SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
MIKONID 750 mg/200 mg/100 mg vaginal ovule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vaginal ovule contains:

Active substance(s):

Metronidazole	750 mg
Miconazole nitrate	200 mg
Lidocaine (Base)	100 mg

Excipient(s):
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Vaginal ovule
Off-white, homogeneous, custom-shaped ovule

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

4.2. Posology and method of administration
Posology/frequency of administration and duration of the treatment:
Do not use without consulting a physician.

Unless recommended by the physician otherwise:
For the initial treatment, 1 vaginal ovule is applied into the vagina for 7 days at nights. For recurrent resistant cases, application of 1 vaginal ovule at night for 14 days is recommended.

Using the product during the period of menstruation may lessen the activity of MIKONID and may cause difficulty in using, therefore it is not recommended to use during these periods.

Method of Administration:
The product is for intravaginal use only. While lying on your back, with the help of the finger cots available in the package insert MIKONID into the vagina.

Do not swallow or do not use otherwise.

Additional information for special populations:
Renal/Hepatic Failure:
The half-life of metronidazole in renal failure is not changed. Therefore, reducing the dose of metronidazole is not necessary; however, in severe renal dysfunction, which requires hemodialysis, dose adjustment should be made.

In serious hepatic failure, metronidazole clearance is impaired. In patients with hepatic encephalopathy, the increase in plasma concentrations of metronidazole may lead to increased symptoms of encephalopathy therefore should be used cautiously. Daily dose of metronidazole in hepatic encephalopathy patients should be reduced to 1/3.

In patients with hepatic dysfunction, the half-life of lidocaine may be increased two fold or more. Renal dysfunction does not affect the pharmacokinetics of lidocaine, but may increase the accumulation of metabolites. In patients with hepatic and/or renal dysfunction, these considerations should be taken into account before using MIKONID.

Pediatric population:
It is not used in children under 12 years old.

Geriatric population:
Adult dosage is applied to those over 65 years of age.

4.3. Contraindications
MIKONID should not be used;

- in patients with hypersensitivity to any of the active substances, their derivatives, amide type local anesthetics or any of the excipients contained in this product (see Section 6.1),
- in patients using alcohol during the treatment or within 3 days after the treatment,
- in patients using disulfiram during the treatment or within the last 2 weeks,
- during the first trimester,
- in pregnant women with trichomonal vaginitis during the first trimester,
- in porphyria, epilepsy or severe hepatic dysfunction.
- It should not be used with birth control methods such as diaphragm and condoms.

4.4. Special warnings and precautions for use
Metronidazole
Systemic administration of metronidazole at high doses and for long duration may cause to peripheral neuropathy and convulsion.

Metronidazole has no direct activity against aerobic or facultative anaerobic bacteria. If the use of vaginal suppositories containing metronidazole is required for more than 10 days, regular clinical and laboratory monitoring (especially the number of leukocytes) and follow-up of patients for peripheral or central neuropathy (such as paresthesia, ataxia, dizziness, and convulsive seizures) are recommended.

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

Serious cases of bullous skin reaction such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or acute generalized exanthematous pustulosis (AGEP) have been reported with the use of metronidazole. If symptoms or signs of these diseases appear, treatment with metronidazole should be discontinued immediately.

The elimination half-life of metronidazole remains unchanged in case of renal failure. Therefore, the dose of metronidazole need not be reduced. In these patients, however,

metronidazole metabolites remain. The clinical significance of this condition is currently unknown.

In patients under hemodialysis, metronidazole and its metabolites are effectively removed during dialysis, which lasts 8 hours. Therefore, metronidazole should be re-administered after hemodialysis.

In patients with renal failure who undergo intermittent peritoneal dialysis (IPD) or continuous peritoneal dialysis (CAPD), a routine adjustment of the dose of metronidazole-containing vaginal ovules is not required.

Metronidazole is mainly metabolized by hepatic oxidation. Substantial impairment of metronidazole clearance may occur in the presence of advanced hepatic insufficiency. Significant cumulation may occur in patients with hepatic encephalopathy and the resulting high plasma concentrations of metronidazole may contribute to the symptoms of the encephalopathy. Therefore, metronidazole should be administered with caution in patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.

