ASPRACIN™

ایسپریسن

(A z i t h r o m y c i n)

QUALITATIVE AND QUANTITATIVE COMPOSITION

ASPRACIN 250 mg tablets

Each film-coated tablet contains:

Azithromycin (as Dihydrate USP).....250 mg

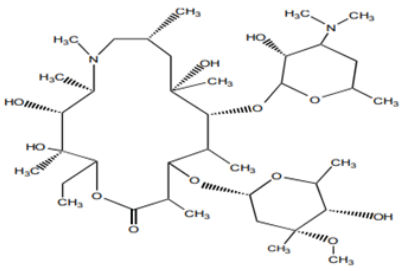
ASPRACIN 500 mg tablets

Each film-coated tablet contains:

Azithromycin (as Dihydrate USP).....500 mg

DESCRIPTION

ASPRACIN (Azithromycin) tablets contain the active ingredient azithromycin, a macrolide antibacterial drug, for oral administration. Azithromycin has the chemical name (2R,3S,4R,5R,8R,10R,11R,12S,13S,14R) 13-[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo -hexopyranosyl) oxy] - 2 - ethyl - 3,4,10- trihydroxy-3,5,6,8,10,12,14-heptamethyl-11 - [[3,4,6-trideoxy-3- (dimethylamino) -β-D- xylo - hexopyranosyl]oxy]-1 oxa-6 - azacyclopentadecan - 15 -one. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00. Azithromycin has the following structural formula:



CLINICAL INFORMATION

Indications

ASPRACIN (Azithromycin) is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Recommended dosages and durations of therapy in adult and pediatric patient populations vary in these 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 pneumonia
- Community-acquired pneumonia (>6 months of age) due to Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumonia, 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

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)

Dosage and Administration

Adult Patients

Infection	Recommended Dose/Duration of Therapy
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
Due to the indicated organisms	

Pediatric Patients

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.
Due to the indicated organisms	

Dosage Adjustment

Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen

Administration Requirements

ASPRACIN (Azithromycin) tablets and oral solution can be taken with or without food.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ASPRACIN (Azithromycin) and other antibacterial drugs, ASPRACIN (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.

Contraindications

Hypersensitivity

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

Hepatic Dysfunction

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

Warnings and Precautions

Hypersensitivity

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome, and toxic epidermal necrolysis are known to occur in patients on azithromycin therapy. Fatalities are known to occur. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are also known to occur. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy is 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 is discontinued.

Hepatotoxicity

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure are known to occur, some of which are result 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 is known to occur. 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, are known to occur with treatment with macrolides, including azithromycin. Torsades de pointes are known to occur spontaneously during clinical practice 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, bradyarrhythmias 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 is known to occur 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 is known 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

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome are known to occur 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.

Interactions

Nelfinavir

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin is known result in 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

Concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time is not affected in the dedicated drug interaction 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 are known to occur with azithromycin; however, no specific drug interaction is known to evaluate potential drug-drug interactions. However, drug interactions are known to occur 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.

Pregnancy and Breastfeeding

Category B

Insufficient data is available in pregnant women; therefore, azithromycin should be used during pregnancy only if clearly needed.

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

Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery.

Adverse Reactions

Allergic

Arthralgia, edema, urticaria, and angioedema

Cardiovascular

Arrhythmias including ventricular tachycardia and hypotension, QT prolongation and torsades de pointes

Gastrointestinal

Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and tongue discoloration

Laboratory Abnormalities

Adults

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

Overdose

In the event of overdosage, general symptomatic and supportive measures are indicated as required.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Antibacterials for systemic use; macrolids; azithromycin

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 is known to be active against most isolates of the following microorganisms;

Gram-Positive Bacteria

Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumonia, Streptococcus pyogenes.

Gram-Negative Bacteria

Haemophilus ducreyi, Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae.

Other Bacteria

Chlamydophila pneumonia, Chlamydia trachomatis, Mycoplasma pneumonia.

Pharmacokinetic Properties

Absorption

A single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food is known to increase C_{max} by 23% but have no effect on AUC.

When azithromycin oral suspension is administered with food to adult healthy male individuals, C_{max} may be increased by 56% and AUC is known to be 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 is known to penetrate into human tissues, including skin, lung, tonsil, and cervix. Extensive tissue distribution may be confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there is insufficient data 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 may be noted in cerebrospinal fluid (less than 0.01 mcg/mL) in the presence of noninflamed meninges.

Metabolism

Metabolism of azithromycin is not evaluated.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral doses may be 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.

PHARMACEUTICAL INFORMATION

Shelf life

2 years

Special Precautions for Storage

Do not store above 30°C.

Protect from light and moisture.

Keep out of the reach of children.

ہدایات:

۳۰ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔

دوا کو روشنی اور نمی سے محفوظ رکھیں۔ بچوں کی پہنچ سے دور رکھیں۔

Nature and contents of container

ASPRACIN (Azithromycin) 250 mg tablets are available in a pack of 6's (1 x 6's).

ASPRACIN (Azithromycin) 500 mg tablets are available in a pack of 6's (1 x 6's).

MANUFACTURED BY:

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An OBS Group Company

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October 2020

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