SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
NOVO-VULOTRAN FORTE L Vaginal Suppository

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vaginal ovule contains

Active substances:
Metronidazole 750 mg
Miconazole nitrate 200 mg
Lidocaine 100 mg

Excipients with known effect:
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Vaginal ovule.
A homogenous, white-off to yellow colored, ellipsoid ovule with a conventional dosage form.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
It is used in the treatment of candidal vulvovaginitis due to *Candida albicans*, in bacterial vaginitis due to anaerobic bacteria and *Gardnerella vaginalis* and in mixed vaginal infections.

4.2 Posology and method of administration
Posology/frequency and duration of administration:
It should not be used without consulting a physician.
If it is not advised to the contrary by a physician:
For the initial treatment, 1 ovule should be inserted deep into the vagina at nights for 7 days.
In recurrent resistant cases, 1 vaginal ovule at nights for 14 days may be recommended.

Administration of NOVO-VULOTRAN FORTE L during menstrual period is not recommended, as the efficacy may decrease or the application can be more difficult.

Method of administration:
Only for intravaginal use. NOVO-VULOTRAN FORTE L should be inserted deep into the vagina in supine lying position, using disposable fingerstalls provided in the package. Not to be swallowed or applied by other routes.

Additional information for special populations:
Renal/Hepatic impairment:
In renal impairment, 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 in severe renal function insufficiency requiring hemodialysis.

In severe hepatic impairment, metronidazole clearance may be impaired. Metronidazole may increase encephalopathy symptoms due to increased plasma levels and therefore it should be used carefully in hepatic encephalopathy patients. The daily dose of metronidazole must be reduced to 1/3 in patients with hepatic encephalopathy.

The half-life of lidocaine may be prolonged two folds or more in patients with impaired liver function. Impaired renal function does not affect the pharmacokinetics of lidocaine but may increase accumulation of metabolites. These features should be taken into account by patients with liver and/or renal function disorders who will use NOVO-VULOTRAN FORTE L.

Pediatric population:
Not to be used in children under 12 years of age.

Geriatric population:
Adult dose should be applied for elderly over 65 years.

4.3 Contraindications
NOVO-VULOTRAN FORTE L should not be used:
- In patients with hypersensitivity to the active substances in its composition, or their derivatives such as imidazole derivatives, or to any of the excipients listed in section 6.1,
- In patients who drink alcohol during treatment or at least 48 hours after end of treatment,
- In patients who use disulfiram during treatment or anytime within last 2 weeks,
- During the first trimester of pregnancy,
- In patients with trichomonal vaginitis during the first trimester of pregnancy,
- In cases of porphyria, epilepsy and severe hepatic dysfunction.

4.4 Special warnings and precautions for use
If NOVO-VULOTRAN FORTE L administration is necessary for more than 10 days, regular clinical and laboratory monitoring (especially leukocyte count) is recommended and patients should be monitored for adverse reactions such as peripheral or central neuropathy (e.g. paresthesia, ataxia, dizziness, convulsive seizures).

Systemic metronidazole should be used with caution in patients with active or chronic severe peripheral and central nervous system disease due to the risk of neurological deterioration.

Cases of serious hepatotoxicity/acute liver failure, including cases with fatal outcome that began very rapidly after initiation of treatment, have been reported with products containing metronidazole for systemic use in patients with Cockayne syndrome. In this population, metronidazole should be used after careful benefit/risk assessment and only if no alternative treatment is available. Liver function tests should be performed immediately before the start of treatment, throughout treatment and thereafter until liver function is within normal limits or baseline values are reached. If liver function tests become significantly elevated during treatment, the drug should be discontinued.

Patients with Cockayne syndrome should be advised to promptly report any symptoms of possible liver damage to the doctor and to stop taking metronidazole.

Cases of serious bullous skin reactions, such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or acute generalized exanthematous pustulosis (AGEP), have been reported with metronidazole. If symptoms or signs of SJS, TEN or AGEP are present, NOVO-VULOTRAN FORTE L treatment should be discontinued immediately.

