**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Mistol 500 mg Suppositories.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vaginal suppository contains
Metronidazole BP …..….. 500 mg

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

White to light yellow colour torpedo shaped suppositories.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Mistol is used for the local treatment of Trichomonal and nonspecific vaginitis.

### 4.2 Posology and method of administration

Posology

The drug is allowed to use only for the treatment of adult patients.

Trichomonal vaginitis: 1 vaginal suppository once daily for 10 days. Suppository administered deeply into the vagina.

Nonspecific vaginitis: 1 vaginal suppository administered deeply into the vagina, 1 time a day for 7 days. Absolutely essential is the simultaneous treatment of sexual partner of the patient, even in the absence of his symptoms of infection.
The maximum duration of treatment with Mistol shall not exceed 10 days, and the number of courses of treatment - 2-3 per year.

Route of administration: Vaginal

### 4.3 Contraindications

Hypersensitivity to metronidazole or to other imidazole derivatives.

This medicinal product is not recommended in combination with disulfiram or alcohol (see. Section "Interaction with other medicinal products and other forms of interaction")

Children: The medicine is contraindicated for use in children.

### 4.4 Special warnings and precautions for use

Metronidazole has no direct effect on aerobic or facultative anaerobic bacteria.

Metronidazole should not be used for more than 10 days and no more than 2 or 3 times a year. Alcohol

consumption should be avoided during the therapy with metronidazole (disulfiram effect (see "Interaction with other medicinal products and other forms of interaction").

There is a possibility of persisting gonococcal infection after elimination of trichomonal infection.

In dialysis patients' metronidazole and its metabolites are eliminated in 8 hours after hemodialysis, hence metronidazole should be administered after hemodialysis.

Dose correction is not required in patients with renal insufficiency who undergo peritoneal dialysis.

In cases of ataxia, dizziness or confused mental state the therapy should be discontinued. Aggravation of neurological status should be considered in patients with severe, chronic or progressing diseases of the peripheral or central nervous system.

Patients with hematologic disorders in history or when administered high doses of the medicine and/or for a long duration of time are advised to undergo blood test especially for determination of the number of leukocytes.

Mistol should be administered with caution in patients with hepatic encephalopathy. Dose for patients with hepatic encephalopathy should be reduced to one third and can be administered once daily.

The continuation of the therapy in patients with leucopenia depends on severity the infectious disease.

When administered for a long period it is advised to monitor the patient for signs of adverse effects, such as, central or peripheral neuropathy (paresthesia, ataxia, dizziness, cramps)

Patients should be warned that metronidazole may darken urine (due to metronidazole active metabolite).
Administration of vaginal suppositories increases the chances of latex rupture when using condoms or diaphragms.

## 4.5 Interaction with other medicinal products and other forms of interaction

Disulfiram: acute transient disorders with delirium (acute delirium onset, confused mental state) have been reported in patients who were using metronidazole and disulfiram concurrently.

Alcohol: alcoholic beverages and drugs containing alcohol should not be consumed during therapy and for at least one day afterwards because of the possibility of a disulfiram-like reaction (flushing, erythema, vomiting, tachycardia).

Oral anticoagulant therapy (warfarin type): potentiation of the effect of oral anticoagulants and increased hemorrhagic risk caused by decreased hepatic metabolism. Prothrombin level and INR level (international normalised ratio) should be more frequently monitored. It is advised to adjust the dosage of oral anticoagulant during treatment with metronidazole and for 8 days after its discontinuation.

Lithium: Plasma levels of lithium may be increased by metronidazole. Plasma concentration of lithium, creatinine and electrolytes should be monitored in patients under treatment with lithium while they receive metronidazole.

Cyclosporin: there is risk of elevation of cyclosporin serum levels. Serum cyclosporin and serum

creatinine should be closely monitored when coadministration with metronidazole is necessary.

Phenytoin or phenobarbital: causes decrease of metronidazole plasma concentration.

5-fluorouracil: reduced clearance of 5-fluorouracil results in increased toxicity of 5-fluorouracil.

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

Changes in the international normalised ratio (INR) level:
Multiple incidents of potentiation of the anticoagulant effect after oral administration have been reported in patients undergoing antibacterial therapy. The risk factors of such potentiation tendency are determined by present infections or frank inflammation, age, general state of health. In such conditions it appears to be hard to determine to what extent infection or its treatment affects INR balance. However some classes of antibiotics play a major role, among them are fluoroquinolones, macrolides, cyclones, cotrimoxazole and some cephalosporins.

Laboratory reports. Metronidazole may immobilize treponema and thus may lead to falsely positive Nelson's test.

## 4.6 Fertility, Pregnancy and lactation

Pregnancy
There are no reports of specific teratogenic or fetotoxic effects due to metronidazole in clinical trials. However, absence of such risk can be demonstrated only through epidemiologic studies. Hence metronidazole may be prescribed to pregnant women only in case of necessity.

Lactation
Metronidazole is excreted in milk. Hence it is not recommended to administer metronidazole during lactation period.

