# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

TRIMIC FORTE L Vaginal Suppositories

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal suppository contains:
Metronidazole 750 mg
Miconazole nitrate 200 mg
Lidocaine 100 mg

For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Vaginal Suppositories
White to off white opaque bullet shaped suppositories.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Trimic Forte L Vaginal Suppository 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 suppository 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 suppository at night for 14 days is recommended.
Only for intravaginal use. TRIMIC FORTE L vaginal suppository should be applied in lying position. Not to be swallowed or applied by other routes.

- Wash your hands.
- Do not open vaginal suppository 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.
- Remove one vaginal suppository from the strip and hold it in fingertips.
- Remove any foil or plastic wrapping stuck to the vaginal suppository.
- Sit or lie down with your knees bent and legs apart.
- Gently insert the vaginal suppository into the vagina as far as comfortably possible using your fingers.
- Wash your hands again.

**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 / 3rd 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 Trimic Forte L.

**Paediatric population:**
Not to be used in children under 12.

**CONTRAINDICATIONS**

Trimic Forte L should not be used

- in patients known to be hypersensitive to the active ingredients or their derivatives,
- who take alcohol during treatment or at least 3 days after end of treatment,
- who use disulfiram during treatment or 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 liver function disorders.

**4.4 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 a course of treatment, because of the possibility of disulfiram -like reactions.

High doses and long term systemic usage may cause peripheral neuropathy and convulsion. Should not be used in young people (girls) who are not sexually mature.

Lidocaine may cause cardiac rhythm disorders, difficulty in breathing, coma and even death especially when applied to to extensive skin surfaces and especially under occlusion.

These effects are not possible to arise when TRIMIC FORTE Lis applied intravaginally as suppositories and as indicated on "Dosage and administration" section.

Suppositories should not contact contraceptive diaphragms or condoms since they can cause damage on rubber.

During treatment with TRIMIC FORTE L 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**.**

**4.5 Interaction with other medicinal products**

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, and 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).
Due to lidocaine absorption, the following interactions 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.

**Paediatric population:**
No interaction studies have been performed on children.

**4.6 Pregnancy and lactation General recommendation**
Pregnancy category is C.

**Women of childbearing potential / Contraception**

Since the effects of active ingredients comprised by TRIMIC FORTE L combination on born growth are not known exactly, people who need to administer the drug 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 humans is not known.
There is no sufficient data on the use of TRIMIC FORTE L in pregnant women in the first trimester. Therefore TRIMIC 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 should not be administered in the period of pregnancy unless it is necessary.

**Lactation Period**
Breastfeeding should be discontinued during therapy, since metronidazole appears in milk. Breastfeeding can be started again 24-48 hours after the end of treatment.
It is not known whether lidocaine appears in human milk or not. Caution should be exercised when lidocaine is administered to a nursing woman.

**Reproduction / Fertility**
There is no evidence regarding any negative effect on fertility in humans or animals of either metronidazole, or miconazole nitrate or lidocaine when given alone.

**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.
Use of TRIMIC FORTE L can cause dizziness, ataxia, fatigue and weakness therefore may effect driving or operating machinery.

**4.8 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 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. In vaginitis since the vaginal mucosa may be inflammed, vaginal burning, itching and vaginal irritation symptoms may occur when the first vaginal Suppository is administered or towards the third day of the therapy. These symptoms decrease very fast and disappear when the therapy is continued. If there is severe irritation, treatment should be discontinued. Absorption level of lidocaine from TRIMIC FORTE L is very low.
Adverse effects really appearing with local anaesthetics are observed on less

than 1/1000 of the patients.

Undesirable effects that may arise due to systemic use of the active ingredients comprised by TRIMIC FORTE L are listed below:

**Blood and lymph system disorders:**
Not known: Leukopenia

**Immune system disorders:**
Very rare: Hypersensitivity reactions, allergic reactions (anaphylactic shock may occur on serious cases)

**Psychiatric disorders:**
Uncommon: Depression
Very rare: Mental changes

**Nervous system disorders:**
Common: vertigo, headache
Not known: Fatigue, weakness, malaise, tingling, loss of sensation, parastesia, peripheral neuropathy due to intensive and/or prolonged metronidazole therapy, numbness, disorientation, agitation, psychosis, seizure, speech impairment, hyperesthesia, hypoesthesia, lethargy, hallucination, sensation of heat, ataxia, convulsion, nervousness, uneasiness, euphoria, confusion, ringing in the ears, somnolence, fuzzy or double vision, cold, tremor, loss of consciousness, coma (rare), anxiety, insomnia.

**Cardiovascular disorders**
Not known: Arrhythmia, bradycardia, arteriospasm, decrease in blood pressure, cardiovascular collapse, increase in defibrillator threshold, edema, flushing, heart block, hypotension, sinus node suppression.
Absorption of lidocaine from TRIMIC FORTE L is very low and no such side effects are reported until now.

**Gastrointestinal disorders:**
Not known: Taste changes, metallic taste in the mouth, vomiting, nausea, constipation, dry mouth, diarrhoea, lack of appetite, abdominal pain or cramp

**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 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**
Healthcare professionals are requested to report any suspected adverse reactions the National Regulatory Authority reporting systems via national

Pharmacovigilance Electronic Reporting Systems' Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org"

**4.9 Overdose**

If large quantities of the suppositories are applied, systemic effects due to metronidazole may occur; however, no life-critical indications are expected due to metronidazole applied through vaginal route.

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

## 5. PHARMACOLOGICAL PROPERTIES:

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antibacterial, antiprotozoal, antifungal, anaesthetic TRIMIC FORTE L contains miconazole nitrate for antifungal, metronidazole for antibacterial and antitrichomonal effects and also lidocaine for local anaesthetic effect.

Miconazole nitrate which 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.

**5.2 Pharmacokinetic Properties**

**General properties Absorption:**

Miconazole nitrate: Absorption of miconazole nitrate by the intravaginal route is very low (approximately 1.4% of dose). Following the application of NEO-PENOTRAN® FORTE L, no miconazole nitrate could be detected in plasma.

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.

Lidocaine: Lidocaine is absorbed from injured skin and mucous membranes in very low amounts. Following application of NEO-PENOTRAN® FORTE L, lidocaine was absorbed minimally and steady state levels in plasma ranged 0.04 - 1 µg/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 faeces. 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 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%.
Lidocaine: Excreted in urine as metabolites and unchanged form (10% of the applied dose).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients
Hard fat (Witepsol S-55)

### 6.2 Incompatibilities
There is no known incompatibility.

### 6.3 Shelf life
24 months

### 6.4 Special precautions for storage
Store in dry place, below 30°C. Protect from light.

### 6.5 Nature and contents of container

Strip of 7 vaginal suppositories is packed in PVC/PE foil in a mono carton along with pack insert.

**6.6 Special precautions for disposal and other handling:**
None stated.

## 7. MARKETING AUTHORISATION HOLDER

Bliss GVS Pharma Ltd.,
Saki Vihar Road, Andheri (East), Mumbai – 400 072.
India.

## 8. MARKETING AUTHORIZATION NUMBER

H2022/CTD7520/14297

## 9. DATE OF FIRST REGISTRATION

December 2022

## 10. DATE OF REVESION OF THE TEXT

February 2023