the rubber.

Other vaginal products (e.g. tampon, douche or spermicide) should not be used concurrently during the treatment.

Sexual partners with Trichomonas vaginalis should be treated at the same time.

Interaction with other medicaments medicinal products and other forms of interaction
Due to metronidazole absorption, the following interactions can be seen if used concomitantly with the drugs listed below:

Alcohol: Alcohol intolerance (disulfiram-like reaction),
Amiodarone: 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,
Carbamazepine: Increase in blood concentration of carbamazepine,
Cimetidine: Increase in blood level of metronidazole and the risk of neurologic side effects
Cyclosporine: Increase in cyclosporine toxicity,
Disulfiram: Central nervous system related effects (e.g. psychotic reactions),
Fluorouracil: Increase in blood levels of fluorouracil and toxicity,
Lithium: Increase in lithium toxicity,
Phenytoin: Increase in blood levels of phenytoin, decrease in blood levels of metronidazole.
Phenobarbital: Decrease in blood levels of metronidazole.
Oral anticoagulants: Increase in anticoagulant effect (Increase in bleeding risk) 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.
Carbamazepine: Reduction in carbamazepine metabolism,
Cyclosporine: Increase in cyclosporine risk toxicity (renal dysfunction, cholestasis, parasthesias),
Fentanyl: Increase or prolonged effects of opioid (CNS depression, respiratory depression),
Glimepiride: Hypoglycemia
Oxybutynin: Increase in plasma concentration or exposure to oxybutinin, (dry mouth, constipation, headache)
Oxycodone: Increase in oxycodone plasma concentration and reduction in clearence.
Phenytoin and Phosphenytoin: Increase in phenytoin toxicity risk (ataxia, hyperreflexia, nystagmus, tremor)
Pimozide: Increase in cardiotoxicity risk (QT prolongation, torsades de pointes, cardiac arrest),
Tolterodine: Increase in tolterodine bioavailability in individuals with deficient cytochrome P450 2D6 activity,
Trimetrexate: Increase in trimetrexate toxicity (bone marrow suppression, renal and hepatic dysfunction and gastrointestinal ulceration).

Pregnancy and Breast-feeding
General Advice:
Pregnancy category is C. Women of childbearing potential / Birth control (Contraception)

Since the effects of active ingredients in NEO-PENOTRAN® for fetus and newborn growth are not clearly known, women who must use this product should avoid pregnancy with a proper birth control method.

Pregnancy
Preclinical studies on animals regarding the pregnancy, embryonal/fetal growth, perinatal and/or postnatal growth are insufficient. Potential risk for human is not known.

There is insufficient data regarding the use of NEO-PENOTRAN® in the first trimester of pregnancy. Therefore, NEO-PENOTRAN® should not be used in the first trimester of pregnancy. In the second and third trimesters, benefit/risk ratio should be evaluated by a physician, should not be used unless it is necessary.

Breast-feeding
Breastfeeding should be discontinued, since metronidazole appears in milk. Breastfeeding can be started again 24-48 hours after the end of treatment.

Undesirable Effects
The frequency of adverse events listed below is defined using the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1.000 to <1/100), rare (≥1/10.000 to <1/1.000); very rare (<1/10.000), not known (cannot be estimated from the available data).

The frequency of systemic side/adverse 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. In vaginitis, vaginal mucosa could be inflammed, therefore vaginal burning and itching may seen after the first ovule is applied or toward to the third day of the treatment. These symptoms are quickly reduced while the treatment continues. If there is a severe irritation symptoms, the treatment should be stopped.

Undesirable effects regarding systemic use of active ingredients of NEO-PENOTRAN® are listed below:

Blood and lymphatic system disorders:
Not known: Leukopenia
Immune system disorders:
Not known: Hypersensitivity reactions, allergic reactions (anaphylaxis may occur in severe cases)
Psychiatric disorders:
Uncommon: Depression
Very rare: Mental alterations
Nervous system disorders:
Common: Dizziness, headache.
Not known: Tiredness or weakness, ataxia, convulsion, peripheral neuropathy due to intensive and/or prolonged metronidazole therapy.
Gastrointestinal disorders:
Not known: Taste changes, metallic taste, nausea, vomiting, constipation, dry mouth, diarrhea, lack of appetite, abdominal pain or cramp,

General disorders and administration site conditions:
Very common: Vaginal discharge,
Common: Vaginitis, vulvovaginal irritation, pelvic discomfort,
Uncommon: Feeling of thirst,
Rare: Vaginal burning, itching, irritation, stomachache, rash.
Not known: Local irritation and hypersensitivity, contact dermatitis.
These adverse effects are observed rarely since blood concentration of metronidazole is much lower when administered via intravaginal route.

