Tinidazole + Tioconazole + Lidocaine

NEOPENMAX® XL

300 mg / 200 mg / 100 mg Vaginal Suppository

Antibacterial / Antifungal / Local Anesthetic

℞

FORMULATION:

Each vaginal suppository contains 200 mg Tioconazole, 300 mg Tinidazole, and 123.26 mg Lidocaine HCl (equivalent to 100 mg Lidocaine)

PHARMACEUTICAL FORM:

Whitish yellow colored, smooth ovule

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamics:

Tioconazole is a synthetic antifungal agent with a high *in-vitro* efficacy to yeast and fungi (including dermatophytes). Also, it is effective against *Trichomonas vaginalis*, *Gardnerella vaginalis*, *Bacteroides spp*., and some Gram (+) bacteria (including *Staphylococcus* and *Streptococcus spp.*). In clinical studies, tioconazole is found to be effective in the treatment of *Candida albicans* and other *Candida* species (*Torulopsis glabrata*) and to vaginal infections caused by *Trichomonas vaginalis*.

Tioconazole shows its effect by altering permeability of the fungal cell membrane. Ergosterol is an essential component of the fungal cell membrane. Tioconazole inhibits the ergosterol synthesis by interacting with 14α-demethylase, a cytochrome P450 enzyme that converts lanosterol to ergosterol. Inhibition of ergosterol synthesis leads to increase of cellular permeability and therefore to leakage of intracellular phosphorus compounds and potassium across the cell membrane.

Tinidazole is effective against protozoans and anaerobic bacteria. Its antiprotozoal activity includes *Trichomonas vaginalis, Entamoeba histolytica* and *Giardia lamblia*. Tinidazole is effective against *Gardnerella vaginalis* and to the majority of anaerobic bacteria (*Bacteroides fragilis, Bacteroides melaninogenicus, Bacteroides spp., Clostridium spp*., *Eubacterium spp*., *Peptostreptococcus spp.*, and *Veillonella spp.*).

The complete mechanism of action of tinidazole has not been fully clarified. The reduction of the nitro group is mediated by a ferrodoxin system and a low oxidation reduction potential which is only generated by anaerobic bacteria. This may be the reason for anaerobes having a higher tinidazole uptake than aerobes, although tinidazole can penetrate cell membranes of both types of microorganisms. The reduction process creates reactive intermediates and a diffusion gradient, which enhances tinidazole uptake.

Lidocaine is an amide-type local (topical) anesthetic. It stabilizes the neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby producing local anesthetic action.

Pharmacokinetics:

Absorption:

Tinidazole:

Approximately 10% of tinidazole is absorbed after intravaginal application.

Mean peak plasma level was found to be 1.0 μg/ml, and the time to reach this level (t_{max}) was found as 8.7 hours following administration of vaginal suppository containing 500 mg tinidazole to 6 healthy volunteers.

Tioconazole:

Tioconazole has a negligible systemic absorption after intravaginal application. Mean peak plasma concentration following the administration of 300 mg single dose tioconazole ointment to women with candidal vulvovaginitis was found as 18 ng/mL.

Lidocaine:

Lidocaine is absorbed in very low quantities from abraded skin and mucous membranes.

Distribution:

Tinidazole:

Tinidazole is almost distributed into all tissues and body fluids and crosses the blood-brain barrier. The volume of distribution is 50 liters. Plasma protein binding of tinidazole is 12%. Tinidazole crosses the placental barrier and is secreted in breast milk.

Tioconazole:
In most clinical studies, after a single dose (300 mg) intravaginal tioconazole administration, concentrations in vaginal fluid are found to inhibit Candida albicans reproduction for 2-3 days. It is not known whether tioconazole is secreted in breast milk.

Lidocaine:
Plasma protein binding is 60% - 80%. It crosses the placenta and blood-brain barrier by passive diffusion and is distributed to cerebrospinal fluid, tissues with high perfusion (kidney, liver, heart) and fatty tissue. Distribution volume is 0.8-1.3 L/kg.