## 4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for drowsiness, dizziness, confusion, hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

## 4.8 Undesirable effects

*Gastro-intestinal system:*
- Epigastric pain, nausea, vomiting, diarrhea;
- Inflammation of the mucous membrane of the mouth, glossitis with xerostomia, stomatitis, taste disturbances (metallic taste in the mouth), anorexia, coated tongue;
- Extremely rare - cases of pancreatitis, which are reversible.

*Skin and subcutaneous tissue disorders:*
−hot flashes with hyperemia, itching, rash, which may be accompanied by fever;
− urticaria, angioedema, rare - anaphylactic shock;
− single cases of pustular eruptions and Erythema multiform.

*Nervous system disorders:*
− peripheral sensory neuropathy;
− headache, cramps, dizziness, ataxia, drowsiness;
− very rare – encephalopathy (e.g. confused mental state, high body temperature, photosensitivity, torticollis, hallucinations, paralysis, vision impairment and movement disorder) and subacutecerebellar syndrome(e.g. ataxia, dysarthria, gait disorder, nystagmus, tremor), which may resolve on discontinuation of the drug;
− aseptic meningitis.

*Psychotic disorders:*
− psychotic disorders including confused mental state, hallucinations, depressed mood.

*Eye disorders:*
− temporary vision impairment such as diplopia, myopia, blurred vision, impaired visual acuity, changes in colour perception;
− optic neuropathy / neuritis.

*Blood disorders:*
− in single cases – agranulocytosis, neutropenia, thrombocytopenia, pancytopenia and leucopenia.

*Hepatobiliary disorders:*
− in single cases – increase in liver enzyme levels (AST, ALT, alkaline phosphatase), cholangiolitic or mixed hepatitis and involvement of liver cells (hepatocytes), sometimes with jaundice;
− reported cases of liver impairment, which required liver transplantation in patients undergoing treatment with metronidazole and other antibiotics.

*Musculo-skeletal system and connective tissue disorders*
– very rare – myodynia, arthrodynia.

*Other side effects:*
− high body temperature.

During the treatment urine may acquire brown colour due to colouring agents as the metronidazole metabolic product dissolved in water.

Reporting of suspected adverse reactions
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 via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll-free call 8482 to Ethiopian food and drug authority (EFDA).

### 4.9 Overdose

Symptom may be observed like leucopenia, neuropathy, ataxia, vomiting, mild disorientation. Since specific antidote is unknown, symptomatic treatment is recommended.

## 5. PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group**:** Gynecological anti-infectives and antiseptics,
ATC code**:** G01A F01

Metronidazole belongs to the nitro-5 imidazole and has a broad spectrum of action. concentration limits that allow you to differentiate susceptible (S) strains of moderate sensitivity and strains of moderate sensitivity - from resistant strains (R), are as follows: S <4 mg / l and R> 4 mg/l.
Sensitive to the drug: Peptostreptococcus spp., Clostridium spp., Bacteroides spp., Fusobacterium spp., Porphyromonas, Bilophila, Helicobacter pylori, Prevotella spp., Veilonella. Metronidazole is holding back the development of the simplest – Trichomonas vaginalis, Giardia intestinalis (Lamblia intestinalis), Entamoeba histolytica. Steady sensitive to the drug: Bifidobacterium spp., Eubacterium spp. Insensitive microorganism strains: Propionibacterium, Actinomyces, Mobiluncus.

The authority/EFDA will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

## 5.2 Pharmacokinetic properties

Following intravaginal administration systemic absorption is minimal. Plasma
half-life is 8-10 hours.
Plasma protein binding is small (less than 20%).
There is rapid and considerable diffusion in the lungs, kidney, liver, bile, cerebro-spinial fluid, skin, saliva and vaginal secretions. It crosses the placental barrier and is excreted in breast milk.

Metabolism is essentially hepatic: two non-conjugated oxidated active metabolites (5 to 30% activity) are formed.

Excretion is chiefly urinary: 35 to 65% of the administered dose is excreted in urine in the form of metronidazole and its oxidated metabolites.

## 5.3 Preclinical safety data

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.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Hard Fat

## 6.2 Incompatibilities

Not applicable

## 6.3 Shelf life

3 years

## 6.4 Special precautions for storage

Store at a temperature below 30°C. Do not freeze.
Keep medicine out of reach of children.

## 6.5 Nature and contents of container

5 vaginal suppositories are packed in PVC/PE strip, such 2 strips are packed in a carton along with packaging insert.

## 6.6 Special precautions for disposal and other handling

No special requirements

# 7. MARKETING AUTHORISATION HOLDER

Kusum Healthcare Pvt. Ltd.
SP-289(A), RIICO Industrial Area,
Chopanki, Bhiwadi, Dist. Alwar, Rajasthan, India

# 8. MARKETING AUTHORISATION NUMBER(S)

07038/09108/NMR/2021

# 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 January 2022

# 10. DATE OF REVISION OF THE TEXT

08/2023

# 11. REFERENCES

SmPC published on electronic medicines compendium
https://www.medicines.org.uk/emc#gref

The MHRA published product information
https://products.mhra.gov.uk/

Human medicine European public assessment report
https://www.ema.europa.eu/en/medicines