# METRAL

## Instructions for the medicinal product

**Trade name:** Metral.
**International Nonproprietary Name:** Metronidazole.
**Dosage form:** Solution for infusion.
**Composition:** Each 100 ml contains:
Metronidazole USP 500 mg;
Excipients q.s.
**Pharmacotherapeutic group:** Antibacterials for systemic use. Imidazole derivatives.
**ATC Code:** J01XD01.
**Pharmacological action:**
*Pharmacodynamics:*
Anti protozoal and antimicrobial drug, a derivative of 5-nitroimidazole. The mechanism of action is to restore the biochemical 5 - nitrogroup intracellular transport proteins anaerobic bacteria and protozoa. Restored 5-nitro group interacts with the DNA of bacterial cells, inhibiting the synthesis of nucleic acids, which leads to the death of the bacteria.
Active against Trichomonas vaginalis, Entamoeba histolytica, and obligate anaerobes Bacteroides spp. (Including Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides vulgatus), Fusobacterium spp., some gram-positive microorganism (Eubacterium spp., Clostridium spp., Peptococcus niger, Peptostreptococcus spp.).
Minimum inhibitory concentration for this strains is 0.125-6.25 mcg / ml.
In combination with amoxicillin is active against Helicobacter pylori (amoxicillin inhibits the development of resistance to metronidazole).
Aerobic microorganisms and facultative anaerobes is sensitive to Metronidazole, but in the presence of mixed flora (aerobes and anaerobes) metronidazole acts synergistically with antibiotics which is effective against common aerobes.
Increases the sensitivity of tumors to radiation, causes sensitization to alcohol ( as disulfiram action).
*Pharmacokinetics:*
It has high penetration, reaching bactericidal concentrations in most tissues and body fluids, including the lungs, kidneys, liver, skin, cerebrospinal fluid, brain, bile, saliva, amniotic fluid, oral abscesses, vaginal secretions, semen, breast milk, the blood-brain penetrates and placental barrier.
Vd: adults - approximately 0.55 l/kg, newborns - 0.54-0.81 l/kg. Relationship to plasma proteins -10-20%.
By intravenous infusion of 500 mg over 20 min Cmax in serum after 1 h - 35.2 mcg/ml. The concentration of drug in the blood after 4 h - 33.9 mcg/ml after 8 h - 25.7 mcg/ml; Cmin in the subsequent introduction is - 18 mcg/ml. Tmax - 30-60 min. Therapeutic concentration is maintained for 6-8 hours. Under normal bile, concentration of metronidazole in the bile after intravenous infusion can greatly exceed the concentration in plasma.
The body metabolism about 30-60% of metronidazole by hydroxylation, oxidation and glucuronidation. The major metabolite (2-oxi-metronidazol) also has anti protozoal and antimicrobial effect.
T1/2 with in normal liver function - 8 hours (from 6 to 12 hours), in alcoholic liver disease -18 h (from 10 to 29 hours), in newborns, born at 28-30 weeks gestation - about 75 hours, 32-35 weeks - 35 hours, 36-40 weeks - 25 hours. Excreted by the kidneys 60-80% (20% unchanged), through the intestines - about 6-15%. In severe renal impairment (creatinine clearance less than 10 ml / min) in patients after repeated introduction may be observers a cumulation of metronidazole in serum, therefore the dose should be reduced by half.
Metronidazole and major metabolites are rapidly removed from the blood by hemodialysis (T1/2 reduced till 2.6 hours). In peritoneal dialysis appears in small quantities.
**Indications for use:**
- Protozoal infections;
- Extraintestinal amebiasis, including amebic liver abscess;
- Intestinal amebiasis (amebic dysentery);
- Trichomoniasi, trichomonas vaginitis, trichomonas urethritis;
- Infections, caused by Bacteroides spp. (including Bacteroides fragilis, Bacteroides distasonis, Bacteroides ovatus, Bacteroides thetaiotaomicron, Bacteroides vulgatus);
- Bone and joint infections;
- Infections of the CNS, including meningitis;
- Brain abscess;
- Bacterial endocarditis;
- Pneumonia, lung abscess;
- Empyema;
- Sepsis;
- Infections, caused by species of Clostridium spp., Peptococcus niger and Peptostreptococcus spp.;
- Infections, of the abdomen (peritonitis, abscess of the liver);
- Pelvic infections (endometritis, abscess of the fallopian tubes and ovaries, infection of vaginal vault);
- Pseudomembranous colitis (associated with the use of antibiotics);
- Gastritis or duodenal ulcer associated with Helicobacter pylori;
- Prophylaxis of postoperative complications (especially intervention colon, adrectal area, appendectomy, gynecological surgery);
- Radiation therapy of patients with tumors - as a radio sensitizing drug in cases where resistance is due to tumor hypoxia in tumor cells.

**Contraindications:**
- Increased sensitivity.