In renal failure, the half-life of metronidazole does not change. Therefore, there is no need to

reduce the metronidazole dose. However, in such patients, metabolites of metronidazole may accumulate in the blood. The clinical significance of this is currently unknown.

In patients receiving hemodialysis, metronidazole and its metabolites are effectively eliminated during an 8-hour dialysis period. Therefore, metronidazole should be re-administered immediately after hemodialysis.

In patients with renal impairment undergoing intermittent peritoneal dialysis (IPD) or continuous ambulatory peritoneal dialysis (CAPD), no routine dosage adjustment of NOVO-VULOTRAN FORTE L is required.

In severe liver failure, metronidazole clearance becomes difficult. Metronidazole should be used with caution in patients with hepatic encephalopathy as its plasma concentration may increase and thus increase the symptoms of encephalopathy. The oral daily dose of metronidazole should be reduced by one-third and given as a single dose in patients with hepatic encephalopathy.

Patients should be warned that darkening of the urine color might occur. Due to insufficient evidence regarding the risk of mutagenicity in humans (see section 5.3), use of NOVO-VULOTRAN FORTE L for longer than necessary should be carefully considered.

Since a disulfiram-like reaction may occur, patients should not consume alcohol during the treatment and until 48 hours after the treatment ends.

Depending on systemic use, metronidazole may cause peripheral neuropathy and convulsions at high doses and in long-term use. Psychotic reactions have been reported with concurrent systemic use of metronidazole and disulfiram.

It should not be used on virgins and girls who have not reached sexual maturity.

Lidocaine, especially when applied to large skin surfaces and particularly under occlusion, can cause heart rhythm disturbances, breathing difficulties, coma and even death.

These effects are not possible to arise when NOVO-VULOTRAN FORTE L is applied intravaginally as ovules and as indicated in the “Posology/frequency and duration of administration” section.

Contact with contraceptive agents such as latex-containing condoms and diaphragms may reduce the effectiveness of contraceptive agents. For this reason, NOVO-VULOTRAN FORTE L should not be brought into contact with a contraceptive diaphragm or condom.

NOVO-VULOTRAN FORTE L should not be used with other vaginal products (e.g. tampons, douche and spermicide) during treatment.

In cases of trichomonal vaginitis, treatment of the patient's partner is also necessary.

Since there is insufficient evidence regarding the risk of mutagenicity in humans (see section 5.3), caution should be taken when using NOVO-VULOTRAN FORTE L for longer than normal periods.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions due to metronidazole absorption can be seen if used with the drugs below:

Alcohol: Patients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction.

Disulfiram: Psychotic reactions have been reported in patients receiving concomitant metronidazole.

Warfarin-type oral anticoagulants: When used together with oral metronidazole, the dose of oral anticoagulant may need to be reduced as the effectiveness of anticoagulant treatment may increase. Therefore, in combined use, prothrombin levels should be checked frequently. It does not interact with heparin.

Lithium: Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously oral metronidazole. Lithium treatment should be tapered or withdrawn before administering metronidazole. Plasma concentrations of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Phenobarbital-phenytoin: Increases the elimination of metronidazole, reducing its half-life to 3 hours.

5-fluorouracil: Metronidazole reduces the clearance of 5-fluorouracil and may therefore lead to increased toxicity of 5-fluorouracil.

Cyclosporine: Increased serum levels of cyclosporine may occur. If co-administration with metronidazole is necessary, serum cyclosporine and serum creatinine levels should be closely monitored.

Busulfan: Metronidazole may increase the plasma concentration of busulfan and thus its toxicity.

Amiodarone: Metronidazole inhibits the metabolism of amiodarone. Increased risk of cardiotoxicity (prolongation of QTc interval, torsade de pointes, cardiac arrest).

Astemizole and terfenadine: They should definitely not be used.

