Brand Name : METAGO-250 TABLETS **Generic Name :** Metronidazole Tablets BP 250 mg	2021
Module 1 Administrative Information and Product Information **1.5** Product Information	**Confidential**

1.5 PRODUCT INFORMATION

1.5.1 Prescribing information (Summary of products characteristics)

SUMMARY PRODUCT CHARACTERISTICS

1. Name of drug product:

METAGO-250 TABLETS (Metronidazole Tablets BP 250 mg)

2. Qualitative and Quantitative Composition:

Each uncoated tablet contains: Metronidazole BP 250 mg

3. Pharmaceutical form:

White, round, flat, uncoated tablets, having break line on one side and other side plain of each tablets.

4. Clinical particulars:

4.1 Therapeutic Indications:

Protozoal infections

Metronidazole is the drug of choice for the treatment of trichomoniasis. A single 2 g dose is as effective as the original, longer regimen consisting of 250 mg two to three times daily for 7 – 10 days. Male partners can also be treated with the single dose. Topical therapy as the vaginal suppository or cream is rarely used as an alternative because of the inconvenience and long duration of treatment (one insert or one application of cream nightly for 10 – 20 days). For cases that persist after oral treatment and where 'resistant' trichomonads are suspected, a combination of oral and topical therapy may be effective. In clinical circumstances where low systemic levels would be desirable, for example in pregnancy, topical treatment might be indicated.

In giardiasis, 2 g daily for 3 days is as effective as a longer course of 250 mg two to three times daily for 5 – 10 days. In children, the usual dose is 25 – 35 mg.kg-1 daily in tow divided doses. For pregnant women who require treatment, a non-absorbable

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aminoglycoside, paromomycin, may be tried first and metronidazole used if initial treatment fails.

Metronidazole is effective in symptomatic amoebic intestinal disease and amoebic abscess at a dose of 750 mg three times daily for 5 – 10 days. It is less effective in asymptomatic intestinal infection. In children, the dose is 35 – 50 mg.kg-1 daily in three divided doses.

Serious anaerobic bacterial infections

For serious anaerobic bacterial infections, metronidazole is usually given at a dose of 500 mg three times daily. Although it is effective against most clinically important anaerobes, its marked activity against lower gut anaerobes, including Bacteroides fragilis (and related strains), Fusobacterium and Clostridium species make it very useful in the treatment of intra-abdominal and pelvic sepsis, in which these organisms are implicated. The excellent distribution into most body tissues and its consistently bacterial effect make it also the drug of choice for many serous infections, including meningitis, cerebral abscess, and endocarditis.
Because many infections in which anaerobes are present are mixed an include aerobic bacteria, treatment with metronidazole is usually combined with an antibiotic effective against aerobes (a penicillin, cephalosporin or aminoglycoside).

Eradication of Helicobacter pylori infection

Chronic duodenal ulcer disease is usually associated with H.pylori infection; eradication of infection accelerates ulcer healing and reduces the frequency of relapse. Eradication of H.pylori can usually be achieved using the combination of bismuth, metronidazole, and another antibiotic (most often amoxicillin or tetracycline) in a 2-week course. Such ‘triple therapy’ can eradicate H.pylori in 85% of patients; in the UK, triple therapy is used most commonly for relapsing duodenal ulcer but may also be used for symptomatic H. pylori gastritis.

Clostridium difficile colitis

Oral metronidazole is an alternative and less expensive agent than vancomycin in antibiotic-associated colitis. The usual dose is 250 mg four times daily for 5-10 days. Although rare. C. difficile colitis has followed the use of metronidazole in the treatment of other infection.

Bacterial vaginosis

Metronidazole at a dose of 500 mg twice daily for 7 days is effective in the treatment of bacterial vaginosis. A single 2 g dose appears to be as effective. The organisms implicated in this clinical entity include Gardnerella vaginalis. Mobiluncus spp. And various anaerobic organisms. All these organisms are exquisitely or moderately susceptible to metronidazole under anaerobic conditions.

Antibiotic prophylaxis

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Metronidazole has been shown to be effective for prophylaxis in colorectal and pelvic surgery. The drug in usually administered either ractally or intravenously preoperatively at doses of 500-1000 mg. Because its spectrum is limited to anaerobes, other drugs effective against aerobic organisms are often also administered concurrently.