Patients should be warned that metronidazole may darken urine color.

Due to inadequate evidence on the mutagenicity risk in humans (see section 5.3), the use of metronidazole for longer treatment than usually required should be carefully considered.

Since disulfiram-like reaction can be observed, alcohol should not be taken during treatment and for at least 48 hours after treatment.

Risk of hepatotoxicity and death in patients with Cockayne syndrome:
Cases of severe hepatotoxicity/acute hepatic failure, including cases with a fatal outcome with very rapid onset after treatment initiation in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should therefore be used after careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests should be performed before treatment, within the first 2-3 days after initiation of treatment, frequently during treatment and after end of treatment. If elevation of liver function tests occurs, discontinue use of metronidazole and monitor liver function tests until the baseline values are reached.

Advise patients with Cockayne syndrome or their relatives to stop taking metronidazole immediately if they experience any symptoms of potential liver injury, such as abdominal pain, nausea, change in stool color or jaundice, and to contact their healthcare provider.

Miconazole
Severe hypersensitivity reactions, including anaphylaxis and angioedema, have been reported during treatment with miconazole-containing vaginal capsules and other miconazole-containing formulations (see section 4.8). Treatment should be discontinued if a reaction similar to hypersensitivity or irritation occurs.

If there is an infection in the sexual partner, appropriate treatment should be performed.

Miconazole does not stain skin or clothing.

The combination of vaginal anti-infectives and latex condoms or diaphragms can reduce the effectiveness of latex contraceptive agents. Therefore, MIKONID and latex condoms or diaphragms should not be used together.

Lidocaine
Repeated doses of lidocaine may cause increased blood levels of lidocaine. Lidocaine should be used with caution in patients who may be more sensitive to the systemic effects of lidocaine, including acutely ill, debilitated, or elderly patients.

Lidocaine, if applied especially to a large surface of skin and especially under the occlusion, may lead to cardiac arrhythmia, respiratory difficulties, coma and even death.

These effects are unlikely to occur when administered intravaginally in the form of ovule, as specified in "**Posology/frequency of administration and duration of the treatment**".

Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) did not show cross-sensitivity to lidocaine. However, lidocaine should be used with caution in individuals with a history of drug sensitivity, especially if the etiologic agent is unclear. Patients with severe hepatic disease are at higher risk of developing toxic plasma concentrations of lidocaine as they are unable to metabolize local anesthetics normally.

The product should not be used in young people who are not sexually mature and **virgin**.

As ovules may reduce the effectiveness of contraceptive diaphragm and condoms, concurrent use with contraceptive diaphragm and condoms should be avoided.

During the treatment with MIKONID other vaginal products (e.g., tampons, douche, and spermicides) should not be used.

4.5. Interactions with other medicinal products and other forms of interaction
Interactions may develop due to absorption of metronidazole in concomitant use with:

Alcohol: Alcohol intolerance (disulfiram-like reaction),
Due to the possibility of a disulfiram-like reaction, patients should be warned not to drink alcohol during treatment with metronidazole and for at least 48 hours after treatment.

Amiodarone: Increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest),

Astemizole and terfenadine: Metronidazole inhibits the metabolism of these drugs thereby increases their plasma concentrations,

Disulfiram: Central nervous system related effects (psychotic reactions),

Phenytoin: Increased plasma levels of phenytoin, decreased plasma levels of metronidazole,

Phenobarbital: Decrease in plasma levels of metronidazole,
Patients receiving phenobarbital or phenytoin metabolize metronidazole at a much greater rate than normally, reducing the half-life to about 3 hours.

Fluorouracil: Increase in plasma levels and toxicity of fluorouracil,
Metronizadole reduces the clearance of 5 fluorouracil and therefore, concomitant use may result in an increase in toxicity of 5 fluorouracil.

Carbamazepine: Increase in plasma concentrations of carbamazepine,

Lithium: Increased lithium toxicity,
Lithium retention accompanied by evidence of possible renal damage has been reported in patients treated simultaneously with lithium and 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.