- Leukopenia (including in anemia);
- Organic CNS lesions (including, epilepsy);
- Hepatic failure (in the case of high doses);
- Pregnancy (I trimester);
- Lactation.

*Carefully:* pregnancy (II and III trimester) only in life indications, renal/hepatic failure.
**Dosage and Direction for use:**
Metral infusion should be infused intravenously at an approximate rate of 5 ml/min. Oral medication should be substituted as soon as feasible.
*Prophylaxis against anaerobic infection:* Chiefly in the context of abdominal (especially colorectal) and gynaecological surgery.
*Adults:*
500mg shortly before operation, repeated 8 hourly. Oral doses of 200 mg or 400 mg 8 hourly to be started as soon as feasible.
*Children:*
*Children < 12 years:* 20-30mg/kg as a single dose given 1-2 hours before surgery.
*Newborns with a gestation age < 40 weeks:* 10mg/kg body weight as a single dose before operation.
*Anaerobic Infections:* Treatment for seven days should be satisfactory for most patients but, depending upon clinical and bacteriological assessments, the physician might decide to prolong treatment e.g. for the eradication of infection from sites which cannot be drained or are liable to endogenous recontamination by anaerobic pathogens from the gut, oropharynx or genital tract.
*Treatment of established anaerobic infections:* Intravenous route is to be used initially if patient's symptoms preclude oral therapy.
*Adults:*
500 mg 8 hourly.
*Children:*
*Children > 8 weeks to 12 years of age:* The usual daily dose is 20-30mg/kg/day as a single dose or divided into 7.5mg/kg every 8 hours. The daily dose may be increased to 40mg/kg, depending on the severity of the infection. Duration of treatment is usually 7 days.
*Children < 8 weeks of age:* 15mg/kg as a single dose daily or divided into 7.5mg/kg every 12 hours. *In newborns with a gestation age < 40 weeks*, accumulation of metronidazole can occur during the first week of life, therefore the concentrations of metronidazole in serum should preferable be monitored after a few days therapy.
*Bacterial vaginosis:*
*Adolescents:* 400mg twice daily for 5-7 days or 2000mg as a single dose.
*Urogenital trichomoniasis:*
*Adults and adolescents:* 2000mg as a single dose or 200mg 3 times daily for 7 days or 400mg twice daily for 5-7 days
*Children < 10 years:* 40mg/kg orally as a single dose or 15-30 mg/kg/day divided in 2-3 doses for 7 days; not to exceed 2000mg/dose
*Giardiasis:*
*> 10 years:* 2000mg once daily for 3 days, or 400mg three times daily for 5 days, or 500mg twice daily for 7 to 10 days.
*Children 7 to 10 years:* 1000mg once daily for 3 days.
*Children 3 to 7 years:* 600 to 800mg once daily for 3 days.
*Children 1 to 3 years:* 500mg once daily for 3 days.
*Alternatively, as expressed in mg per kg of body weight:* 15-40mg/kg/day divided in 2-3 doses.
*Amoebiasis:*
*> 10 years:* 400 to 800mg 3 times daily for 5-10 days.
*Children 7 to 10 years:* 200 to 400mg 3 times daily for 5-10 days.
*Children 3 to 7 years:* 100 to 200mg 4 times daily for 5-10 days.
*Children 1 to 3 years:* 100 to 200mg 3 times daily for 5-10 days.
*Alternatively, doses may be expressed by body weight:* 35 to 50mg/kg daily in 3 divided doses for 5 to 10 days, not to exceed 2400mg/day
*Eradication of Helicobacter pylori in paediatric patients:* As a part of a combination therapy, 20mg/kg/day not to exceed 500mg twice daily for 7-14 days. Official guidelines should be consulted before initiating therapy.
*Elderly:*
Caution is advised in the elderly. Particularly at high doses although there is limited information available on modification of dosage.
**Side-effects:**
The frequency of adverse events listed below is defined using the following convention:
very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).
Serious adverse reactions occur rarely with standard recommended regimens. Clinicians who contemplate continuous therapy for the relief of chronic conditions, for periods longer than those recommended, are advised to consider the possible therapeutic benefit against the risk of peripheral neuropathy.
*Blood and lymphatic system disorders:* Very rare: agranulocytosis, neutropenia, thrombocytopenia, pancytopenia. Not known: leucopenia.
*Immune system disorders:* Rare: anaphylaxis. Not known: angiodema, urticaria, fever.
*Metabolism and nutrition disorders:* Not known: anorexia.
*Psychiatric disorders:* Very rare: psychotic disorders, including confusion and hallucinations. Not known: depressed mood.
*Nervous system disorders:*Very rare: encephalopathy (eg. confusion, fever, headache, hallucinations, paralysis, light sensitivity, disturbances in sight and movement, stiff neck) and subacute cerebellar syndrome (eg. ataxia, dysathria, gait impairment, nystagmus and tremor) which may resolve on discontinuation of the drug; drowsiness, dizziness, convulsions, headaches.