Treatment of Crohn's disease

In a large multicenter trial, metronidazole at a dose of 400 mg twice daily orally for 4 months was shown to be slightly more effective than sulfasalazine in active Crohn's disease. In another double-blind trial, metronidazole (20 and 10 mg.kg) was found to be superior to placebo. Failure to respond to sulfasalazine may warrant a trial of metronidazole.

Dental infections

Anaerobic bacteria play a major role in various dental infections, including pericoronitis, acute ulcerative gingivitis, periapical infections, and osteitis (including dry socket). Metronidazole is used at a dose of 200 mg three times daily for 3-7 days.

Radiosensitization of malignancies

Metronidazole given as a radioenhancer was shown to delay tumor regrowth in patients with glioblastoma multiforme. However, in patients with metastatic epidural spinal cord compression treated with metronidazole prior to radiotherapy, no significant beneficial long-term effect was noted. This application of metronidazole, therefore, may be limited.

4.2 Posology and Method of Administration:

Adults

For acute intestinal amebiasis (acute amebic dysentery): 750 mg orally three times daily for 5 to 10 days.

For amebic liver abscess

750 mg orally three times daily for 5 to 10 days.

Children

35 to 50 mg/kg/24 hours divided into three doses, orally for 10 days.

Anaerobic bacterial infections

In the treatment of most serious anaerobic infections, intravenous Metronidazole is usually administered initially.

The usual adult oral dosage is 7.5 mg/kg every 6 hours. A maximum of 4 g should not be exceeded during a 24 hour period.

The usual duration of therapy is 7 to 10 days; however, infections of the bone and joint lower respiratory tract, and endocardium may require longer treatment.
Patients with severe hepatic disease metabolize Metronidazole slowly, with resultant accumulation of Metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Close monitoring of plasma Metronidazole levels and toxicity is recommended.

The dose of Metronidazole should not be specifically reduced in anuric patients because accumulated metabolites may be rapidly removed by dialysis.

Method of administration : Oral.

4.3 Contraindications:

Hypersensitivity to metronidazole

This is very rare and usually is manifested as a maculopapular rash on the trunk and neck. A fixed drug eruption caused by metronidazole has also been reported. Acute neurological deterioration within hours of ingestion of metronidazole can also occur.

Concurrent use of alcohol

Metronidazole produces a disulfiram-like effect with hypotension and flushing when used concurrently with ethyl alcohol. Patients should abstain from alcoholic beverages for at least 48 h following discontinuation of therapy with metronidazole.

History of serious neurological disease

Because of its potential neurotoxicity, metronidazole may aggravate pre-existing neurological disease, including in patients with a convulsion disorder. This is a relative contraindication, since metronidazole is very effective in the treatment of cerebral abscesses and meningitis caused by susceptible anaerobes.

Severe hepatic failure

Metronidazole is primarily metabolized by the liver and, therefore, toxic accumulation of the parent compound could occur in patients with severe hepatic failure.

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4.4 Special Warnings and Precautions for Use :

Patients with severe hepatic disease metabolize Metronidazole slowly, with resultant accumulation of Metronidazole and its metabolites in the plasma. Accordingly, for such patients, doses below those usually recommended should be administered cautiously. Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with Metronidazole and requires treatment with a condidacidal agent.

Information for patients

Alcoholic beverages should be avoided while taking Metronidazole and for at least three days afterward.

4.5 Interaction with other medicinal products, and other forms of interaction:

Potentially hazardous interactions

Metronidazole interacts with racemic and (S)-(-)- warfarin and increases the blood levels of warfarin, causing a hypothrombinemic effect. It is postulated that metronidazole inhibits ring oxidation of (S)-(-)-warfarin and therefore, impairs total body clearance of warfarin.

Other significant interactions

Premedication with metronidazole did not affect the metabolic disposition of phenytoin, diazepam or antipyrine, the metabolism of which depends upon oxidative drug metabolism (a cytochrome P450 system). Theophylline pharmacokinetics were also not affected, although theophylline is metabolized by dealkylation and hydroxylation in the liver. Cimetidine, in contrast, prolongs the half-life of metronidazole through reduction of its total plasma clearance.

Metronidazole and disulfiram when given concurrently have caused an acute psychosis.

Potentially useful interactions

Metronidazole can be combined with other antimicrobials for an additive or synergistic effect. There is no evidence to suggest that metronidazole antagonizes the activity of other antimicrobials.