Carbamazepine: The mechanism of interaction is not known. However, metronidazole probably inhibits the metabolism of carbamazepine.

Vecuronium: (non-depolarizing neuromuscular blocking drug); Metronidazole potentiates the action of vecuronium.

Cholestyramine: May lead to decreased absorption of metronidazole and thus reduced effectiveness.

Ergot alkaloids: Metronidazole inhibits the cytochrome P450 3A4 system, thereby decreasing the metabolism of ergot derivatives. The risk of ergotism (nausea, vomiting, and vasospastic ischemia) increases.

Metronidazole immobilizes treponema and therefore gives a false positive result in the Treponema pallidum immobilization test.

Metronidazole may cause changes in AST (SGOT), ALT (SGPT), LDH, triglycerides or glucose measurements when measured using the ultraviolet absorbance method.

Interactions due to miconazole nitrate absorption can be seen if used concomitantly with the drugs below:

Acenocoumarol, Anisindione, Dicoumarol, Phenindione, Phenprocoumon, Warfarin: Increased bleeding risk.

Astemizole, cisapride and terfenadine: Miconazole inhibits metabolism of these drugs and increases their 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: Increased plasma concentration and decreased clearance of oxycodone.

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

Cyclosporine: Increase in cyclosporine toxicity risk (renal dysfunction, cholestasis, paresthesia).

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

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

Interactions due to lidocaine absorption can be seen if used concomitantly with the drugs below:

Antiarrhythmic products: Increase in lidocaine toxicity.

Phenytoin or barbiturates: Decrease in lidocaine plasma level.

Propranolol: Decrease in lidocaine plasma clearance.

Cimetidine: Decrease in lidocaine plasma clearance.

Additional information on special populations:
No interaction studies have been conducted on special populations.

Pediatric population:
No interaction studies have been conducted on children.

4.6 Fertility, pregnancy and lactation

General principles

Pregnancy category is C.

Women with childbearing potential/Contraception
Since the effects of the active substances in NOVO-VULOTRAN FORTE L on fetus and newborn development are not completely known, patients who need to administer the drug should avoid pregnancy with a proper birth control method.

Pregnancy
Animal studies are insufficient regarding effects on pregnancy, embryonal/fetal development, birth and/or postnatal development. Potential risk for humans is not known.

There is no sufficient data on the use of NOVO-VULOTRAN FORTE L in pregnant women in the first trimester. Therefore, NOVO-VULOTRAN FORTE L should not be used in the first trimester of pregnancy. The benefit/risk ratio in the second and third trimesters of pregnancy should be evaluated by a physician and the drug should not be used during pregnancy unless it is necessary.

Breastfeeding
Since metronidazole passes into breast milk, the baby should be weaned during treatment, and breastfeeding can be continued 24-48 hours after the treatment ends.

Although it is not known whether lidocaine passes into breast milk, it is recommended to use it with caution in breastfeeding women.

Fertility
There is no evidence that metronidazole, miconazole nitrate and lidocaine, when given alone, have any deleterious effects on the fertility of humans or animals.

4.7 Effects on ability to drive and use machinery

Systemic use of metronidazole may affect the ability to drive and use machinery. Compared with systemic application, metronidazole is absorbed at lower rates through vaginal route. Since the use of NOVO-VULOTRAN FORTE L may cause dizziness, ataxia, fatigue and weakness, it may affect your ability to drive a motor vehicle and use machines.

4.8 Undesirable effects

The frequency of adverse events 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 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%). These symptoms may be prevented with the local anesthetic action of lidocaine contained in the ovules. Since the vaginal mucosa may become inflamed in vaginitis, symptoms of vaginal irritation, burning and itching may occur when the first vaginal ovule is applied or towards the third day of treatment. These symptoms decrease very fast and disappear when the therapy is continued. If there are signs of severe irritation, treatment should be discontinued.

The absorption of lidocaine from NOVO-VULOTRAN FORTE L is very low. Actual adverse reactions with local anesthetics occur in less than 1/1,000 of patients.

