

Macrobac

(Azithromycin U.S.P.)

میکروبیک

(ایزیتھرومائسین یو.ایس.پی.)

COMPOSITION

Each **Macrobac** 250mg capsule contains Azithromycin (as dihydrate) equivalent to 250mg Azithromycin. (Product contains Lactose)
Each **Macrobac** 500mg tablet contains Azithromycin (as dihydrate) equivalent to 500 mg Azithromycin. Each 5mL **Macrobac** reconstituted suspension contains Azithromycin dihydrate equivalent to 200mg Azithromycin.

PHARMACOLOGICAL PROPERTIES

Mode of Action: Macrobac is a macrolide antibiotic belonging to the azalide group. The mechanism of action of Azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50s sub-unit and inhibition of peptide translocation.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by in vitro incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was > 30 after one hour incubation. In vivo studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Pharmacokinetic Properties

Absorption: Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2-3 hours after taking the medicinal product.

Distribution: Orally administered Azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of Azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.

Binding to serum proteins varies according to plasma concentration.

Elimination: The terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of Azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

MICROBIOLOGY

Aerobic and facultative gram-positive microorganisms	Aerobic and facultative gram-negative microorganisms	Other microorganisms
Staphylococcus aureus Streptococcus agalactiae Streptococcus pneumoniae Streptococcus pyogenes	Haemophilus ducreyi Haemophilus influenzae Moraxella catarrhalis Neisseria gonorrhoeae	Chlamydia pneumoniae Chlamydia trachomatis Mycoplasma pneumoniae

Note: Most strains of Enterococcus faecalis and methicillin-resistant staphylococci are resistant to Azithromycin. At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for Azithromycin. However, the safety and effectiveness of Azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic and facultative gram-positive microorganisms	Aerobic and facultative gram-negative microorganisms	Anaerobic microorganisms	Other microorganisms
Streptococci (Groups C, F, G) Viridans group streptococci	Bordetella pertussis Legionella pneumophila	Peptostreptococcus species Prevotella bivia	Ureaplasma urealyticum

INDICATIONS

Macrobac (Azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia) caused by susceptible strains of the designated microorganisms in the specific conditions listed below.

Adults

- Acute bacterial exacerbations of chronic obstructive pulmonary disease
- Acute bacterial sinusitis
- Community-acquired pneumonia (Note: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness)
- Pharyngitis/tonsillitis
- Uncomplicated skin and skin structure infections (abscesses usually require surgical drainage)
- Urethritis and cervicitis
- Genital ulcer disease in men

Pediatric Patients

- Acute otitis media
- Community-acquired pneumonia (Note: Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness)
- Pharyngitis/tonsillitis

DOSAGE AND ADMINISTRATION

Macrobac capsule should be taken at least 1 hour before or 2 hours after meal and antacid. **Macrobac** tablet can be taken with or without food.

Adults

Infection	Recommended Dose/Duration of Therapy
Community-acquired pneumonia (mild severity) Pharyngitis/tonsillitis (second line therapy) Skin/skin structure (uncomplicated)	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Acute bacterial exacerbations of chronic obstructive pulmonary disease (mild to moderate)	500 mg QD x 3 days OR 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Acute bacterial sinusitis Genital ulcer disease (chancroid) Non-gonococcal urethritis and cervicitis Gonococcal urethritis and cervicitis	500 mg QD x 3 days One single 1 gram dose One single 1 gram dose One single 2 gram dose

Pediatric Patients

In children under 45Kg body weight: **Macrobac** suspension should be used for children under 45Kg. There is no information on children less than 6 months of age. The dose in children is 10mg/Kg as a single daily dose for 3 days:

Body Weight (Kg)	Age (years)	Dose (mg)	Teaspoonful*/day	Duration
15-25	3-7	200mg OD	1 TSF	3 days
26-35	8-11	300mg OD	One & half TSF	3 days
36-45	12-14	400mg OD	Two TSF	3 days

* 1 Teaspoonful = 5mL.

Over 45 Kg: Dose as per adults.

Directions for Preparation: 15mL: To prepare 15mL suspension add 7.5mL boiled cooled water to the powder by using the given measuring device and shake well to dissolve the powder. **25mL:** To prepare 25mL suspension add 12.5mL boiled cooled water to the powder by using the given measuring device and shake well to dissolve the powder.

Renal failure: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 - 80 mL/min). Caution should be exercised when Azithromycin is administered to patients with severe renal impairment (GFR < 10 mL/min). **Hepatic failure:** Since Azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease.

SIDE EFFECTS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely. **Multiple-dose Regimens:** Overall, the most common treatment-related side effects in adult patients receiving multiple-dose regimens of Azithromycin were related to the gastrointestinal system with diarrhea/loose stools (4-5%), nausea (3%) and abdominal pain (2-3%) being the most frequently reported.