Overdose
When excessive amount of ovule is applied, systemic effects may occur due to metronidazole, but intravaginal metronidazole is not expected to cause life-threatening symptoms.

Symptomatic and supportive treatment should be instituted. There is no specific antidote for metronidazole. Cure can be provided in individuals who ingested a dose of 12 g of metronidazole.
Symptoms of metronidazole overdose are nausea, vomiting, abdominal pain, diarrhea, itching, metallic taste, ataxia, dizziness, paresthesia, convulsion, leukopenia, darkening of urine; symptoms of miconazole nitrate overdose are sore mouth and throat, anorexia, nausea, vomiting, headache, diarrhea.

Pharmacological Properties
Pharmacodynamic properties
Pharmacotherapeutic Group: Antibacterial, antiprotozoal, antifungal
ATC Code: G01AF20
NEO-PENOTRAN® contains miconazole nitrate for antifungal and metronidazole for antibacterial and antitrichomonal effects. Miconazole nitrate which is a synthetic imidazole derivative antifungal has a wide spectrum of activity and is particularly effective against pathogen fungi including Candida albicans. and In addition, miconazole nitrate is effective against Gram (+) bacteria. Miconazole nitrate shows its effect by ergosterol synthesis in the cytoplasmic membrane. Miconazole nitrate changes permeability of the mycotic cell of Candida species and inhibits glucose utilization in vitro. Metronidazole, a 5-nitroimidazole derivative is an antiprotozoal and an antibacterial agent and is effective against several infections caused by anaerobic bacteria and protozoa, such as Trichomonas vaginalis, Gardnerella vaginalis and anaerobic bacteria including anaerobic streptococci. Miconazole nitrate and metronidazole have not synergic or antagonistic effects. In an open, multicentered, non-comparative clinical study with NEO-PENOTRAN® in 179 patients with complaint of vaginal discharge; clinical cure rates for bacterial vaginosis, trichomonal vaginitis and candidal vaginitis are 80.2%, 68.2% and 79%; and microbiological cure rates are 89.5%, 86.4% and 81.8% respectively.

Pharmacokinetic properties

Absorption
Miconazole nitrate: Absorption of miconazole nitrate by the intravaginal route is very low (approximately 1.4% of dose). Following intravaginal application of NEO-PENOTRAN®, miconazole nitrate could not detected in plasma.
Metronidazole: Bioavailability of metronidazole by this route is 20% compared to the oral route. Steady state levels of metronidazole in plasma ranged 1.6 - 7.2 µg/ml after daily intravaginal application of NEO-PENOTRAN®.
Distribution
Miconazole nitrate: The protein binding rate is 90%-93%. Its distribution to cerebrospinal fluid is poor, however it is widely distributed to other tissues. Distribution volume is 1400 L. Metronidazole: It is widely distributed in body tissues and fluids including bile, bone, breast, milk, cerebral abscesses, cerebrospinal fluid, liver and liver abscesses, saliva, seminal fluids and vaginal secretion, and achieves concentrations similar to those in plasma. It crosses the placenta and rapidly enters to fetal circulation. No more than 20% is bound to plasma proteins. Distribution volume is 0.25-0.85 L/kg.
Metabolism
Miconazole nitrate: It is metabolized in liver. Two non-active metabolites are found (2,4-dichlorophenyl-1 H imidazole ethanole and 2,4-dichloromandelic acid) Metronidazole: It is metabolized in the liver by oxidation, hydroxy metabolite is active. Major metabolites of metronidazole, hydroxy and acetic acid metabolites, are excreted in urine. The hydroxy metabolite has 30% of biological activity of metronidazole.
Elimination
Miconazole nitrate: Half-life is 24 hours. Less than 1% is excreted in the urine. Approximatey 50%, usually unchanged, excreted with faeces. Metronidazole: Half-life is 6-11 hours. About 6%-15% of metronidazole dose is excreted with faeces, 60%-80% is unchanged and excreted in urine as its metabolites.

Approximately 20% of metronidazole is excreted in the urine as unchanged drug.

PHARMACEUTICAL PARTICULARS

Name and Strength of Excipient(s)
Witepsol
Incompatibilities
There is not any known incompatibility.
Shelf life
36 months
Special precautions for storage
Store at room temperature below 30°C.
Do not use after the expiration date indicated on the package.
Dosage forms and packaging available
PVC/PE duplex foil casing strips
Pack size:
14 vaginal ovules.

MANUFACTURER
Exeltis Ilac San. ve Tic. A.S.
Tekirdag-TURKEY

MARKETING AUTHORISATION NUMBER(S)
MAL 20032405AZ
SIN11180P

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