Oral anticoagulants: Increase in anticoagulant effect (Increase in bleeding risk),
When warfarin-type oral anticoagulants are used with metronidazole, some increase in anticoagulant effect has been reported. Therefore, the dose may need to be reduced. Prothrombin times should be monitored. There is no interaction with heparin.

Cyclosporine: Increased cyclosporine toxicity,
Patients receiving cyclosporin are at risk of elevated cyclosporine serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.

Cimetidine: Increase in plasma level of metronidazole and increased risk of neurologic side effects.

Busulfan: Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.

During the treatment with metronidazole, interference with the blood levels of liver enzymes, glucose (hexokinase method), theophylline, and procainamide may be observed.

Psychotic reactions have been reported in patients taking concomitant metronidazole and disulfiram.

Due to miconazole nitrate absorption, interactions can be seen if used concomitantly with the following drugs:

Miconazole administered systemically is known to inhibit CYP3A4/2C9. Due to the limited systemic availability after vaginal application, clinically relevant interactions occur very rarely. In patients on oral anticoagulants, such as warfarin, caution should be exercised and anticoagulant effect should be monitored. The effects and side effects of other drugs metabolized by CYP2C9 (e.g., oral hypoglycemics and phenytoin) and also CYP3A4 (e.g., HMG-CoA reductase inhibitors such as simvastatin and lovastatin and calcium channel blockers such as dihydropyridines and verapamil), when co-administered with miconazole, can be increased and caution should be exercised.

Acenocoumarol, Anisindione, Dicumarol, Phenindione, Phenprocoumon, Warfarin: Increased risk of bleeding,

Astemizole, cisapride and terfenadine: Miconazole inhibits the metabolism of these drugs and increases their plasma concentrations,
Phenytoin and Fosphenytoin: Increase in phenytoin toxicity risk (ataxia, hyperreflexia, nystagmus, tremor),
Fentanyl: Increased or prolonged effects of opioid (CNS depression, respiratory depression),
Glimepiride: Hypoglycemia
HMG-CoA reductase inhibitors such as simvastatin and lovastatin: When used together with miconazole, an increase in side effects may occur.
Calcium channel blockers such as dihydropyridines and verapamil: When used together with miconazole, an increase in side effects may occur.
Carbamazepine: Decreased metabolism of carbamazepine,
Oxybutynin: Due to the inhibition of the metabolism of oxybutynin, exposure to oxybutynin, and increased plasma concentrations (dry mouth, constipation, headache),
Oxycodone: Increase in oxycodone plasma concentrations and reduced clearance,
Pimozide: Increase in cardiotoxicity risk (QT prolongation, torsades de pointes, and cardiac arrest),
Cyclosporine: Increased risk of cyclosporine toxicity (renal dysfunction, cholestasis, and paresthesia),
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)

Interactions may develop due to absorption of lidocaine in concomitant use with the following drugs;
Anti-arrhythmic drugs: Increase in lidocaine toxicity
Phenytoin or barbiturates: Decrease in plasma levels of lidocaine
Beta blockers such as propranolol, cimetidine: Decreased lidocaine plasma clearance can result in potentially toxic plasma concentrations when repeated high doses of lidocaine are administered over a long period of time.

The additional risk of systemic toxicity should be considered when high doses of lidocaine are administered to patients using other local anesthetics.

Contact should be avoided between certain latex products such as contraceptive diaphragms or condoms and MIKONID since the constituents of MIKONID may damage the latex (see section 4.4)

Additional information for special populations:
No interaction studies have been performed with special population.

Pediatric population:
No interaction studies have been performed with children.

4.6. Fertility, pregnancy and lactation
General advise
Pregnancy category: C

Women of childbearing potential/Birth control (contraception)
Since the effects of active ingredients in MIKONID for fetus and newborn growth are not

clearly known, women who must use this product should avoid pregnancy by using a proper birth control method.

Pregnancy
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 MIKONID in the first trimester of pregnancy. Therefore, MIKONID 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 during pregnancy unless it is necessary.

