Composition
Each film coated tablet (Amrizole 250 & 500 mg) contains as active ingredient 250 or 500 mg metronidazole.
Excipients:
Dibasic calcium phosphate, Maize starch, Povidone, Colloidal silicon dioxide & Magnesium stearate.

Each 5 ml (Amrizole suspension) contains as active ingredient 200 mg Benzoyl metronidazole.
Excipients:
Sodium phosphate monobasic, Methyl parahydroxy benzoate, Propyl parahydroxy benzoate,
Aluminium magnesium silicate, Sucrose, saccharin sodium, Soluble banana flavour, Glycerol,
Polysorbate 80, Carboxymethyl cellulose, Purified water.

Boxed Warning
Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions described in the indications section below.

Pharmacological properties
# Pharmacodynamic properties:

Metronidazole is an anti-infective agent belonging to 5-nitroimidazole group.

Antibacterial spectrum of metronidazole concerns exclusively anaerobic pathogens:

- Susceptible species:
  More than 90% of the species are susceptible (S).
  Peptostreptococcus, C. perfringens, C. difficile, Bacteroides fragilis, Bacteroides sp.,
  Fusobacterium, Clostridium sp., Prevotella, Veillonella.

- Species with inconstant susceptibility:
  The susceptibility of the pathogens should be tested by an antibiogram.
  Bifidobacterium, Eubacterium.

- Normally resistant species:
  More than 50% of the species are resistant (R).
  Propionibacterium, Actinomyces, Mobiluncus.

- Anti-parasitic activity:
  Trichomonas vaginalis, Giardia intestinalis, Entamoeba histolytica

# Pharmacokinetic properties:

Bioavailability:
- Metronidazole is rapidly absorbed following oral administration, at least 80% is absorbed in less than one hour.
- The serum peak concentrations achieved following oral administration are similar to those obtained following intravenous administration of equivalent doses.
- The oral bioavailability is 100% and not modified by ingestion of food.

Distribution:
- After a single dose administration of 500 mg of metronidazole the average peak serum level is of 10 mg/ml one hour after the ingestion.
- The plasma half-life is 8 to 10 hours.
- The plasma protein binding is low: < 20%.
- The volume of distribution is high, on average of 40 L (i.e. 0.65 L/kg).
- Diffusion is rapid and tissue concentrations are similar to serum concentrations in: lungs, kidneys, liver, skin, bile, CSF, saliva, seminal fluid and vaginal secretions.
- Metronidazole crosses the placental barrier and is excreted in breast milk.

Metabolism:
- Metronidazole is metabolized by oxidation in the liver into two metabolites:
  - The alcoholic metabolite which has a bactericidal activity on the anaerobic pathogens on average 30% in comparison with the metronidazole and an elimination half-life of 11 hours.
  - The acid metabolite is low with a bactericidal activity of 5%.

Elimination:
- Hepatic and biliary concentrations are high. Colon and fecal concentrations are low.
- Excretion is mainly urinary, metronidazole and its metabolites represent 35 to 65% of the ingested dose.

Therapeutic indications
Indications are based on the antiparasitic and antibacterial activity of metronidazole and on its pharmacokinetic characteristics.

They are intended for the treatment of infections due to the pathogens susceptible to metronidazole:
- Amoebiasis.
- Giardiasis.
- Lямблиasis.
- Urogenital trichomoniasis.
- Non specific vaginitis.
- Anaerobic bacterial Infections:
  - Curative treatment of medico-surgical infections due to susceptible anaerobic pathogens.
  - Prophylaxis against infections caused by susceptible anaerobic pathogens in high risk surgical contexts.
Following prophylactic or curative treatment by injection, of infections due to susceptible
anaerobes.

Intra-abdominal infections including peritonitis, intra-abdominal abscess and liver abscess.

Skin and skin structure infections
Gynecologic infections including endometritis, endomyometritis, tubo-ovarian abscess and postsurgical vaginal cuff infection

Bacterial septicemia

Bone and joint infections, as adjunctive therapy.

Central nervous system infections including meningitis and brain abscess

Lower respiratory tract infections including pneumonia, emphysema and lung abscess

Endocarditis

Dosage and method of administration

Amoebiasis:
- Adults: 1.50 g. daily, in 3 divided doses.
- Children: 30 to 40 mg/kg/day in 3 divided doses.