Biotransformation:
Tinidazole:
Tinidazole is partly metabolized by oxidation, hydroxylation, and conjugation. Tinidazole is biotransformed mainly by CYP3A4.

Tioconazole:
Primary metabolite of tioconazole is glucuronide conjugate.
Tioconazole does not appear to be metabolized in vaginal fluid, but a portion of the drug that is absorbed systemically following intravaginal application is metabolized. One reported metabolite is formed from N- glucuronidation of a nitrogen on the imidazole ring, another is formed by O-dethienylation of a chlorothienyl group, hydration to an alcohol, and glucuronidation.

Lidocaine:
It is metabolized in the liver. The active metabolites are monoethylglycinexylidide (MEGX) and glycinexylidide (GX).

Elimination:
Tinidazole:
The plasma half-life of tinidazole is approximately 12-14 hours. Tinidazole is excreted by the liver and the kidneys. Tinidazole is excreted in the urine mainly as unchanged drug (approximately 20-25% of the administered dose). Approximately 12% of the drug is excreted in the feces.

Tioconazole:
After intravaginal application of tioconazole, drug is usually eliminated from plasma in 72 hours.
Following oral tioconazole administration, 25-27% of the dose is excreted in urine as metabolites and 59% of the dose is excreted in feces (principally as unchanged drug).

Lidocaine:
After intravenous administration, 90% of the drug is excreted as metabolites and less than 10% is excreted as unchanged drug in urine.

Preclinical safety data
The active ingredients of Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL), are well known, regularly used substances, and are described in pharmacopoeias. New preclinical safety studies are not conducted because many toxicological studies are available for these substances.

INDICATIONS:
Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL) vaginal suppository is indicated in the treatment of candidal vulvovaginitis caused by *Candida albicans*, bacterial vaginosis caused by *Gardnerella vaginalis* and anaerobic bacteria, trichomonal vaginitis caused by *Trichomonas vaginalis*, and mixed vaginal infections.

CONTRAINDICATIONS:
Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL) should not be used,
- In patients known to be hypersensitive to the active ingredients or their derivatives,
- During the first trimester of pregnancy,
- During lactation,
- In patients with organic neurologic disorders,
- In patients with current picture or history of blood dyscrasia.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Only for intravaginal use. Not to be swallowed or applied by other routes.

As other drugs of similar structure, tinidazole must not be used in patients with current picture or history of blood dyscrasia. Transient leukopenia and neutropenia may develop. In the preclinical and clinical studies, no persistent hematologic abnormalities were observed.

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

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

It should be used carefully in patients with cardiovascular disorders. Lidocaine can lead to heart rhythm disorders, difficulty in breathing, coma and even death if it is applied especially on large skin surfaces under occlusion.

The vaginal suppositories must not be used with contraceptive diaphragms and condoms since the suppository base may damage the rubber. Other vaginal products (e.g. tampon, douche or spermicide) should not be used during the treatment.

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

It is not known if Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL) has influence on the ability to drive and use machines.

PREGNANCY AND LACTATION:
The pregnancy category is C.

Women having child bearing potential/ Birth Control (Contraception)
Since the effects of active ingredients in Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL) 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
Tinidazole crosses the placental barrier. Animal studies are insufficient with respect to effects on pregnancy and/or embryonal/fetal development and/or parturition and/or postnatal development. The potential risk for humans is unknown.

Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL) should not be used in the first trimester due to insufficient data. Usage during the second and third trimesters must be evaluated by the physician according to the benefits/risks ratio, and it should not be used during pregnancy unless clearly necessary.

Lactation
Breastfeeding should be discontinued during the treatment, since tinidazole appears in milk. Breastfeeding can be started again 72 hours after the end of treatment.
It is not known if tioconazole is excreted in milk.
It is not known whether lidocaine is excreted in milk. Caution should be exercised when lidocaine is administered to a breastfeeding woman.