Lactation
Since the tumorigenicity potential of metronidazole is shown in mouse and rat studies, it should be decided whether to continue breastfeeding or drug use by evaluating the importance of drug use for the mother. Metronidazole passes into breast milk in concentrations similar to that found in plasma.

Because metronidazole passes into breast milk, breastfeeding should be discontinued during the treatment; breastfeeding can be started again 24-48 hours after the end of the treatment.

It is not known whether miconazole nitrate passes into breast milk. Caution should be exercised when using MIKONID during breastfeeding.

Lidocaine passes into breast milk. Therefore, caution should be exercised during breastfeeding.

Reproduction/Fertility
There is no evidence of harmful effect on human and animal fertility when metronidazole, miconazole nitrate, or lidocaine is administered alone.

4.7. Effects on ability to drive and use machines
Systemic administration of metronidazole may affect the ability to drive or use machines. Absorption of metronidazole is lower in vaginal application than in systemic administration. Patients should be warned about the potential for drowsiness, dizziness, confusion, ataxia, fatigue, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

4.8. Undesirable effects
Adverse effects can be grouped by frequencies as:
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).

Anaphylaxis and anaphylaxis-like reactions may develop due to hypersensitivity, although its frequency is unknown.

Metronidazole
Metronidazole, when applied intravaginally has much lower plasma levels (2-12%) compared to oral administration, thereby has much lower incidence of systemic side effects. Miconazole

nitrate may cause vaginal irritation (burning-itching) (2-6%) as much as all other imidazole derivative anti-fungal drugs for vaginal administration. These side effects can be prevented by lidocaine's local anesthetic effect present in its ovule composition. Mucosal inflammation is likely in cases of vaginitis; during the initial administration of the vaginal ovule or up to 3 days of the treatment, vaginal irritation symptoms may develop such as burning and itching. With the continuation of the treatment, such complaints usually decrease rapidly and stop. If severe irritation symptoms develop, the treatment should be discontinued.

Serious adverse reactions are rarely seen with the standard recommended treatment regimen. Clinicians who plan treatment longer than recommended for the healing of chronic diseases are advised to consider possible therapeutic benefit against the risk of peripheral neuropathy.

Miconazole nitrate
The safety assessment of the vaginal capsule containing 1200 mg of miconazole nitrate has been performed in a total of 537 women with microbiologically confirmed candidiasis and symptoms (e.g., vulvovaginal itching, burning/irritation), or signs of vulvar erythema, edema, excoriation, or vaginal erythema or edema who participated in 2 single-blind clinical trials. Subjects were treated with miconazole intravaginally, randomly assigned to either a single 1,200 mg capsule, or a 7-day application of 2% vaginal cream

The following side effects have been reported in people treated in these studies.

Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Rash pruritic, urticaria

Reproductive system and breast disorders
Very common: Genital pruritus female, vaginal burning sensation, vulvovaginal discomfort
Common: Dysmenorrhea

Lidocaine
The absorption of lidocaine from MIKONID is very low and no similar side effects have been reported to date. Real adverse effects with local anesthetics are seen in less than 1/1000 of patients.

Immune system disorders
Rare: Allergic reactions (including anaphylactic shock)

Skin and subcutaneous tissue disorders
Common: Irritation, redness, itching or rash

The undesirable effects that can be seen depending on the systemic use of the active substances contained in MIKONID are listed below:

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

Immune system disorders
Rare: Hypersensitivity reactions (including anaphylactic and anaphylactoid reactions), allergic

reactions (in severe cases anaphylactic reaction may be seen)
Unknown: Angioedema, urticaria, fever

Metabolism and nutritional disorders
Not known: anorexia

Psychiatric disorders
Uncommon: Depression
Very rare: Mood changes, psychotic disorders including confusion and hallucinations
Not known: Depressed mood

Nervous system disorders
Common; Dizziness, headache
Very rare: encephalopathy (e.g. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (e.g. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug, drowsiness, dizziness, convulsions, headaches
Not known; Tiredness or weakness, paleness, tingling sensation, numbness, paresthesia; peripheral sensory neuropathy and transient epileptiform seizures (in most cases, neuropathy improved after discontinuation of treatment or dose reduction) when metronidazole is used at high doses and/or for a long time; drowsiness, disorientation, agitation, psychosis, seizure, stuttering, hyperesthesia, hypoesthesia, lethargy, hallucinations, hot-flushes, ataxia, convulsion, irritability, nervousness, euphoria, confusion, tinnitus, somnolence, chill, 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

Cardiac disorders
Unknown; Arrhythmia, bradycardia, arterial spasm, reduced blood pressure, cardiovascular collapse, increase in defibrillator threshold, edema, blush, cardiac block, hypotension, sinoatrial node suppression.