*Not known:* during intensive and/or prolonged metronidazole therapy, peripheral sensory neuropathy or transient epileptiform seizures have been reported. In most cases neuropathy disappeared after treatment was stopped or when dosage was reduced; aseptic meningitis.
*Eye disorders:* Very rare: vision disorders such as diplopia and myopia, which, in most cases, is transient. Not Known: optic neuropathy/neuritis.
*Gastrointestinal disorders:* Not known: taste disorders, oral mucositis, furred tongue, nausea, vomiting, gastro-intestinal disturbances such as epigastric pain and diarrhoea.
*Hepatobiliary disorders:* Very rare: abnormal liver function tests, cholestatic hepatitis, jaundice and pancreatitis which is reversible on drug withdrawal.
*Skin and subcutaneous tissue disorders:* Very rare: skin rashes, pustular eruptions, pruritis, flushing. Not known: erythema multiforme.
*Musculoskeletal, connective tissue and bone disorders:* Very rare: myalgia, arthralgia.
*Renal and urinary disorders:* Very rare: darkening of urine (due to metronidazole metabolite).
**Overdose:**
Symptoms: include nausea, vomiting, ataxia; when taken as a radio sensitizing - cramps, peripheral neuropathy.
Treatment: Not specific antidote, symptomatic and supportive therapy.
**Drug interactions:**
EPatients should be advised not to take alcohol during metronidazole therapy and for at least 48 hours afterwards because of the possibility of a disulfiram-like (antabuse effect) reaction. Psychotic reactions have been reported in patients who were using metronidazole and disulfiram concurrently.
Some potentiation of anticoagulant therapy has been reported when metronidazole has been used with the warfarin type oral anticoagulants. Dosage of the latter may require reducing. Prothrombin times should be monitored. There is no interaction with heparin.
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.
Patients receiving phenobarbital or phenytoin metabolise metronidazole at a much greater rate than normally, reducing the half-life to approximately 3 hours.
Metronidazole reduces the clearance of 5 fluorouracil and can therefore result in increased toxicity of 5 fluorouracil.
Patients receiving ciclosporin are at risk of elevated ciclosporin serum levels. Serum ciclosporin and serum creatinine should be closely monitored when coadministration is necessary.
Plasma levels of busulfan may be increased by metronidazole which may lead to severe busulfan toxicity.
**Cautions:**
Metral has no direct activity against aerobic or facultative anaerobic bacteria.
Regular clinical and laboratory monitoring (especially leucocyte count) are advised if administration of Metral for more than 10 days is considered to be necessary and patients should be monitored for adverse reactions such as peripheral or central neuropathy (such as paraesthesia, ataxia, dizziness, convulsive seizures).
Metral should be used with caution in patients with active or chronic severe peripheral and central nervous system disease due to the risk of neurological aggravation.
There is a possibility that after Trichomonas vaginalis has been eliminated a gonococcal infection might persist.
The elimination half-life of metronidazole remains unchanged in the presence of renal failure. Therefore the dosage of metronidazole needs no reduction. Such patients however retain the metabolites of metronidazole. The clinical significance of this is not known at present.
In patients undergoing haemodialysis metronidazole and metabolites are efficiently removed during an eight hour period of dialysis. Metral should therefore be re-administered immediately after haemodialysis.
No routine adjustment in the dosage of Metral need be made in patients with renal failure undergoing intermittent peritoneal dialysis (IDP) or continuous ambulatory peritoneal dialysis (CAPD).
Metronidazole is mainly metabolised 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. Metral should therefore, be administered with caution to patients with hepatic encephalopathy. The daily dosage should be reduced to one third and may be administered once daily.
Aspartate amino transferase assays may give spuriously low values in patients being treated with Metral depending on the method used.
Patients should be warned that Metral may darken urine.
Cefuroxime is physically and chemically compatible with metronidazole. The following drugs have been shown to be physically compatible in terms of pH and appearance with Metral infusion over the normal period of administration, although there is no evidence of chemical stability: amikacin sulphate, ampicillin sodium, carbenicillin sodium, cephazolin sodium, cefotaxime sodium, cephalothin sodium, chloramphenicol sodium succinate, clindamycin phosphate, gentamicin sulphate, hydrocortisone sodium succinate, latamoxef disodium, netilmicin sulphate and tobramycin sulphate. In patients maintained on intravenous fluids, Metral infusion may be diluted with appropriate volumes of normal saline, dextrose-saline, dextrose 5% w/v or potassium chloride infusions (20 and 40 mmol/litre). Apart from the above, Metral should on no account be mixed with any other substance.
Due to inadequate evidence on the mutagenicity risk in humans, the use of Metral for longer treatment than usually required should be carefully considered.
**Presentation:**
1X1, 100 ml FFS Plastic bottle in a monocarton, with instruction for use.
**Storage:**
Keep in dry place protected from light at a temperature below 30°C. Keep out of reach of children.
**Shelf life:**
Labeled. Do not use after expiry date.
**Distribution Condition:**
Prescription only medicine (POM).