# Azipos®

## (Azithromycin)

Highnoon

### COMPOSITION

**AZIPOS 250mg Capsule:** Each capsule contains:
Azithromycin (as dihydrate) 250mg
**AZIPOS 500mg Tablet:** Each film-coated tablet contains:
Azithromycin (as dihydrate) 500mg

### DESCRIPTION

AZIPOS (azithromycin) is nitrogen-containing macrolide (azalide). Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring.

### MECHANISM OF ACTION

Azithromycin acts by binding to the 23S rRNA of the 50S ribosomal subunit of susceptible microorganisms inhibiting bacterial protein synthesis and impeding the assembly of the 50S ribosomal subunit.

**Resistance**

Azithromycin demonstrates cross resistance with erythromycin. The most frequently encountered mechanism of resistance to azithromycin is modification of the 23S rRNA target, most often by methylation. Ribosomal modifications can determine cross resistance to other macrolides, lincosamides, and streptogramin B (MLSB phenotype).
Antimicrobial Activity Azithromycin has been shown to be active against most isolates of the following microorganisms:

**Gram-Positive Bacteria**

Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes, and in vitro are Beta-hemolytic streptococci (Groups C, F, G), Viridans group streptococci.

**Gram-Negative Bacteria**

Haemophilus ducreyi, Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae and in vitro are Bordetella pertussis, Legionella pneumophila.

**Other Bacteria**

Chlamydophila pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae and in vitro is Ureaplasma urealyticum.

**Anaerobic Bacteria**

In vitro are Prevotella bivia, Peptostreptococcus species.

### PHARMACOKINETICS

Azithromycin given orally is rapidly absorbed and about 40% bioavailable. Peak plasma concentrations occur 2 to 3 hours after oral dose. Azithromycin is extensively distributed into the tissues, and tissue concentration subsequently remain such higher than those in the blood; in contrast to most other antibacterial, plasma concentration are therefore of little value as a guide to efficacy. Higher concentration are taken up into white blood cells. There is a little diffusion into CSF when the meninges are not inflamed. Data from animal studies indicate that the azithromycin crosses the placenta. Small amount of azithromycin are demethylated in the liver, and it is excreted in the bile mainly as unchanged drug and some inactive metabolites have also been detected. About 6% of the oral dose (representing about 20% of the amount in the systemic circulation) is excreted in the urine. The terminal elimination half-life is about 68 hours.

### INDICATIONS AND USAGE

**Adult Patients**

- Acute bacterial exacerbations of chronic bronchitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae.
- Acute bacterial sinusitis due to Haemophilus influenzae, Moraxella catarrhalis, or Streptococcus pneumoniae.
- Otitis media, Pharyngitis & tonsillitis
- Uncomplicated skin and skin structure infections due to Staphylococcus aureus, Streptococcus pyogenes, or Streptococcus agalactiae.
- Mild to moderate typhoid due to multiple antibacterial resistant organisms
- Community acquired pneumonia, low, moderate to high severity
- Antibacterial prophylaxis for insertion of intrauterine device
- Prevention of secondary case of invasive group A streptococcal infection in patients who are allergic to penicillin
- Uncomplicated Gonorrhea
- Urethritis and cervicitis due to Chlamydia trachomatis or Neisseria gonorrhoeae
- Genital ulcer disease in men due to Haemophilus ducreyi (chancroid)

**Pediatric Patients**

- Acute Otitis Media (>6 months of age) caused by Haemophilus Influenza, Moraxella Catarrhalis or Streptococcus Pneumonia.
- Community Acquired Pneumonia (>6 months of age) due to Chlamydophila Pneumonia, Haemophilus Influenza, Mycoplasma Pneumonia, or Streptococcus Pneumonia in patients appropriate for oral therapy.
- Pharyngitis/Tonsillitis (>2 years of age) caused by Streptococcus Pyogenes as an alternative to first line therapy in individuals who cannot use first line therapy.

**Limitations of Use**

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 nosocomial 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).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin and other antibacterial drugs, azithromycin should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

### DOSAGE AND ADMINISTRATION

The dosage of AZIPOS (Azithromycin) is;

- In acute bacterial exacerbations of chronic bronchitis: 500 mg once daily for 3 days or 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2 through 5
- In acute bacterial sinusitis: 500 mg once daily for 3 days.
- In pharyngitis / tonsillitis (second line therapy): 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2 through 5.
- In otitis media: 500mg once daily for 3 days; Alternatively initially 500 mg once daily for 1 day, then 250mg once daily for 4 days.
- In uncomplicated skin and skin structure infections: 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2 through 5.
- In mild to moderate typhoid due to multiple antibacterial resistant organisms:
  - o ***Adult Dose:*** 500 mg once daily for 7 days.
  - o ***Child 6 months and over:*** 10mg/kg (to a maximum of 500 mg) once daily for 7 days.
- In community acquired pneumonia, low to moderate severity: 500 mg once daily for 3 days; Alternatively initially 500 mg once daily for 1 day, then 250mg once daily for 4 days.
- In community acquired pneumonia, high severity: Initially 500 mg once daily intravenously for at least 2 days, then 500mg once daily for a total duration of 7-10 days.
- In antibacterial prophylaxis for insertion of intrauterine device: one single 1000 mg dose.
- In prevention of secondary case of invasive group A streptococcal infection in patients who are allergic to penicillin:
  - o ***Child 6 months to 11 years:*** 12mg/kg once daily (maximum per dose 500mg) for 5 days.
  - o ***Child 12-17 years & Adult:*** 500 mg once daily for 5 days
- In uncomplicated Gonorrhea: one single 1000 mg dose.
- In urethritis and cervicitis: one single 1000 mg dose.
- In genital ulcer disease in men (chancroid): one single 1000 mg dose.

