

LAVOISIER METRONIDAZOLE 0,5 % (500 mg/100 ml), injectable solution for infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION

METRONIDAZOLE	500.00 mg
Hydrogenophosphate of dodecahydrated sodium	24.00 mg
Sodium chloride	795.00 mg
Dihydrogenophosphate of dehydrated sodium	94.00 mg
Water for injectable preparations	100 ml
	s.q

in each single dose bottle

Solution pH ranging from 4.5 to 6.5

PHARMACEUTICAL FORM

Solution for infusion

THERAPEUTIC INDICATIONS

They derive from metronidazole antibacterial and antiparasitic activity and its pharmacokinetic properties. They are restricted to infections caused by germs known as sensitive.

- Curative treatment of medico-surgical infections with sensitive anaerobic germs
- Prophylaxis of post-operative infections to sensitive anaerobic germs in digestive or proctologic surgical operations, associated with an active antibiotic on aerobic germs
- Severe amoebiasis occurring in intestinal or hepatic sites

Injectable metronidazole must be used for patients in whom oral use is not indicated.

The official recommendations on appropriate use of antibacterials should be taken into consideration.

ADMINISTRATION

Administration in slow intravenous infusion, at a rate of a single dose vial of 100 ml (500 mg) in 30 to 60 minutes.

Treatment of anaerobic germs infections

- *Adults:* 1 to 1.50 g daily at a rate of 2 or 3 intravenous perfusions
- *Children:* 30 to 40 mg/kg/daily at a rate of 2 or 3 intravenous perfusions

The switch to oral use with the same dose may be achieved when patient's state permits.

Prophylaxis of postoperative infections in surgery

Antibioprohylaxis must be over a short period of time, generally limited to the peroperative period, 24 hours sometimes, but no more than 48 hours.

- *Adults:* 30 mn before the start of intervention, intravenous injection of a single dose of 1 g
- *Children:* 30 minutes before the start of operation, intravenous injection of a single dose of 20 to 40 mg/kg

Amebiasis

- *Adults:* 1.50 g per day (i.e. 3 intravenous perfusions of 500 mg daily);
- *Children:* 30 to 40 mg/kg/daily in intravenous perfusions.

In hepatic amoebiasis, at the stage of suppuration, draining of the abscess should be associated concomitantly with treatment by metronidazole.

CONTRA-INDICATIONS

- This drug should never be prescribed to patients with hypersensitivity to imidazoles.
- In general, this drug should not be administered concomitantly with disulfirame or alcohol or alcohol-content drugs.

WARNINGS AND PRECAUTIONS FOR USE

- Treatment should be discontinued in the event of ataxia, dizziness or mental confusion.
- Aggravation of the neurological status should not be excluded among patients with severe, fixed or degenerative central and peripheral neurological diseases.
- Alcoholic beverages must be avoided ('antabuse' effect).
- No suspicion of carcinogenicity involved in humans although this product was shown to be carcinogenic in a certain species of mouse, but not in rat and hamster.
- Patients with blood dyscrasia antecedents or high doses treatment and (or) prolonged treatment should have their leucocytic formula monitored. In patients with leucopenia, appropriateness of continuing treatment is dependent on the severity of the infection.
- Have account of sodium salts content.

INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTIONS

Contraindicated interactions

- . Disulfirame: delirious episodes or confusional state.
- . Alcohol: antabuse effect (heat, skin irritation, vomiting, tachycardia).
Alcoholic beverages and content-alcohol medications must be avoided.

Associations requiring extreme caution:

- . Oral anticoagulants (described for warfarin): increased oral anticoagulants effect and risk of hemorrhage (decrease of their hepatic catabolism).
Prothrombine rates and BUN must be closely monitored.
Posology adjustment of oral anticoagulants during treatment by metronidazole and 8 days after suspension of treatment.

Association requiring extreme caution:

- . 5 Fluoro-uracil: increase of 5 Fluoro-uracil toxicity by decrease of its clearance.

Paraclinic examinations

- Metronidazole may block treponemas activity and then produce a false positive in Nelson's test.

Specific problems of BUN imbalance

- In patients receiving antibiotics, it has been reported an increase of the activity of oral anticoagulants in several cases. Infectious or inflammatory response, age and general state of the patient are risk factors. Under these circumstances, it is difficult to make due allowances for infectious pathology and its treatment in onset of BUN imbalance. However, certain classes of antibiotics are more concerned: especially fluoroquinolones, macrolides, cyclines, cotrimoxazole and certain cephalosporines.

PREGNANCY AND LACTATION

Use in Pregnancy

In animals, metronidazole was not shown to be teratogenic or foetotoxic.

