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INSTRUCTION
for medical use

MISTOL®

Composition:
active substance: metronidazole;
1 suppository contains metronidazole 500 mg;
excipients: solid fat.

Pharmaceutical form. Vaginal suppositories.
Basic physical and chemical properties: white to light yellow, torpedo-shaped suppositories.

Pharmacotherapeutic group.
Gynecological antiinfectives and antiseptics.
ATC code: G01A F01.

Pharmacological properties.
Pharmacodynamics.
Metronidazole belongs to nitro-5-imidazoles and has a wide spectrum of action. The MIC breakpoints differentiating susceptible (S) from intermediate strains, and intermediate from resistant (R) strains are as follows: S ≤4 mg/L and R >4 mg/L.
Susceptible to the drug: *Peptostreptococcus spp., Clostridium spp., Bacteroides spp., Fusobacterium spp., Porphyromonus, Bilophila, Helicobacter pylori, Prevotella spp., Veilonella.* Metronidazole inhibits the development of protozoa: *Trichomonas vaginalis, Giardia intestinalis (Lamblia intestinalis), Entamoeba histolytica*. Variably susceptible to the drug: *Bifidobacterium spp., Eubacterium spp*. Unsusceptible strains of microorganisms: *Propionibacterium, Actinomyces, Mobiluncus*.

Pharmacokinetics.
After vaginal administration, systemic penetration is minimal.
The half-life of the plasma is 8–10 hours.
Binding to plasma proteins is negligible (less than 20%).
Rapid and pronounced diffusion in the lungs, kidneys, liver, bile, cerebrospinal fluid, skin, saliva and vaginal secretion. Crosses the placental barrier and is excreted in breast milk.
Metabolism occurs mainly in the liver: two unconjugated oxidized active metabolites are formed (5–30% of activity).
Excretion is mainly by the kidneys: 35–65% of the received dose is excreted in the urine in the form of metronidazole and its oxidized metabolites.

Clinical characteristics.

Indication.

Local treatment of trichomoniasis and nonspecific vaginitis.

Contraindication.

Hypersensitivity to metronidazole or to another component of the drug. Hypersensitivity to imidazole derivatives.

Combinations with disulfiram or alcohol (see "Interaction with other drugs and other types of interactions" section).

Interaction with other drugs and other types of interactions.

Antabuse effect. Many medicinal products trigger an antabuse effect with alcohol and their concomitant use with alcohol is not advisable.

Inadvisable combinations.

Disulfiram.

Cases of acute transient disorders with delirium (acute attack of delirium, confusion) have been reported in patients receiving metronidazole and disulfiram at the same time.

Alcohol (beverage or excipient). Alcoholic beverages and drugs containing alcohol should not be consumed by patients being treated with metronidazole and for at least a day after treatment as disulfiram-like (antabuse) effect (hot flushes, erythema, vomiting, tachycardia) may occur. Alcoholic beverages or medicinal products containing alcohol should not be ingested again until medicinal products have been completely eliminated from the body. The half-life should be used as a reference.

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

Combinations requiring precautions for use.

Oral anticoagulants. Some potentiation of anticoagulant effect and increased hemorrhagic risk caused by decreased hepatic metabolism has been reported. Patients should have their prothrombin levels and international normalized ratio (INR) monitored more frequently. It is recommended to adjust the dose of an oral anticoagulant while taking metronidazole and for 8 days after its withdrawal.

Lithium. Increased blood lithium levels can occur, which can reach toxic levels with signs of lithium overdose. Strict monitoring of blood lithium levels should be performed and the lithium dose adjusted if necessary.

Cyclosporin. Concomitant use could result in increased serum levels of cyclosporin. When it is necessary to co-administer the two drugs together close monitoring of serum cyclosporin and creatinine is advisable.

Rifampicin. Decreased plasma concentrations of metronidazole can occur due to stimulation of its liver metabolism by rifampicin. Clinical monitoring is required during and after treatment with rifampicin. Metronidazole dose may need to be adjusted.

Enzyme-inducing antiepileptic drugs (carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone). Decreased plasma concentrations of metronidazole can occur due to increased liver metabolism by the inducer. Clinical monitoring is required during and after treatment with rifampicin. Metronidazole dose may need to be adjusted.

Combinations to be taken into consideration.

5-fluorouracil (tegafur and capecitabine). Increased fluorouracil toxicity can occur due to decreased clearance.

INR (international normalized ratio) imbalance. Numerous cases of increased oral anticoagulant activity have been reported in patients receiving antibiotics. The severity of the infection or inflammation, age and general health status of the patient appear to be risk factors that determine the tendency to such a complication. Under these circumstances, it seems difficult to determine to what extent the infection itself or its treatment play a role in the INR imbalance. However, certain classes of antibiotics are more involved, particularly fluoroquinolones, macrolides, cyclines, cotrimoxazole and certain cephalosporins.