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4.6 Pregnancy and Lactation:

Pregnancy

When metronidazole has been administered during pregnancy, no adverse effects have been noted in the mother or fetus. However, it is recommended that metronidazole should not be given during the first trimester of pregnancy and avoided during the latter trimesters if possible. If use is deemed necessary, short high-dose regimens are not recommended. The efficacy of metronidazole in serious anaerobic infections has to be weighed against potential, but unproved, mutagenic and teratogenic effects. From limited data, metronidazole appears to cross the placenta, as would be expected from its lipid solubility.

Lactation

Metronidazole penetrates well into breast milk. If exposure of the neonate to metronidazole is to be avoided, breast-feeding should be delayed until 48 h after discontinuing metronidazole in the mother.

4.7 Effects on ability to drive and use machines:

Patients experiencing visual disturbances, dizziness, vertigo, somnolence, or other central nervous system disturbances while taking Metronidazole Tablets refrain from driving or using machines.

4.8 Undesirable effects:

Potentially life-threatening effects

Although the potential tumorgenicity of metronidazole has been intensively reviewed following the report of an increased number of tumors in animals, there is no evidence to date to substantiate an increase of cancer in humans.

Severe or irreversible adverse effects

Patients who have received unusually large doses of metronidazole have developed various central neurological effects, including seizures, ataxia, headaches, and encephalopathy. Seizures have also been reported in patients without known neurological disease who have received usual therapeutic doses. EEG changes have also been noted in patients on metronidazole and it is postulated that the drug may have a specific effect on the limbic structures in the brain.

A sensory peripheral neuropathy has been caused by metronidazole in patients who have received high doses for radiosensitization or prolonged treatment regimes, as in patients with Crohn's disease. Doses of metronidazole larger than 30 g have usually been given in these cases. The peripheral neuropathy is often asymptomatic and is reversible in the majority of patients over a period of weeks to months, although in a minority complete reversal has not occurred after 2 years.

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A reversible neutropenia is also seen in approximately 2% of patients who have received prolonged high doses of metronidazole.

Symptomatic adverse effects

Gastrointestinal upset, including anorexia, nausea, vomiting, and epigastric pain, is the most common adverse effect but is usually mild; however, metronidazole may occasionally cause acute pancreatitis and this should be excluded where abdominal pain in sever or persistent. These symptoms are more pronounced and occur quite commonly after the massive doses of metronidazole that are given for radiosensitization purposes. After single large doses for the treatment of trichomoniasis, giardiasis and bacterial vaginitis, the incidence of reported gastrointestinal upset is usually less than 5%. A metallic taste and mouth dryness, probably caused by the presence of high concentrations of metronidazole in the saliva, and furring of the tongue are also reported. Metronidazole may decrease visual acuity as a result of transient changes in refractive error.

Dermatological reactions are very rare and include a maculopapular rash resembling pityriasis rosea, usually on the trunk and neck, pruritus and fixed drug eruptions. Palpitations and chest pain have also been reported. Darkening of the urine with a reddish-brown discoloration is often reported and is probably caused by an azo group-containing metabolite.

There is a low incidence of phlebitis associated with the intravenous injection of metronidazole.

Microbiologically, administration of metronidazole appears to predispose to vaginal candidiasis through the alteration of the vaginal microflora.

Single case reports have implicated metronidazole in producing gynecomastia and acute pancreatitis.

Other effects

Metronidazole was shown to reduce serum levels of cholesterol and triglycerides up to 40% in patients taking 750 mg three times daily.

4.9 Overdose:

One case report of a voluntary overdose of 4200 mg in a 16-year-old pregnant woman reported that the patient developed disorientation which resolved without specific treatment. Larger does than this reported overdose have been given to patients as a radiosensitizer without sever toxicity.

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5. Pharmacological properties:

5.1 Pharmacodynamic properties:

Metronidazole is very active against the clinically important protozoa Trichomonas vaginalis, Giardia lamblia, and Entamoeba histolytica with minimal inhibition concentrations of approximately 1 $mg.1^{-1}$ of various anaerobic bacteria, metronidazole is especially active against strains of Bacteroides fragilis and related species, Fusobacterium, Clostridium, Peptococcus, and Peptostreptococcus species. Most obligate anaerobes are inhibited by concentrations of 6 $mg.1^{-1}$ or less. It is also moderately active against the facultative anaerobes Gardnerella vaginalis and Campylobacter fetus. The hydroxy metabolite of metronidazole is less active against obligate anaerobes but more active against Gardnerella vaginalis than the parent compound.