Gastrointestinal disorders
Not known; Dysgeusia, oral mucositis, rusty tongue, metallic taste, nausea, vomiting, constipation, dry mouth, epigastric pain, diarrhea, loss of appetite, abdominal pain and cramps.

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:
Common: Irritation, redness, itching or rash
Very rare: skin rashes, pustular eruptions, acute generalised exanthematous pustulosis, pruritus, flushing
Not known: erythema multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis, fixed drug eruption, angioedema

Musculoskeletal, connective tissue and bone disorders:
Very rare: myalgia, arthralgia.

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

Reproductive system and breast diseases
Not known: vaginal irritation, pelvic cramps

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, abdominal pain, rash
Not known: Local irritation and hypersensitivity, contact dermatitis

These adverse effects are observed rarely since the blood levels of metronidazole and lidocaine are much lower in intravaginal administration compared to systemic administration.

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 Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel.: 800 314 00 08; fax: 0 312 218 35 99).

4.9. Overdose and treatment
Metronidazole
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.

In case of overdose, symptomatic and supportive treatment is introduced. There is no specific antidote to metronidazole. Symptomatic and supportive treatment should be administered in suspected cases of massive overdose. Single oral doses of metronidazole, up to 12g have been reported in suicide attempts and accidental overdoses. 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, mild disorientation, dizziness, paresthesia, convulsion, leukopenia, darkening of urine.

Miconazole nitrate
In case of accidental ingestion, vomiting and diarrhoea may occur. Symptoms of miconazole

nitrate overdose are sore mouth and throat, anorexia, nausea and headache. In this case, symptomatic and supportive therapy should be administered.

Lidocaine
If applied on a large surface of the skin, especially at very high dosages, may cause blurred vision, dizziness or drowsiness, chest pain, chills, cardiac arrhythmia, respiratory difficulties, coma and even death. The risk of developing acute toxicity due to lidocaine is very low, its symptoms are convulsions and depression.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Gynecological antiinfectives and antiseptics, combinations of imidazole derivatives
ATC Code: G01AF20

MIKONID contains miconazole nitrate for antifungal and metronidazole for antibacterial and antitrichomonal effects, and lidocaine for local anesthetic effects.

Miconazole nitrate, metronidazole and lidocaine have not synergic or antagonistic effects.

In an efficacy and safety study with miconazole nitrate, metronidazole, and lidocaine containing ovule conducted on 35 vaginitis patients, microbiological cure rates at Day 8 (Visit 2) and in Week 3 (Visit 3) were 84% and 92%, respectively; and the clinical cure rate for the same periods were 88%.

Metronidazole
Metronidazole, a member of 5-nitroimidazole group, is an antiprotozoal and an antibacterial agent, effective against most infections, which involve anaerobic bacteria and protozoa. Metronidazole is effective against protozoa called as *Trichomonas vaginalis, Entamoeba histolytica, Giardia lamblia* and anaerobic bacteria including *Gardnerella vaginalis* and anaerobic streptococci.

Miconazole nitrate
Miconazole is a synthetic imidazole antifungal agent with a broad spectrum of activity against pathogenic fungi (including yeasts and dermatophytes) including *Candida albicans* and gram-positive bacteria (staphylococcus and streptococcus spp).
Miconazole combines a potent antifungal activity against common dermatophytes and yeasts with an antibacterial activity against certain gram-positive bacilli and cocci.
Miconazole inhibits the biosynthesis of ergosterol in fungi and changes the composition of other lipid components in the membrane, resulting in fungal cell necrosis.
Miconazole nitrate changes permeability of the mycotic cell and inhibits glucose utilization *in vitro* against *Candida* species.
In general, miconazole has a very rapid effect on the itching symptom that often accompanies dermatophyte and yeast infections.