Undesirable effects that may occur due to systemic use of the active substances contained in NOVO-VULOTRAN FORTE L are listed below.

Blood and lymphatic system disorders
Very rare: Agranulocytosis, neutropenia, thrombocytopenia, pancytopenia
Not known: Leucopenia, methemoglobinemia

Immune system disorders
Rare: Anaphylaxis
Not known: Angioedema, urticaria, fever

Metabolism and nutrition disorders
Not known: Anorexia

Psychiatric disorders
Very rare: Mood swings, psychotic disorders including confusion and hallucinations
Not known: Depressive mood

Nervous system disorders
Very rare: Encephalopathy (e.g. confusion, fever, headache, hallucination, paralysis, sensitivity to light, movement disorder, neck stiffness) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) that may resolve with drug discontinuation, and subacute cerebellar syndrome (e.g. ataxia, dysarthria, gait disturbance, nystagmus and tremor), dizziness, convulsions, insomnia, headache
Not known: During intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced. Fatigue or weakness, paleness, tingling, loss of sensation, paresthesia, disorientation, agitation, psychosis, seizure, speech impairment, hyperesthesia, hypoesthesia, lethargy, hallucinations, heat sensation,

nervousness, uneasiness, euphoria, drowsiness, blurred or double vision, chills, tremor, loss of consciousness, coma (rare), anxiety, insomnia, aseptic meningitis

Eye disorders
Very rare: Vision disorders such as diplopia and myopia, which, in most cases, is transient
Not known: Optic neuropathy/neuritis

Ear and labyrinth disorders
Not known: Hearing impaired/hearing loss (including sensorineural), tinnitus

Gastrointestinal disorders
Not known: Taste disorders; oral mucositis; metallic taste in the mouth; nausea; vomiting; gastrointestinal disturbances such as epigastric pain and diarrhea; dry mouth; loss of appetite; abdominal pain or cramp

Hepatobiliary disorders
Very rare: Increase in liver enzymes (AST, ALT, alkaline phosphatase); cholestatic or mixed hepatitis and hepatocellular liver injury; jaundice and pancreatitis which is reversible on drug withdrawal. Cases of liver failure requiring liver transplant have been reported in patients treated with metronidazole in combination with other antibiotic drugs.

Skin and subcutaneous tissue disorders
Very rare: Skin rashes, pustular eruptions, acute generalized exanthematous pustulosis, pruritus, facial flushing
Not known: Erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption

Musculoskeletal, connective tissue and bone disorders
Very rare: Myalgia, arthralgia

Renal and urinary disorders
Very rare: Darkening of urine (due to metronidazole metabolite)

General disorders and administration site conditions
Very common: Vaginal discharge
Common: Vaginitis, vulvovaginal irritation, pelvic inconvenience
Uncommon: Thirst
Rare: Vaginal burning, itching and irritation, abdominal pain, skin rash, allergic reactions (anaphylactic shock)
Not known: Local irritation and sensitivity, contact dermatitis
These side effects occur very rarely because of low blood levels of metronidazole and lidocaine after intravaginal application compared with systemic applications.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

If large quantities of the ovule are applied, systemic effects due to metronidazole may be seen; however, no life-threatening effects are expected due to intravaginal metronidazole application. In cases of overdosage, a symptomatic and supportive treatment should be instituted. There is no specific antidote for metronidazole overdosage. Oral overdoses of metronidazole, up to 12 grams have been reported in suicide attempts. Symptoms were limited to vomiting, ataxia and slight disorientation.

Symptoms due to metronidazole may include nausea, vomiting, abdominal pain, diarrhea, itching, metallic taste, ataxia, dizziness, paresthesia, convulsion, leucopenia, darkening of urine. Symptoms due to miconazole nitrate may include burning sensation in the mouth and throat, anorexia, nausea, vomiting, headache, diarrhea.