Metronidazole does not usually inhibit DNA synthesis in normal human cells because oxygen prevents the reduction of the 5-nitro group. However, it does act as a chemical radiosensitizer for hypoxic malignant cells because of its high affinity for electrons. In addition, it can produce a disulfiram-like effect (nausea, vomiting, flushing headache) with concurrent ethyl alcohol ingestion.

5.2 Pharmacokinetic Properties:

High performance liquid chromatography (HPLC) methods are the preferred analytical assays for the measurement of metronidazole and its individual metabolites. The limit of detection in one assay was approximately 10 $\mu g.1^{-1}$ and the limit of accurate quantification 20 – 50 $mg.1^{-1}$. Microbiological assays, developed first and usually employing Clostridium species, can also be used but measure both the parent compound and the microbiologically active metabolites.

The bioavailability of oral metronidazole approaches 100%. A mean value for maximum plasma concentration, C_{max}, of 3.7 – 6.2 $mg.1^{-1}$ is seen after 250 mg orally, while 500 mg produces a C_{max} of 9.8 – 1.3 $mg.1^{-1}$. The time to maximum concentration, T_{max}, varies between 0.25 and 4 h. With multiple dosing there is some accumulation, with C_{max} and through, C_{min}, values after 400 mg twice daily of 11.2 – 17.4 $mg.1^{-1}$ and 5.5 $mg.1^{-1}$, respectively. Serum levels are directly proportional to dose over a wide dosing range.

The disposition of metronidazole is affected by age and disease. Metabolic elimination is substantially reduced in preterm neonates and the elimination half-life t1/2 correlates with gestational age. The metabolic clearance metronidazole is significantly lower in severely malnourished children than following nutritional rehabilitation.

Pharmacokinetic parameters have been derived after intravenous infusions of metronidazole. At steady state, a regimen of 500 mg every 8 h produces a mean C_{max}

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of 26 – 27.4 $mg.1^{-1}$ and a mean C_{min} of 12.0 – 15.5 $mg.1^{-1}$. After intravenous dosing t1/2 varies between 6 and 9 h; the apparent volume of distribution is between 0.6 and 1.1 $l.kg^{-1}$; and the systemic clearance is between 68.8 and 86.4 $ml.min^{-1}$.

When metronidazole is given as suppository or pessary the bioavailability is about 50% 25%, respectively. After rectal administration of 500 mg, mean C_{max} is about 5 $mg.1^{-1}$, with a T_{max} of about 4 h. After vaginal administration of 500 mg, mean C_{max} is 1 – 2 $mg.1^{-1}$, with a Tmax of 8 – 24 h.

Oral absorption	90 – 100%
Presystemic metabolism	negligible
Plasma half-life	
range	6 – 9 h
Volume of distribution	0.6 – 1.1 $I.kg^{-1}$
Plasma protein binding	0 – 20%

Metronidazole is widely and rapidly distributed throughout the body. This is reflected in its large volume of distribution. Therapeutic levels of metronidazole are found in various tissues, including bile, breast milk, synovial fluid, and saliva, in which serum and tissue levels are approximately the same. Levels in the CSF vary between 60 and 100% of the serum level concentration. In the aqueous humor, levels are approximately 40% of that of the serum and in bone the levels of metronidazole are approximately 75% those of serum. Metronidazole penetrates amoebic and pyogenic abscesses very well, including cerebral abscesses.

The major route of elimination of metronidazole and its metabolites is through the urine. Approximately 60 – 80% of the total administered dose is recovered as (a) the parent drug (10 – 20%) and (b) its major metabolites (the hydroxy) (30 – 40%) and acid metabolites (10 – 20%) over 48 h as determined by HPLC.

Renal failure does not change the half-life of metronidazole. However, since the major metabolites of metronidazole, the acid and hydroxy metabolites, are primarily excreted in the urine, these accumulate in renal failure. The half-life of the hydroxy metabolite in one study was 34 h and for the acid metabolite 138 h.

The type of dialysis required in renal failure patients will affect the elimination of metronidazole and its metabolites. Hemodialysis reduces the half-life of metronidazole from 9 h to approximately 3 h. The half-lives of the metabolites of metronidazole are also reduced, with the half-life of the hydroxy metabolite decreasing from 34 to 8 h and the acid metabolite from 138 to 7.9 h. The type of dialyzer membrane appears to affect the clearances of metronidazole and the hydroxy metabolite.

