SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

INVEL FORTE L Vaginal Suppositories

2. COMPOSITION

Each vaginal pessary contains:

Metronidazole	750 mg
Miconazole nitrate	200 mg
Lidocaine	100mg

Excipients:
Hard fat

3. PHARMACEUTICAL FORM

Vaginal Suppositories
White opaque bullet shape suppositories

4. CLINICAL PARTICULARS

4.1 Therapeutic indications.

INVEL Forte L Vaginal Pessary 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

Dosage and 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 Pessary 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 Pessary at night for 14 days is recommended.

Method of Administration:
Only for intravaginal use. INVEL FORTE L Pessary should be applied in lying position. Not to be swallowed or applied by other routes.

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.
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 INVEL Forte L.

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
INVEL 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 special 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 INVEL FORTE Lis applied intravaginally as Pessaries and as indicated on “Dosage and administration” section.
Pessaries should not contact contraceptive diaphragms or condoms since they can cause damage on rubber.
During treatment with INVEL 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 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).
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.
Additional information about special population:
No interaction studies have been conducted on special populations.

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

4.6 Pregnancy and lactation

Pregnancy and lactation General recommendation
Pregnancy category is C.

Women of childbearing potential / Contraception
Since the effects of active ingredients comprised by INVEL FORTE L combination on fetus and newborn 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 INVEL FORTE L in pregnant women in the first trimester.
Therefore INVEL 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 INVEL 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 Pessary 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 INVEL 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 INVEL 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 INVEL 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, diarrhea, 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.

<u>Reporting of suspected adverse reactions</u>

Reporting suspected adverse reactions after authorisation 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 to **TMDA**

4.9 Overdose

If large quantities of the Pessary 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, 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. 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

Mechanism of action

Pharmacotherapeutic group: Antibacterial, antiprotozoal, antifungal, anaesthetics INVEL FORTE L contains miconazole nitrate for antifungal, metronidazole for antibacterial and antitrichomonal effects and also lidocaine for local anaesthetics 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

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).

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. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:
Hard fat.

6.2 Incompatibilities
There is no known incompatibility.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Keep out of reach of children.
Protect from light and moisture.
Store below 30^{o}C.

6.5 Nature and contents of container.
Invel Forte L is available in blister pack containing 7 vaginal suppositories.

6.6 Special precautions for disposal <and other handling>
Not applicable.

7. MARKETING AUTHORIZATION HOLDER
Mega Lifesciences Public Company Limited
384 Moo 4, Pattana 3 Road,
Bangpoo Industrial Estate, Soi 6, Preaksa, Muang Samutprakarn,
Samutprakarn 10280, Thailand

8. MARKETING AUTHORIZATION NUMBER (S)

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9. DATE OF FIRST REGISTRATION

21st September, 2022

10. DATE OF REVISION OF THE TEXT