

↓ Front

210 mm

Size: 210 (L) x 280 (H) mm

Folding size: 30 x 60 mm

Carton size: 36 x 20 x 85 mm



AZITHROMYCIN Dihydrate

AZILIDE

250 mg Film Coated Tablet

500 mg Film Coated Tablet

ANTIBACTERIAL

PRODUCT NAME:
Azithromycin

DOSAGE FORM AND STRENGTH:
Azithromycin Tablets 250/500mg

PHARMACOLOGIC CATEGORY: Antibacterial

PRODUCT DESCRIPTION:

250 mg: White, oblong shaped, film coated tablets with plain on both surfaces.
500 mg: White to off white, oblong shaped, film coated tablets with break line one surface and plain on the other surface.

FORMULATION/COMPOSITION:

Each film coated tablet contains:
Azithromycin (as Dihydrate) 250 mg
Azithromycin (as Dihydrate) 500 mg

PHARMACODYNAMICS/PHARMACOKINETICS:

Pharmacodynamics:

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 Streptogramins B (MLSB phenotype).

Antimicrobial Activity

Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

Gram-Positive Bacteria

Staphylococcus aureus; *Streptococcus agalactiae*; *Streptococcus pneumoniae*; *Streptococcus pyogenes*

Gram-Negative Bacteria

Haemophilus ducreyi; *Haemophilus influenzae*; *Moraxella catarrhalis*; *Neisseria gonorrhoeae*

Other Bacteria

Chlamydophila pneumoniae; *Chlamydia trachomatis*; *Mycoplasma pneumoniae*

Pharmacokinetics:

Absorption

The absolute bioavailability of azithromycin 250 mg capsules is 38%.

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase Cmax by 23% but had no effect on AUC.

When azithromycin oral suspension was administered with food to 28 adult healthy male subjects, Cmax increased by 56% and AUC was unchanged.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL.

The antibacterial activity of azithromycin is pH related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Azithromycin has been shown to penetrate into human tissues, including skin, lung, tonsil, and cervix. Extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, very low concentrations were noted in cerebrospinal fluid (less than 0.01 mcg/mL) in the presence of noninflamed meninges.

Metabolism

In vitro and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. 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.

INDICATIONS:

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*.
- Community-acquired pneumonia due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* in patients appropriate for oral therapy.
- Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.
- Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

- Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.
- Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

Pediatric Patients

- Acute otitis media (>6 months of age) caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*
- Community-acquired pneumonia (>6 months of age) due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, or *Streptococcus pneumoniae* 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.

DOSAGE AND MODE/ROUTE OF ADMINISTRATION:

Adult Patients

Infection	Recommended Dose/Duration of Therapy
DUE TO THE INDICATED ORGANISMS	
Community-acquired pneumonia 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	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
Acute bacterial sinusitis	500 mg once daily for 3 days
Genital ulcer disease (chancroid)	One single 1 gram dose
Non-gonococcal urethritis and cervicitis	One single 1 gram dose
Gonococcal urethritis and cervicitis	One single 2 gram dose

Azithromycin tablets can be taken with or without food.

2.2 Pediatric Patients

Infection	Recommended Dose/Duration of Therapy
1 see dosing tables below for maximum doses evaluated by indication	
DUE TO THE INDICATED ORGANISMS	
Acute otitis media	30 mg/kg as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on Day 1 followed by 5 mg/kg/day on Days 2 through 5.
Acute bacterial sinusitis	10 mg/kg once daily for 3 days.
Community-acquired pneumonia	10 mg/kg as a single dose on Day 1 followed by 5 mg/kg once daily on Days 2 through 5.
Pharyngitis/tonsillitis	12 mg/kg once daily for 5 days.

CONTRAINDICATIONS & PRECAUTION(S), WARNING(S):

Hypersensitivity

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.

Heaptic Dysfunction

Azithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

PRECAUTIONS & WARNINGS:

Hypersensitivity

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.

Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is presently unknown.

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.

Hepatotoxicity

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.

Infantile Hypertrophic Pyloric Stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), IHPS has been reported. Direct parents and caregivers to contact their physician if vomiting or irritability with feeding occurs.

QT Prolongation

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. Cases of torsades de pointes have been spontaneously reported during post marketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradycardia or uncompensated heart failure
- Patients on drugs known to prolong the QT interval
- Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and 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 Diarrhea (CDAD)

Clostridium difficile-associated diarrhea has been reported with use of nearly all antibacterial

agents, including AZITHROMYCIN, and may range in severity from mild diarrhea 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 diarrhea 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 Myasthenia Gravis

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

Use in Sexually Transmitted Infections

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 gonorrhea performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Development of Drug-Resistant Bacteria

Prescribing 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.

PREGNANCY AND LACTATION:

Pregnancy

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.

Lactation

Azithromycin has been reported to be excreted in human breast milk in small amounts. Caution should be exercised when azithromycin is administered to a nursing woman.