In hepatic amoebiasis, at the abscess stage, the abscess must be evacuated concomitantly with metronidazole treatment. The duration of the treatment is 7 consecutive days.

Giardiasis:
- Adults: 0.750 to 1 g daily for 5 consecutive days.
- Children: from 2 to 5 years: 250 mg/day, from 5 to 10 years: 375 mg/day, from 10 to 15 years: 500 mg/day.

Lambliasis: For 5 consecutive days,
- Adults: 750mg to 1 g per day.
- Children: from 2 to 5 years: 250 mg daily, from 5 to 10 years: 375 mg daily, from 10 to 15 years: 500 mg daily.

Trichomoniasis:
- In females (urethritis and vaginitis due to Trichomonas): single dose of 2 g or 500 mg/day by oral route in two divided doses for 10 days. Whether or not the partner presents clinical signs of infection with Trichomonas vaginalis, he must be treated concurrently, even in the absence of positive laboratory tests.
- In males (urethritis due to Trichomoniasis): 2 g in a single dose, or 500 mg by oral route in 2 divided doses for 10 days.

Non-specific Vaginalis:
500 mg, twice daily for 7 days. The partner must be treated simultaneously.

Anaerobic infections (as first line or substitute treatment):
- Adults: 1 to 1.5 g/day.
- Children: 20 to 30 mg/kg/day.
Surgical chemoprophylaxis:
Metronidazole must be combined with a product active against Enterobacteria.
- Adults: One 500 mg dose every 8 hours. Beginning the treatment approximately 48 hours before surgery, appears to be effective. The last dose must be administered at the latest 12 hours before surgery. The goal of chemoprophylaxis is to reduce the bacterial inoculum in the gastrointestinal tract at the time of surgery; it is therefore useless to continue the antibiotic in the postoperative period, at last by the oral route.
- Children: same protocol at a dosage of 20 to 30 mg/kg/day.

Contraindications
Hypersensitivity to imidazoles.

Warnings and precautions
Warnings:
- Treatment should be discontinued in case of ataxia, vertigo, hallucinations or mental confusion.
- Risk of aggravation of the neurological condition must be taken into account in patients with active or chronic severe central or peripheral neurological disorders.
- Alcohol should be avoided during metronidazole administration and one day after because of the possibility of disulfiram-like reaction (Antabuse effect).

Precautions:
- There is no suspicion of carcinogenicity in man although the product has proved carcinogenic in a certain strain of mouse.
- Differential blood count especially leucocytes should be monitored, if there is a history of blood dyscrasias or in high dose and/or prolonged treatment than the recommended dosages. Should leucopenia occurs, treatment continuation will depend on the severity of the infection.
- Patients should be monitored for adverse reactions as peripheral and central neuropathy (i.e. parasthesia, dizziness, ataxia, convulsive seizures).
- Metronidazole should be administered with caution in patients with hepatic encephalopathy.
- Known or previously unrecognized candidiasis may present more prominent symptoms during therapy with metronidazole and requires treatment with a candidacidal agent.
- Prescribing Amrizole in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- Patients should be counseled that antibacterial drugs including Amrizole should only be used to treat bacterial infections. They do not treat viral infections (e.g. the common cold). When Amrizole is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the immediate treatment and increase the likelihood that bacteria will develop resistance and will not be treatable by Amrizole or other antibacterial drugs in the future.

Driving vehicle/perform hazardous tasks
Driving vehicle or performing other hazardous tasks:
Patients should be warned about the potential adverse reactions; confusion, dizziness,
hallucinations, convulsions or transient visual disorders, and advised not to drive or operate machinery if these symptoms occur.