Reproduction / Fertility
In a 60-day fertility study, tinidazole reduced fertility and produced testicular histopathology in male rats at a 600 mg/kg/day dose level. Spermatogenic effects resulted from 300 and 600 mg/kg/day dose levels. The no observed adverse reaction level for testicular and spermatogenic effects was 100 mg/kg/day. This effect is characteristic of agents in the 5-nitroimidazole class.

No impairment of fertility was seen in male rats when oral tioconazole doses up to 150 mg/kg/day is administered. However, there was evidence of preimplantation loss in female rats at oral dose levels above 35 mg/kg/day.

There is no evidence that lidocaine has harmful effects on animal or human fertility.

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).

Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL) is well tolerated in the application site.

Adverse effects related to the systemic usage of the active ingredients in Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL) are listed below, although they are not reported in the vaginal administration. Since blood levels of tinidazole, tioconazole and lidocaine are lower in the intravaginal administration, these adverse effects are expected to be seen more rarely. Inform your physician if you experience any of the undesirable effect.

Blood and lymphatic system disorders:
Not known: Leukopenia (temporary), neutropenia

Immune system disorders:
Not known: Allergic reactions (anaphylactic shock can be seen in severe cases)

Nervous system disorders:
Common: Weakness, fatigue, malaise, headache, dizziness
Not known: Ataxia, coma (rare), confusion (rare), depression (rare), loss of sensation, drowsiness, insomnia, sleep disturbances, anxiety, psychosis, seizure, speech impairment, agitation, apprehension, vertigo, peripheral neuropathy, convulsion, cramp, superexcitation, disorientation, euphoria, hallucination, hyperesthesia, lethargy.

Cardiac and vascular disorders:
Not known: Arrhythmia, bradycardia, arterial spasm, cardiovascular collapse, increase in the defibrillator threshold, edema, flushing, heart block, hypotension, sinus node suppression.

Gastrointestinal disorders:
Common: Metallic/bitter taste, nausea, anorexia, loss of appetite, flatulence, dyspepsia, abdominal cramp, epigastric discomfort, vomiting, constipation
Not known: Stomachache, diarrhea, furred tongue (rare), stomatitis, tongue discoloration, dry mouth, pseudomembranous colitis

Skin and subcutaneous tissue disorders:
Not known: Itching, urticaria, angioneurotic edema, cutaneous eruption

Renal and urinary disorders:
Common: Darkened urine

General disorders and administration site conditions:
Not known: Local burning, urinary burning, edema, local irritation, itching, vaginal discharge, dyspareunia, nocturia, vaginal pain

If you experience any of the following, stop using Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL) and inform your physician or consult to the emergency service of the nearest hospital immediately:
- Serious skin rashes
- Swelling in the face, lips, tongue and throat, shortness of breath.

INFORM YOUR PHYSICIAN WHENEVER AN UNEXPECTED EFFECT IS OBSERVED.

INTERACTIONS:
Due to tinidazole absorption, the following interactions can be seen if used concomitantly with the drugs below:
Acenocoumarol, Anisindione, Dicoumarol, Phenindione, Phenprocoumon, Warfarin: Increase in bleeding risk,
Cholestyramine: Decrease in the efficacy of tinidazole,
Cimetidine: Increase in plasma concentrations of tinidazole,
Cyclosporine: Increase in levels of cyclosporine,
Disulfiram: Central nervous system related effects (e.g. psychotic reactions),
Fluorouracil: Increase in plasma levels of fluorouracil and signs of a potential fluorouracil intoxication (granulocytopenia, anemia, thrombocytopenia, stomatitis, vomiting),
Fosphenytoin: Increase in fosphenytoin toxicity and/or decrease in plasma concentrations of tinidazole,
Ketoconazole: Increase in plasma concentrations of tinidazole,
Lithium: Increase in plasma concentrations of lithium and signs of lithium intoxication (weakness, shaking, polydipsia, confusion),

Phenobarbital: Decrease in plasma concentrations of tinidazole,
Phenytoin: Increase of a potential phenytoin intoxication and/or decrease in plasma concentrations of tinidazole,
Rifampin: Decrease in plasma concentrations of tinidazole,
Tacrolimus: Increase in levels of tacrolimus,
CYP3A4 inducers/inhibitors: Decrease in the efficacy of tinidazole or increase in the risk of adverse reactions (CYP3A4 inhibitors such as cimetidine and ketoconazole, may prolong the half-life and decrease the plasma clearance of tinidazole and increasing the plasma concentrations of tinidazole).