Interactions with laboratory tests. Metronidazole may immobilize treponemes, and thus lead to false positive results for the Nelson test.

Special warnings and precautions for use.

Patients with severe, chronic or progressive diseases of the peripheral or central nervous system (CNS) are at risk of neurological aggravation.

In patients who have a history of hematological disorders or who are receiving high-dose and/or long-term treatment, regular blood tests, and particularly leukocyte counts, should be performed.

In case of prolonged treatment, occurrence of adverse reactions such as paresthesia, ataxia, dizziness and convulsive crises should be checked.

Patients should be warned that metronidazole may darken urine (due to active metabolite).

Hypersensitivity / skin and appendages. Allergic reactions, including anaphylactic shock, can occur and be life-threatening (see "Adverse reactions" section). In this case, treatment with metronidazole must be discontinued and appropriate medical treatment initiated.

If, at the start of treatment, patients experience generalized erythema with fever and pustules, acute generalized exanthematous pustulosis should be suspected (see "Adverse reactions" section). If this occurs, treatment must be discontinued and any further administration of metronidazole alone or in combination with other agents is contraindicated.

Cases of severe skin reactions including Stevens-Johnson syndrome, Lyell's syndrome, acute generalized acute respiratory pustulosis (AGAP) have been reported with metronidazole. Patients must be informed of the signs and symptoms of these conditions and the skin should be closely monitored.

If any signs or symptoms of Stevens-Johnson syndrome, Lyell's syndrome (e.g., progressive skin rash often with blisters or mucosal lesions) or generalized erythema with fever and pustules occur, treatment must be discontinued and any further administration of metronidazole alone or in combination with other agents is contraindicated.

Central nervous system. If symptoms indicative of encephalopathy or cerebellar syndrome (see "Adverse reactions" section) appear, patient management should be immediately reassessed and metronidazole treatment discontinued.

Cases of encephalopathy have been reported as part of post-marketing surveillance of this medicinal product. Cases of MRI changes associated with encephalopathy have also been observed (see "Adverse reactions" section). Damage is most often located in the cerebellum (particularly in the dentate nucleus) and in the splenium of the corpus callosum. Most cases of encephalopathy and MRI changes are reversible on treatment discontinuation. Very rare cases of fatal outcome have been reported.

Patients should be monitored for warning signs of encephalopathy, and exacerbation of symptoms in patients with CNS disorders.

If aseptic meningitis occurs during treatment, rechallenge with metronidazole is not recommended, and an assessment of the benefit/risk ratio should be carried out for patients with serious infection.

Peripheral nervous system. Patients should be monitored for warning signs of peripheral neuropathy, particularly in long-term treatment or in patients with severe, chronic or progressive peripheral neurological disorders.

Psychiatric disorders. From administration of the first doses, patients may experience psychotic reactions, including self-endangering behaviour, particularly if they have a history of psychiatric disorders (see "Adverse reactions" section). If this happens, metronidazole must be discontinued, the physician informed and appropriate therapeutic measures instituted immediately.

Hematological effects. In patients who have a history of hematological disorders or who are receiving high-dose and/or long-term treatment, regular blood tests, and particularly leukocyte counts, should be performed.

In patients with leucopoenia, continued treatment will depend on how serious the infection is.

Interaction with other medicinal products. Concomitant use of metronidazole and alcohol is not recommended (see "Interaction with other drugs and other types of interactions" section).

Concomitant use of metronidazole and busulfan is not recommended (see "Interaction with other drugs and other types of interactions" section).

Concomitant use of metronidazole and disulfiram is not recommended (see "Interaction with other drugs and other types of interactions" section).

Other types of interactions. The maximum duration of treatment with metronidazole should not exceed 10 days, and the number of treatment courses should be 2–3 per year.
The simultaneous use of suppositories with condoms or diaphragms may increase the risk of rupture of the latex.
Hepatotoxicity in patients with Cockayne syndrome. Cases of severe acute hepatic failure, including cases with a fatal outcome with very rapid onset in patients with Cockayne syndrome have been reported with products containing metronidazole for systemic use. In this population, metronidazole should not be used unless the benefit is considered to outweigh the risk and only if no alternative treatment is available.
Liver function tests must be performed just prior to the start of therapy, throughout and after end of treatment until liver function is within normal ranges, or until the baseline values are reached. If the liver function tests become markedly elevated during treatment, the drug should be discontinued.
Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician and stop taking metronidazole (see "Adverse reactions" section).