Peritoneal dialysis does not appear to affect the elimination of metronidazole or its metabolites and, therefore, the recommendations for patients in severe renal failure would pertain.

Since metronidazole is metabolized in the liver by oxidative mechanisms, it would be expected that its pharmacokinetics would be affected in patients with impaired liver function. In one study involving 10 patients with severe liver disease, after a single intravenous dose, the total body clearance of metronidazole was reduced by approximately 66% and the terminal serum half-life (β phase) was increased to 19.9 h from the 7.9 h seen in normal patients. The production of the hydroxy metabolite was delayed, with peak serum levels occurring at 22 h in liver failure patients, in contrast to 8 h in normal patients The total urinary excretion of the hydroxy and acid metabolites was markedly reduced over 48 h. The excretion of unchanged metronidazole in contrast, was not significantly different in normal patients and patients with liver failure. The degree of conjugation of the metabolites did not appear to be affected in patients with liver failure. No studies examining the fate of metronidazole or its metabolites in patients with severe liver failure on multiple dose regimens have been reported, but a reduction in the daily dose by 50% may be prudent with measurement of serum levels.

Concentration-effect relationship

Metronidazole exerts a very rapid bactericidal effect in anaerobic microorganisms at concentrations slightly above those producing an inhibitory effect. The radiosensitizing property of metronidazole requires approximately 5 – 10 times the usual dose given for its antimicrobial effect.

Metabolism

Metronidazole is metabolized primarily in the liver to various oxidative metabolites which are excreted partially conjugated as glucuronides in the urine. The major metabolites of metronidazole are 1-(2-hydroxyethyl)-2-hydroxymethyl-5-nitroimidazole, the hydroxy metabolite, and 1-acetic acid-2-methyl-5-nitroimidazole, the acid metabolite. A very small percentage may be reduced in the gut to acetamide. Approximately 14% of the administered dose of metronidazole is detected in the feces as determined by ^{14}C tracer studies.

After a single intravenous dose of metronidazole, peak levels of the hydroxy metabolite are measured in the serum at concentrations 10 – 20% of those of unchanged drug at approximately 8 h. The acid metabolite, in contrast, is usually not measurable after a single dose in the serum. After multiple doses, there is accumulation of the metabolites in the serum (hydroxy metabolite 30% of unchanged drug and acid metabolite 3%). In patients on oral therapy, the concentrations of the hydroxy metabolite became quite constant and averaged 7.5 and 3.2 $mg.1^{-1}$ on doses of 1000 and 400 mg daily, respectively. The half-life of the hydroxy metabolite was shown to be approximately 11 h in one study.

5.3 Pre-clinical safety data:

Metronidazole and some of its metabolites have been shown to be mutagenic in certain bacterial test systems (Ames test). The basis for the mutagenic effect (and antimicrobial effect) appears to be dependent upon the reduction of the 5-nitro group,

which normally would not occur to any significant degree in normal mammalian cells. It could possibly occur in very hypoxic or necrotic tissue. The tumorgenicity of metronidazole has been demonstrated in certain laboratory animals, but not in humans although it should be noted that metronidazole does induce DNA single-strand breaks in the lymphocytes of patients on standard does of the drug. Moreover, there is no firm evidence for teratogenicity or embryotoxicity with metronidazole in animals or in humans. At dose levels approximately 5 – 10 times those used in humans, metronidazole caused microscopic changes in the liver in monkeys and central nervous system effects (ataxia, tremors, prostration) in dogs. Evidence that caused concern regarding cytogenic effects has not been corroborated.

6. Pharmaceutical particulars:

6.1 List of Excipients:

Dibasic calcium phosphate	BP
Maize starch	BP
Gelatin	BP
Sodium methyl paraben	BP
Sodium propyl paraben	BP
Povidone (PVPK 30)	BP
Maize starch	BP
Purified talc	BP
Maize starch	BP
Magnesium stearate	BP
Colloidal silicon dioxide	BP

6.2 Incompatibilities:
None Reported

6.3 Shelf-Life:
36 months from the date of manufacture.

6.4 Special Precautions for Storage:
Store in a cool, dry and dark place. Protect from light.

6.5 Nature and Contents of Container:
1000 tablets packed in one Jar. Such jar packed in unit jar along with its package insert. Such jar packed in export worthy shipper.

6.6 Special precautions for disposal:
None reported.

7. Registrant:

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India.

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Vasai (E), Dist. Thane,
India.

9. Date of revision of the text :