Due to tioconazole absorption, the following interactions can be seen if used concomitantly with the drugs below:
Oxycodone: Simultaneous administration of tioconazole and oxycodone may increase the plasma concentration of oxycodone and decrease the clearance of oxycodone.

Due to lidocaine absorption, the following interactions can be seen if used concomitantly with the drugs below,
Propranolol: Decrease in the plasma clearance of lidocaine,
Cimetidine: Decrease in the plasma clearance of lidocaine,
Antiarrhythmic products: Increase in lidocaine toxicity,
Phenytoin or barbiturates: Decrease in the plasma level of lidocaine.

Additional Information on Special Populations
No interaction study has been conducted in special population

Additional Information on Pediatric Population:
No interaction study has been conducted in pediatric population

DOSAGE AND METHOD OF ADMINISTRATION:
Do not use without consulting a physician. If it is not advised otherwise by a physician, 1 suppository should be inserted high into the vagina at night for 3 days. It is not advised to be used twice a day by no means. Administration during menstrual period is not recommended due to impaired efficacy and difficulty of administration.

Suppositories should be inserted in lying position high into the vagina. If possible, do not stand up for half an hour after placing the suppository.
Only for intravaginal use. Not to be swallowed or applied by other routes.

Additional Information on Special Populations
Elderly (over 65 years): Same as for younger adults
Should not be used in children under 12 years old.

Renal/Liver failure:
No significant changes in the pharmacokinetic parameters (CrCL < 22 mL/min.) of tinidazole were found in patients with severe renal failure. Therefore, dosage adjustment is not necessary in patients with that condition. Clearance of tinidazole increases significantly during hemodialysis and the half-life reduces from 12 hours to 4.9 hours. During a 6-hour dialysis procedure, 43% of the available tinidazole was eliminated. If tinidazole will be applied before hemodialysis, the administration of half-dose of recommended tinidazole after hemodialysis is advised.

There is no data about the pharmacokinetic of tinidazole for the patients with hepatic failure. Recommended dose of tinidazole must be administered carefully in patients with hepatic failure.

Lidocaine half-life may be prolonged two folds or more in patients with hepatic failure. Renal failure does not affect the pharmacokinetics of lidocaine, however it may increase the accumulation of metabolites. These characteristics should be taken in consideration by patients with hepatic and/or renal failure who will use Tioconazole + Tinidazole + Lidocaine (Neopenmax® XL).

OVERDOSAGE AND TREATMENT:
If accidental ingestion of large quantities of the product occurs, systemic effects can be seen according to the active ingredients, but it is not expected to cause life threatening symptoms when it is applied via vaginal route.

There is no specific antidote for tinidazole. Symptomatic and supportive treatment is instituted. Gastric emptying may be applied. Side/adverse effects are not known with overdose.

Overdose is unlikely to occur with local administration due to the negligible systemic absorption level of tioconazole.

When very high doses of lidocaine are administrated topically, heart rhythm disorders, difficulty in breathing, coma and even death can be seen.

PHARMACEUTICAL PARTICULARS:
INCOMPATIBILITIES: There is no known incompatibility
EXCIPIENT: Hard Fat

STORAGE CONDITIONS:
Store at temperatures not exceeding 30°C. Keep out of reach and sight of children and keep in its original package. Do not use after expiration date indicated on the package.

SHELF-LIFE:
Please see outer carton

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph Seek medical attention immediately at the first sign of any adverse drug reaction.

AVAILABILITY:
PVC/PE Duplex Foil Casing Strips (Box of 3's)
DR- XY48443

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