Interactions with other medications
- Disulfiram: Disulfiram may lead to delirium or mental confusion (psychotic reactions).
- Alcohol: Alcoholic beverages and drugs containing alcohol should be avoided during treatment with metronidazole and at least one day after discontinuing treatment because of the possibility of disulfiram-like (antabuse effect) reaction (flushing, vomiting, and tachycardia).
- Warfarin: Because of the potentiation of oral anticoagulants effect and hemorrhagic risk (decrease in the oral anticoagulants hepatic catabolism), prothrombin level should be monitored more frequently. Oral anticoagulant dosage must be adjusted during metronidazole treatment and 8 days after discontinuation.
- Vecuronium (non-depolarising neuromuscular blocking agent): Metronidazole potentiates the action of vecuronium.
- 5-fluoro-uracil: Metronidazole increases the toxic effect of 5-fluorouracil due to 5-fluorouracil reduced clearance.
- Lithium: Plasma levels of lithium may be increased by metronidazole. Plasma lithium concentration, creatinine and electrolytes should be monitored in patients who are co-administered lithium and metronidazole.
- Cyclosporin: Risk of cyclosporin serum levels elevation. Serum cyclosporin and serum creatinine should be closely monitored when coadministration is necessary.
- Phenytoin or phenobarbital: Increased elimination of metronidazole results in reduced plasma levels.
- Busulfan: Plasma levels of busulfan may be increased by metronidazole, which may lead to severe busulfan toxicity.

Interactions with lab investigations
Metronidazole may immobilise Treponema and hence result in a false positive Treponema palladium immobilisation test.

Pregnancy and lactation
Pregnancy Category B:
Metronidazole has not shown evidence of teratogenicity or fetotoxicity in animal studies. Case studies of several hundred pregnancies in which metronidazole were administered during the first trimester did not show evidence of any particular malformation. Studies of identical number of patients treated with metronidazole after the first trimester have not shown evidence of fetal toxicity. Therefore, pregnancy is not a contraindication for the use of metronidazole, however it should be used very cautiously in cases of necessity.

Lactation:
Metronidazole should be avoided due to the fact that it passes into breast milk.

Carcinogenesis
Metronidazole has shown evidence of carcinogenic activity in a number of studies involving
chronic, oral administration in mice and rats.

Undesirable effects

Two serious adverse reactions reported in patients treated with metronidazole have been convulsive seizures and peripheral neuropathy, the latter characterized mainly by numbness or paresthesia of an extremity. Since persistent peripheral neuropathy has been reported in some patients receiving prolonged administration of metronidazole, patients should be specifically warned about these reactions and should be told to stop the drug and report immediately to their physicians if any neurologic symptoms occur.

The most common adverse reactions reported have been referable to the gastrointestinal tract, particularly nausea reported by about 12% of patients, sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping. Constipation has also been reported.

The following reactions have also been reported during treatment with metronidazole:

- Mouth: A sharp, unpleasant metallic taste is not unusual. Furry tongue, glossitis, and stomatitis have occurred; these may be associated with a sudden overgrowth of Candida which may occur during therapy.
- Hematopoietic: reversible neutropenia (leukopenia); rarely, reversible thrombocytopenia.
- Cardiovascular: Flattening of the T-wave may be seen in electrocardiographic tracings.
- Central Nervous System: Convulsive seizures, peripheral neuropathy, dizziness, vertigo, incoordination, ataxia, confusion, irritability, depression, weakness, and insomnia.
- Hypersensitivity: Urticaria, erythematous rash, flushing, nasal congestion, dryness of the mouth (or vagina or vulva), and fever.
- Renal: Dysuria, cystitis, polyuria, incontinence, and a sense of pelvic pressure. Instances of darkened urine have been reported by approximately one patient in 100,000. Although the pigment which is probably responsible for this phenomenon has not been positively identified, it is almost certainly a metabolite of metronidazole and seems to have no clinical significance.
- Other: proliferation of Candida in the vagina, dyspareunia, decrease of libido, proctitis and fleeting joint pains, sometimes resembling serum sickness. If patients receiving metronidazole drink alcoholic beverages, they may experience abdominal distress, nausea, vomiting, flushing, or headache. A modification of the taste of alcoholic beverages has also been reported. Rare cases of pancreatitis, which generally abated on withdrawal of the drug, have been reported.

Overdosage

Single oral doses of metronidazole, up to 12 g have been reported. Symptoms were limited to vomiting, ataxia and slight disorientation.

There is no specific antidote for metronidazole overdosages. In case of suspected massive overdosages, a symptomatic and supportive treatment should be instituted.

Storage

Store at temperature not exceeding 30C.

Presentations

Amrizole 250 & 500 mg Tablets: A carton box containing 2 strips (PVC/Al) each of 10 tablets +
Amrizole suspension: A carton box containing a plastic bottle of 120 ml + pamphlet.
Company
Produced by:
Amriya For Pharmaceutical Industries,
Alexandria - Egypt