- Observations of several hundreds of pregnancies with exposure to metronidazole for the first trimester have not shown any particular malformative effect.
- Studies in the same number of patients treated beyond the first trimester have not revealed any foetotoxic effect.
- Therefore, use in pregnancy of metronidazole is not a contraindication if absolutely necessary

Use in lactation

Metronidazole should not be administered to lactating mothers as it passes into the breast milk.

ADVERSE REACTION

In very rare instances, yet they may occur:

- minor gastrointestinal tract disturbances: nausea, metal taste in the mouth, anorexia, epigastric cramps, vomiting, diarrhoea.

Exceptionally:

- Cutaneomucous symptoms: urticaria, vasomotor disorders, pruritus,
- Neuro-psyche signs: cephalgia, dizziness, mental confusion, convulsions,
- Cases of pancreatitis, reversible with suspension of treatment.

With high posology and/or prolonged treatment:

- Leucopenia,
- Peripheral sensitive neuropathies always reversible with suspension of treatment.

A brown-reddish coloration of urine may also be observed because of the presence of water-soluble pigments from product metabolism.

CLINICAL PHARMACOLOGY

Pharmacodynamics

ANTIBIOTIC of the family of nitro-5 Imidazol (J: Anti-infectious)

ANTIBACTERIAL ACTIVITY SPECTRUM

The critical concentrations separate sensitive strains from strains with intermediate sensitivity and these latter from resistant strains:

S ≥ 4 mg/l and R >4 mg/l

The prevalence of acquired resistance may vary depending on geography and weather for certain species. It is then useful to have information on the prevalence of local resistance, especially for the treatment of severe infections. These data can only provide some guidance on the probabilities of the sensitivity of a bacterial strain to this antibiotic.

When resistance prevalence variability in France is known for a bacterial species, it is indicated on the table below:

Categories	Frequency of resistance acquired in France (>10 %) (extreme values)
SENSITIVE SPECIES	
Aerobes with negative Gram	
HELICOBACTER PYLORI	30 %
Anaerobes	
<i>Bacteroides fragilis</i>	
<i>Bifidobacterium</i>	60-70 %
<i>Bilophila</i>	
<i>Clostridium</i>	
<i>Difficult Clostridium</i>	
<i>Clostridium perfringens</i>	
<i>Eubacterium</i>	20 – 30 %
<i>Fusobacterium</i>	
<i>Peptostreptococcus</i>	
<i>Prevotella</i>	
<i>Prophyromonas</i>	
<i>Veillonella</i>	

Categories	Frequency of resistance acquired in France (>10 %) (extreme values)
RESISTANT SPECIES	
Aerobes with negative Gram	
<i>Actinomyces</i>	
Anaerobes	
<i>Mobiluncus</i>	
<i>Propionibacterium acnes</i>	

Categories	Frequency of resistance acquired in France (>10 %) (extreme values)
ANTIPARASITIC ACTIVITY	
<i>Entamoeba histolytica</i>	
<i>Trichomonas vaginalis</i>	
<i>Giardia intestinalis</i>	

Pharmacokinetics

Distribution

Intravenous injection of 500 mg of metronidazole produces after a single infusion an average peak of 18 mg/l at the end of a 20-minutes infusion.

Repeat infusion:

- . every 8 hours produces the same average peak,
- . every 12 hours an average peak of 13 mg/l.

Plasma half-life is from 8 to 10 hours.

Serum proteins binding of metronidazole is low (<10 %). Distribution is fast and large in the lungs, kidneys, liver, skin, bile, CSF, saliva, seminal liquid, vaginal secretions.

It crosses the placental barrier and passes into the breast milk.

Biotransformation

Metronidazole produces primarily two metabolites with no conjugation and endowed with antibacterial activity (10 to 30%).

Elimination

Metronidazole concentrates primarily on liver and bile, its colic concentration is low.

Major path of excretion is in urine (40 to 70 %, with about 20 % unchanged), inducing a brown-reddish coloration of urine.

In patients with renal insufficiency, elimination half-life is unchanged and no dose adjustment is required. In hemodialysis, metronidazole is rapidly eliminated and half-life reduced to 2 hours 30.

PHARMACEUTICAL DATA

Incompatibilities

Do not mix aztreonam with amino acid solutions, cefamandole and dopamine.
Do not introduce any additive drug into bottle.

Shelf life

3 years

Storage special precautions

To be stored in a dark place.

Nature and contents of container

100 ml bottle (type II glass) of 125 ml, closed with a chlorobutyl stopper and capsule.

PACKAGING AND PRODUCT LICENSE NUMBER

Hospital Packaging:

MA 561 574-6: 100 ml bottle (type II glass) - 24 bottles package - Approved for institutions.

CONDITIONS OF PRESCRIPTION AND DELIVERY

List I. Reserved to hospital use.

DATE OF REVISION

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