No other treatment-related side effects occurred in patients on the multiple-dose regimens of Azithromycin with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.

Gastrointestinal: Dyspepsia, flatulence, vomiting, melena and cholestatic jaundice.

Genitourinary: Monilia, vaginitis and nephritis.

Nervous System: Dizziness, headache, vertigo and somnolence.

General: Fatigue.

Allergic: Rash, pruritus, photosensitivity and angioedema.

Single 1-gram Dose Regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of **Macrobac** were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single one-gram dosing regimen of Azithromycin with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%) and vaginitis (1%).

Single 2-gram Dose Regimen: Overall, the most common side effects in patients receiving a single 2-gram dose of

Azithromycin were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%) and dizziness (1%). The majority of these complaints were mild in nature.

Post-Marketing Experience: Adverse events reported with Azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria and angioedema.

Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension. There have been rare reports of QT prolongation and torsades de pointes.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis and rare reports of tongue discoloration.

General: Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal).

Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death.

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.

Psychiatric: Aggressive reaction and anxiety.

Skin/Appendages: Pruritus, rarely serious skin reactions including erythema multiforme, Stevens Johnson Syndrome and toxic epidermal necrolysis.

Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus and reports of taste/smell perversion and/or loss.

Laboratory Abnormalities: Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils and blood glucose; elevated serum creatine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline. When follow-up was provided, changes in laboratory tests appeared to be reversible. In multiple-dose clinical trials involving more than 5000 patients, four patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

DRUG INTERACTION

Antacids: In a pharmacokinetic study on the effect of concomitant administration of antacids and Azithromycin, no effect on the total bio-availability was seen, although the peak serum levels were reduced by 30%. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

Cimetidine: A single dose of cimetidine administered 2 hours before Azithromycin had no effect on the pharmacokinetics of Azithromycin.

Cyclosporin: Caution should be exercised before considering coadministration of these two drugs. If coadministration is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Digoxin: Some of the macrolide antibiotics have been reported to impair the metabolism of digoxin (in the gut) in some patients. Therefore, in patients receiving concomitant Azithromycin and digoxin the possibility of raised digoxin levels should be borne in mind, and digoxin levels monitored.

Ergot Derivatives: Because of the theoretical possibility of ergotism, Azithromycin and ergot derivatives should not be coadministered.

Nelfinavir: Co-administration of Azithromycin (1200mg) and nelfinavir at a steady state (750mg three times daily) resulted in a 100% increase in Azithromycin absorption and bioavailability. The clinical consequences of this interaction are unknown, caution should be exercised when prescribing Azithromycin to patients taking nelfinavir.

Theophylline: Theophylline levels may be increased in patients taking Azithromycin.

Coumarin-Type Oral Anticoagulants: There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of Azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when Azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Zidovudine: Administration of Azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

WARNINGS

- As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with Azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
- Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).
- Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Azithromycin. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.

PRECAUTIONS

General: Because Azithromycin is principally eliminated via the liver, caution should be exercised when Azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR < 10 mL/min, caution should be exercised when prescribing Azithromycin in these patients.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with Azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving Azithromycin therapy.

Prescribing Azithromycin 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.

Pregnancy: Pregnancy Category B. In the animal studies, no evidence of harm to the fetus due to Azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers: It is not known whether Azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Azithromycin is administered to a nursing woman.

Geriatric Use: Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. But greater sensitivity of some older individuals cannot be ruled out.

OVERDOSE

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

CONTRAINDICATIONS

- Macrobac** is contraindicated in patients with known hypersensitivity to Azithromycin, erythromycin, any macrolide or ketolide antibiotic.
- Because of the theoretical possibility of ergotism, **Macrobac** and ergot derivatives should not be coadministered.

PRESENTATION

Macrobac capsule 250 mg	: 6's/pack.
Macrobac tablet 500 mg	: 6's/pack.
Macrobac tablet 500 mg	: 12's/pack.
Macrobac suspension 200mg/5mL	: 15mL (after reconstitution).
Macrobac suspension 200mg/5mL	: 25mL (after reconstitution).

DOSAGE

As directed by the physician.

INSTRUCTIONS

- Store below 30°C.
- Keep out of reach of children.
- For suspension only:
 - Shake well before use.
 - For accurate measurement of dosage, use the provided measuring spoon.
 - Reconstituted suspension should be stored in refrigerator and use within 5 days.
 - Keep cap tightly closed after use.
 - Do not freeze.
 - Discard any unused suspension.

Detailed prescribing information is available on request.

Manufactured by:
AsianContinental (Pvt.) Ltd.
D-32, S.I.T.E. II, Super Highway,
Karachi-Pakistan.



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LFT/006/07