The paediatric dose in respiratory tract infection, otitis media, skin and soft tissue infections:

- o Child 6 months to 17 years: 10 mg/kg once daily (maximum per dose 500 mg) for 3 days.
- o Child 6 months to 17 years (body weight 15-25kg): 200 mg once daily for 3 days.
- o Child 6 months to 17 years (body weight 26-35kg): 300 mg once daily for 3 days.
- o Child 6 months to 17 years (body weight 36-45kg): 400 mg once daily for 3 days.

The capsule formulation should be given at least 1 hour before and 2 hours after meal.

### CONTRAINDICATIONS

- It is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.
- It is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

### WARNINGS AND PRECAUTIONS

- Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy.
- Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.
- Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.
- Following the use of azithromycin in neonates (treatment up to 42 days of life), Infantile Hypertrophic Pyloric Stenosis (IHPS) has been reported. If vomiting or irritability with feeding occurs contact medical practitioner immediately.
- Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Medical practitioner should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:
  - o Patients with known prolongation of the QT interval,
  - o A history of torsades de pointes, congenital long QT syndrome,
  - o Bradyarrhythmias or uncompensated heart failure
  - o Patients on drugs known to prolong the QT interval
  - o Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia,
  - o Clinically significant bradycardia, and
  - o In patients receiving Class IA (quinidine,procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

- Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of C. difficile.
  C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.
- Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.
- Azithromycin at the recommended dose, should not be relied upon to treat syphilis. Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhoea performed at the time of diagnosis.
- Azithromycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- Some observational studies have shown an approximately two fold increased short term potential risk of acute cardiovascular death in adults exposed to azithromycin relative to other antibacterial drugs including amoxicillin. The five days cardiovascular mortality observed in these studies ranged from 20 to 400 per million azithromycin treatment courses. This potential risk was noted to be greater during the first five days of azithomycin use and does not appear to be limited to those patients with pre existing cardiovascular diseases, consider balancing this potential risk with treatment benefits when prescribing azithromycin.

### ADVERSE REACTIONS

The reported adverse events of azithromycin are; hypersensitivity, hepatotoxicity, Infantile Hypertrophic Pyloric Stenosis(IHPS), cardiovascular deaths, Clostridium Difficile Associated Diarrhea (CDAD), exacerbation of Myasthenia Gravis, angioedema, cholestatic jaundice, nausea, vomiting, diarrhoea, or abdominal pain, palpitations, chest pain, dyspepsia, flatulence, melena, oral moniliasis, vaginitis, nephritis, dizziness, headache, vertigo, somnolence, fatigue, rash, pruritus, photosensitivity, angioedema, acute otitis media, headache, constipation, anorexia, enteritis, gastritis, anaemia, leukopenia, hyperkinesia, agitation, nervousness, insomnia, face edema, fungal infection, malaise, pain, allergic reaction, cough, pharyngitis, pleural effusion, rhinitis, eczema, fungal dermatitis, sweating, urticaria, vesiculobullous rash and conjunctivitis.

The additional report adverse events of azithromycin are; arthralgia, edema, arrhythmias including ventricular tachycardia and hypotension, QT prolongation and torsades de pointes, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, tongue discoloration, asthenia, paresthesia, anaphylaxis, interstitial nephritis, acute renal failure, vaginitis, thrombocytopenia, abnormal liver function, hepatic necrosis, hepatic failure, convulsions, vertigo, hyperactivity, syncope, aggressive reaction, anxiety, serious skin reactions including erythema multiforme, AGEP, Stevens-Johnson Syndrome, toxic epidermal necrolysis, DRESS, hearing disturbances including hearing loss, deafness, tinnitus, 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. Leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH, and phosphate.

### DRUG INTERACTIONS

The following are drug interactions;

- Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.
- Concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.
- Careful monitoring of patients is advised when digoxin, colchicine or phenytoin are used with azithromycin. Drug interactions have been observed with other macrolide products.

### USE IN SPECIFIC POPULATION

**Pregnancy**

Available data from published observational studies, case series, and case reports over several decades do not suggest an increased risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes with azithromycin use in pregnant women.

**Lactation**

Azithromycin is present in human milk. There are no available data on the effects of azithromycin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for azithromycin and any potential adverse effects on the breastfed infant from azithromycin or from the underlying maternal condition. Breast feeding women should be advised to monitor the breastfed infant for diarrhoea, vomiting, or rash.

**Paediatric Use**

Safety and effectiveness in the treatment of paediatric patients with acute otitis media, acute bacterial sinusitis and community-acquired pneumonia under 6 months of age have not been established. Safety and effectiveness in the treatment of paediatric patients with pharyngitis / tonsillitis under 2 years of age have not been established.

**Geriatric Use**

No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients.

### OVERDOSAGE

In the event of overdosage, general symptomatic and supportive measures are indicated as required. Adverse reactions experienced at higher of Azithromycin than recommended doses were similar to those seen at normal doses particularly nausea, diarrhoea, and vomiting.

### DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

### PRESENTATION

**Azipos 250mg Capsules:** Alu. Alu. Blister pack of 1 x 10's.
**Azipos 500mg Tablets:** Alu. Alu. Blister pack of 1 x 6's.

# ایزیپوس®

(ایزتھرومائسین)

**خوراک و ہدایات:**

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
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خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔


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**Marketed by**
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