Lidocaine may cause cardiac rhythm disorders, shortage of breath, coma and even death particularly if applied to extensive skin surfaces and especially in very high doses.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives and antiseptics, excluding combinations with corticosteroids; Combinations of imidazole derivatives.
ATC code: G01AF20

NOVO-VULOTRAN FORTE L contains the active substances miconazole nitrate for antifungal effect, metronidazole for antibacterial and antitrichomonal effect and lidocaine for local anesthetic effect. Miconazole nitrate that is a synthetic imidazole antifungal agent has a wide spectrum of activity and is particularly effective against pathogen fungi including Candida albicans. In addition, miconazole nitrate is effective against Gram-positive 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.

Lidocaine stabilizes the neuronal membrane by inhibiting the conduction of impulses, thereby producing local anesthetic action. Miconazole, metronidazole and lidocaine are not synergic or antagonistic.

Miconazole, metronidazole and lidocaine are neither synergistic nor antagonistic.

In an efficacy and safety study conducted with miconazole, metronidazole and lidocaine combination on 35 patients with vaginitis, microbiologic cure rates are determined as 84% and 92% for the 8th day (Visit 2) and 3rd week (Visit 3) respectively and clinical cure rates are 88% in the same periods.

5.2 Pharmacokinetic properties

General properties

Absorption:
Miconazole nitrate
Absorption of miconazole nitrate by the intravaginal route is very low (approximately 1.2% of the dose). Following the application of metronidazole and miconazole nitrate and lidocaine combination, no miconazole nitrate could be detected in plasma.

Metronidazole
Bioavailability of metronidazole by the intravaginal route is approximately 20% compared to oral administration. Steady state levels of metronidazole in plasma ranged 1.1-5.0 mcg/mL after application of metronidazole and miconazole nitrate and lidocaine combination.

Lidocaine
Lidocaine is absorbed in very low amounts from injured skin and mucous membranes. Following administration of metronidazole and miconazole nitrate and lidocaine combination, lidocaine was absorbed minimally and steady state levels in plasma ranged 0.04-1 mcg/mL.

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.

Lidocaine
Lidocaine applied through oral or intravenous route is determined in bowels, urine and in low amounts in feces. It is found in the urine as unchanged drug and its metabolites. Lidocaine binds with plasma proteins (primarily to α1-acidglycoprotein, less to albumin) in a ratio 33-80%. Distribution volume is 0.8-1.3 L/kg.

Biotransformation:
Miconazole nitrate
It is metabolized in the liver. It 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
It is metabolized in the liver. It has active metabolites monoethylglicinexylidide (MEGX) and glicinexylidide (GX).

Elimination:

Miconazole nitrate
Half-life is 24 hours. Less than 1% of it is excreted via the kidneys. Approximately 50% is excreted, mostly unchanged, in the feces.

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

Lidocaine
Excreted via the kidneys as metabolites and unchanged form (10% of the applied dose).

Linearity/Non-linearity:
No data available.

5.3 Preclinical safety data
Metronidazole
Metronidazole has been shown to be carcinogenic in the mouse and in the rat following chronic oral administration however similar studies in the hamster have given negative results. Epidemiological studies have provided no clear evidence of an increased carcinogenic risk in humans.

Metronidazole has been shown to be mutagenic in bacteria *in vitro*. In studies conducted in mammalian cells *in vitro* as well as in rodent or humans *in vivo*, there was inadequate evidence of a mutagenic effect of metronidazole, with some studies reporting mutagenic effects.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Polyethylene glycol 1000
Witepsol

6.2 Incompatibilities
There are no known incompatibilities.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at room temperature below 25°C.

6.5 Nature and contents of container
A custom-made Opaque PVC/PE was used as the primary packaging material.
Supplied in a cardboard box with 7 ovules, 7 fingerstalls and a package leaflet.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2016/347

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 20.04.2016
Date of latest renewal :

10. DATE OF REVISION OF THE TEXT

14.08.2023