Lidocaine
Lidocaine applied to intact skin provides dermal analgesia with the release of lidocaine from the cream into the epidermal and dermal layers of the skin and the deposition of lidocaine around pain receptors and nerve endings. Lidocaine is an amide type local anesthetic that stabilizes neuronal membranes by inhibiting the ionic fluxes necessary for the initiation and

transmission of impulses, thereby realizing the local anesthetic effect. The onset, depth, and duration of dermal analgesia provided by lidocaine are primarily dependent on the duration of administration. Lidocaine may cause transient peripheral vasoconstriction followed by transient vasodilation at the application site.

When applied in cream form over 30 to 60 minutes, lidocaine has been shown in clinical studies to provide reliable analgesia. If adequate analgesia is not provided, the cream may remain on the skin after this time. There is limited data showing that lidocaine and similar lidocaine-based formulations are systemically safe for application times longer than 60 minutes for cannulation procedures and large surface area topical treatments.

5.2. Pharmacokinetic properties
General characteristics
Absorption:
Miconazole nitrate: Absorption of intravaginal miconazole nitrate is very low (approximately 1-2% of dose). Following intravaginal application of miconazole nitrate, metronidazole and lidocaine containing ovule, miconazole nitrate could not be detected in plasma.

Plasma concentrations of miconazole are measurable within 2 hours of administration in some subjects, with maximal levels seen 12 to 24 hours after administration. Plasma concentrations decline slowly thereafter and were still measurable in most subjects 96 hours post-dose. A second dose administered 48 hours later resulted in a plasma profile similar to that of the first dose.

Metronidazole: Unlike oral administration, bioavailability of metronidazole in intravaginal administration is roughly 20%. Following the administration of miconazole nitrate, metronidazole, and lidocaine containing ovule, steady state levels of metronidazole in plasma reached to 1.1-5.0 μg/ml.

Lidocaine: The amount of systemically absorbed lidocaine is directly related to both the application time and the application area. Lidocaine is absorbed in very low amounts through damaged skin and mucous membranes. Absorption is expected to increase when applied to the mucosa or damaged skin. Following the application of the ovule containing miconazole nitrate, metronidazole and lidocaine, lidocaine was absorbed at a very low level in the plasma, and the plasma steady-state levels reached 0.04 - 1 μg /ml.

Distribution:
Miconazole nitrate: The protein-binding rate was 88.2%. Its distribution to cerebrospinal fluid is poor; however, it is widely distributed to other tissues. Distribution volume is 1400 L.

Metronidazole: Metronidazole is widely distributed to all body tissues and fluids, including bile, bone, breasts, breast milk, cerebral abscess, cerebrospinal fluid, liver and hepatic abscess, saliva, seminal and vaginal fluids in concentrations similar to those found in plasma. It crosses placenta and rapidly enters to fetal circulation. The protein-binding rate was maximum 20%. Distribution volume is 0.25-0.85 L/kg.

Lidocaine: Following intravenous administration, concentrations of the lidocaine metabolites monoethylglycinexilide (MEGX) and glycineexilide (GX) in serum range from 11% to 36% and 5% to 11%, respectively. The elimination half-life of lidocaine from plasma following IV administration is approximately 65 to 150 minutes (mean 110, ± 24 SD, n = 13). This half-life

may be increased in cardiac or hepatic dysfunction. More than 98% of the absorbed dose of lidocaine can be recovered in the urine as metabolites or parent drug. Systemic clearance is 10 to 20 mL/min/kg (mean 13, ± 3 SD, n = 13).

When administered via oral or intravenous route, lidocaine was obtained in the intestines, urine and to a lower extent in the feces. Unchanged drug and its metabolites were assayed in urine. The percentage of lidocaine binds to plasma proteins (primarily to α1-acid glycoprotein, to a lesser extent to albumin) is 33 to 80%. Distribution volume is 0.8-1.3 L/kg.