Use during pregnancy or breast-feeding.
Pregnancy.
There is no evidence from animal studies that metronidazole is teratogenic. Since the teratogenic effect is not observed in animals, no malformative effect is expected in humans. Results of large number of clinical trials did not seem to show any particular teratogenic or fetotoxic effects of metronidazole. However, only epidemiological studies would make it possible to rule out any risk. Therefore, metronidazole may be prescribed during pregnancy if necessary.
Breast-feeding.
Since metronidazole is excreted in human milk, administration should be avoided in breast-feeding women.

Effects on ability to drive and use machines.
Patients should be warned of the potential risk of dizziness, confusion, hallucinations, seizures or vision disorders, and should be advised not to drive or operate machines if they experience such symptoms.

Posology and method of administration.
The drug should be used in adult patients only.
The vaginal suppository should be inserted deep into the vagina.

Indications	*Single dose*	*Dosage frequency*	*Duration of therapy*	*Simultaneous use with tablet forms of metronidazole*
Trichomonal vaginitis	1 vaginal suppository	Once a day	10 days	Is necessary
Nonspecific vaginitis			7 days	Used when necessary

The sexual partner should absolutely be treated concomitantly, whether presenting with clinical signs of infection or not.
The maximum duration of treatment with Mistol® should not exceed 10 days, and the number of treatment courses should be 2–3 per year.

Children.
The drug is contraindicated in children.

Overdose.
Oral administration of up to 12 g of metronidazole as a single dose has been reported in cases of attempted suicide and accidental overdose. Leukopenia, neuropathy, ataxia, vomiting, mild disorientation may be observed.

Treatment. Since there is no specific antidote to metronidazole, symptomatic treatment should be instituted.

Adverse reactions.
Gastrointestinal disorders: minor gastrointestinal disorders (epigastric pain, nausea, vomiting, diarrhea), inflammation of the mucous membrane of the mouth, glossitis with dry mouth, stomatitis, taste disorders (metallic taste in the mouth), anorexia, discoloration or change in the appearance of the tongue (mycosis), furred tongue, pancreatitis, reversible on treatment discontinuation.
Skin and subcutaneous tissue disorders: hot flushes with hyperemia, pruritus, skin rash occasionally with fever, urticaria, angioedema, anaphylactic shock (see "Special warnings and precautions for use" section), very rare cases of acute generalized exanthematous pustulosis (see "Special warnings and precautions for use" section), toxic epidermal necrolysis (Lyell's syndrome), fixed drug eruption, Stevens-Johnson syndrome, erythema multiforme.
Nervous system disorders: peripheral sensory neuropathy, headache, vertigo, confusion, seizures, ataxia, somnolence; encephalopathy*, sub-acute cerebellar syndrome**, aseptic meningitis (see "Special warnings and precautions for use" section).
Psychiatric disorders: hallucinations, psychotic reactions with paranoia and/or delirium possibly accompanied by suicidal ideation or suicide attempts in some isolated cases (see "Special warnings and precautions for use" section), depressed mood.
Eye disorders: transient vision disorders (e.g., diplopia, myopia, blurred vision, reduced visual acuity, impaired color vision), optic neuropathy / neuritis.
Hematologic disorders: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia and leukopenia.
Hepatobiliary disorders: elevated liver enzyme levels (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase), acute cholestatic or mixed hepatitis; hepatocellular liver injury (sometimes with jaundice); hepatocellular insufficiency (possibly with complications requiring liver transplantation).
Ear and labyrinth disorders: impaired hearing, hearing loss (including sensorineural); tinnitus.
Musculoskeletal system and connective tissue disorders: myalgia, arthralgia.
Other adverse reactions: fever, urine can appear reddish-brown as pigments may be found due to metabolism of the metronidazole.
* Clinical manifestations of encephalopathy (confusion, increased body temperature, increased sensitivity to light, torticollis, hallucinations, paralysis, visual and movement disorders) may be accompanied by reversible changes on MRI and disappear on treatment discontinuation. Very rare cases of fatal outcome have been reported (see "Special warnings and precautions for use" section).
** Clinical manifestations of sub-acute cerebellar syndrome (ataxia, dysarthria, gait disturbances, nystagmus, tremor) can disappear on treatment discontinuation (see "Special warnings and precautions for use" section).
Cases of severe unreversible hepatotoxicity / acute liver failure of very rapid onset after treatment initiation, including cases with fatal outcome, have occurred in patients with Cockayne syndrome who were administered metronidazole intended for systemic use (see "Contraindications" section).

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. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf-life.
3 years.

Storage conditions.
Store in original package at temperature below 25°C.
Keep out of reach of children.

Package.
5 suppositories in a strip. 2 strips in a cardboard package.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

Date of last revision.