INTERACTIONS:

Nelfinavir

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.

Warfarin

Spontaneous post marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Potential Drug-Drug Interactions with Macrolides

Interactions with digoxin or phenytoin have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin or phenytoin is used concomitantly with azithromycin careful monitoring of patients is advised.

ADVERSE DRUG REACTIONS:

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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 adverse reactions of angioedema and cholestatic jaundice were reported. Approximately 0.7% of the patients (adults and pediatric patients) from the 5-day multiple-dose clinical trials discontinued Azithromycin (azithromycin) therapy because of treatment-related adverse reactions. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related adverse reactions was 0.6%. In clinical trials in pediatric patients given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related adverse reactions was approximately 1%. Most of the adverse reactions leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain.

Adults

Multiple-dose regimens: Overall, the most common treatment-related adverse reactions in adult patients receiving multiple-dose regimens of Azithromycin were related to the gastrointestinal system with diarrhea/loose stools (4 to 5%), nausea (3%), and abdominal pain (2 to 3%) being the most frequently reported.

No other adverse reactions occurred in patients on the multiple-dose regimens of Azithromycin with a frequency greater than 1%. Adverse reactions 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 adverse reactions in patients receiving a single-dose regimen of 1 gram of Azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Adverse reactions that occurred in patients on the single 1-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 adverse reactions in patients receiving a single 2-gram dose of Azithromycin were related to the gastrointestinal system. Adverse reactions 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%).

(1%). The majority of these complaints were mild in nature.
Pediatric Patients

Single and Multiple-dose regimens: The types of adverse reactions in pediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in pediatric patients.

With any of the treatment regimens, no other adverse reactions occurred in pediatric patients treated with Azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Cardiovascular: Chest pain.

Gastrointestinal: Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools, and oral moniliasis.

Hematologic and Lymphatic: Anemia and leukopenia.

Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, and insomnia.

General: Fever, face edema, fatigue, fungal infection, malaise, and pain.

Allergic: Rash and allergic reaction.

Respiratory: Cough, pharyngitis, pleural effusion, and rhinitis.

Skin and Appendages: Eczema, fungal dermatitis, pruritus, sweating, urticaria, and vesiculobullous rash.

Special Senses: Conjunctivitis.

Post marketing Experience

The following adverse reactions have been identified during post-approval use of azithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions 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 reports of QT prolongation and torsades de pointes.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.

General: Asthenia, paresthesia, fatigue, malaise, and anaphylaxis.

Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: Abnormal liver function, hepatitis, cholesteric jaundice, hepatic necrosis, and hepatic failure.

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

Psychiatric: Aggressive reaction and anxiety.

Skin/Appendages: Pruritus serious skin reactions including erythema multiform, AGEP, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and DRESS.

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

OVERDOSAGE AND TREATMENT:

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

STORAGE CONDITION:

STORE AT A TEMPERATURES NOT EXCEEDING 30°C.

DOSAGE FORMS AND PACKAGING AVAILABLE:

250 mg: Alu/Alu Blister Pack of 6's (Box of 6's and 30's)

500 mg: Alu/Alu Blister pack of 3's (Box of 3's and 30's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):

Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:

Marketing Authorization Holder

Brown & Burk Philippines Inc
U-501, 5/F, SEDCCO 1 Bldg., 120 Rada cor.,
Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:

MICRO LABS LIMITED

92, SIPCOT, HOSUR-635 126,
TAMIL NADU, INDIA

CAUTION STATEMENT:

FOODS, DRUGS, DEVICES, AND COSMETICS ACT PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

ADR REPORTING STATEMENT:

FOR SUSPECTED ADVERSE DRUG REACTION, REPORT TO THE FDA: www.fda.gov.ph

Seek medical attention immediately at the first sign of Adverse Drug Reaction.

REGISTRATION NUMBER:

250 mg: DRP-8772

500 mg: DRP-8183

DATE OF FIRST AUTHORIZATION:

250 mg: 19 DEC, 2013

500 mg: 19 DEC, 2013

DATE OF REVISION OF PACKAGE INSERT:

April 2018

EXG-ML01I-1134/A

MICRO LABS LIMITED, BANGALORE, INDIA							
1	Product Name	Azilide		Colours Used <input checked="" type="checkbox"/> BLACK			
2	Strength	250 mg & 500 mg					
3	Component	Leaflet					
4	Category	Export - Philippines					
5	Dimension	210 (L) x 280 (H) mm					
6	Artwork Code	EXG-ML01I-1134/A					
7	Pharma Code	N/A					
8	Reason for Change	Size and New Regulation text					
		Prepared by (DTP)	Approved by				
Sign	Date		Checked by (PD)	Head CQA	Head Production/Packing (Site)	Head QC (Site)	Head QA (Site)
Sign	Kanthalraju L.						
Date	31-05-2021						