Biotransformation:
Miconazole nitrate: Metabolized in liver. It has two non-active metabolites. (2,4-dichlorophenyl-1 H imidazole ethanol and 2,4-dichloromandelic acid)

Metronidazole: Metabolized in the liver by oxidation, hydroxy metabolite is active. Two major metabolites of metronidazole are acetic acid and hydroxy; the latter metabolite has 30% of biological activity of metronidazole.

Lidocaine: It is unknown whether it is metabolized in the skin. Lidocaine is rapidly broken down by the liver into a number of metabolites, including monoethylglycinxylidide (MEGX) and glycinexylidide (GX), both of which are similar to but less potent than lidocaine. The pharmacological activity of the 2,6-xylidine metabolite is unknown, but it is a carcinogen in rats.

Elimination:
Miconazole nitrate: Half-life is 24 hour. Less than 1% of it eliminated by the kidneys. Approximately 50% is excreted in the feces mostly unchanged.

Metronidazole: Half-life is 6 to 11 hours. When administered systemically or topically, about 6 to 15% of metronidazole dose is excreted in the feces; 60 to 80% is excreted in the urine unchanged and as metabolites. The rate of unchanged drug excreted in the urine is 20%.

Lidocaine: It is excreted by the kidneys in its metabolites and unchanged form (10% of the administered dose).

5.3. Preclinical safety data
Preclinical data obtained from pharmacological, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproduction toxicity studies revealed no special hazard for humans.

A microbiological study conducted *in vitro* showed no synergic or antagonistic interactions between the active substances of the combination against *Candida albicans, Streptococcus* (Lancefield's Group B), *Gardnerella vaginalis* and *Trichomonas vaginalis.*

To evaluate the acute toxicity in female rats a study was carried out with the combination of 750 mg metronidazole and 200 mg miconazole nitrate and no potentiation or synergism and no lethal or toxic effects of active substances were observed.

In a vaginal mucous irritation study in female Beagle dogs with the combination of metronidazole and miconazole nitrate, it was concluded that the combination did not produce vaginal mucous irritation, and alteration in the clinical, biochemical and hematological values.

In the same study, no local and systemic toxic effects were established due to the combination.

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, while other studies were negative.

Miconazole nitrate:
Preclinical data reveal no special hazard for humans based on studies of local irritation, single and repeated dose toxicity, genotoxicity, and toxicity to reproduction.

Lidocaine:
Adequate studies have not been conducted to evaluate the mutagenic and carcinogenic potential of lidocaine and its effects on fertility.

The mutagenic potential of lidocaine HCl has been tested in the Ames Salmonella/mammalian microsome test and by analysis of structural chromosome aberrations in human lymphocytes in vitro, and by mouse micronucleus test in vivo. There was no indication in these tests of any mutagenic effects. The mutagenicity of 2,6-xylidine, a metabolite of lidocaine, has been studied in different tests with mixed results. The compound was found to be weakly mutagenic in the Ames test only under metabolic activation conditions. In addition, 2,6-xylidine was observed to be mutagenic at the thymidine kinase locus, with or without activation, and induced chromosome aberrations and sister chromatic exchanges at solution concentrations of 1.2 mg / ml. No evidence of genotoxicity was found in in vivo experiments measuring unscheduled DNA synthesis in mouse hepatocytes, chromosomal damage in polychromatic erythrocytes, or preferential killing of DNA repair-deficient bacteria in liver, lung, kidney, testes, and blood from mice. However, covalent binding studies of DNA from liver and ethmoid turbinates in rats indicate that 2,6-xylidine may be genotoxic under certain conditions in vivo.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Polyethylene glycol 400
Hard fat.

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. Do not refrigerate.

Do not use the product after the expiry date indicated on the package.

6.5. Nature and contents of container
It is presented in white PVC/PE strips of 7 ovules in a box with 7 pieces of LDPE finger cots

6.6. Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with "Directive on Control of Medical Waste" and "Directive on the Control of Packaging and Packaging Waste".

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

2017/549

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

Date of the first authorization: 20.07.2017
Date of the renewal of the authorization:

10. DATE OF REVISION OF THE TEXT

17.08.2021