Front

ACASIA®

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

Tablet, Capsule & Suspension

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COMPOSITION:

ACASIA Capsule 250 mg:
Each capsule contains:
Azithromycin (as dihydrate) USP ..... 250 mg.

Product Specs.: CCL Pharmaceuticals

ACASIA Tablet 500 mg:
Each film coated tablet contains:
Azithromycin (as dihydrate) USP ..... 500 mg.

Product Specs.: USP

ACASIA Suspension 100 mg/5 ml:
Each 5 ml contains:
Azithromycin dihydrate equivalent to
Azithromycin ..... 100 mg.

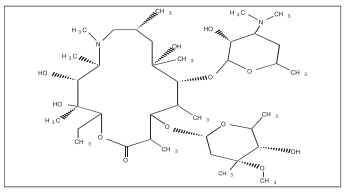
Product Specs.: CCL Pharmaceuticals

ACASIA Suspension 200 mg/5 ml:
Each 5 ml contains:
Azithromycin dihydrate equivalent to
Azithromycin ..... 200 mg.

Product Specs.: CCL Pharmaceuticals

DESCRIPTION:

ACASIA (azithromycin capsules, tablets and oral suspension) contain the active ingredient azithromycin, a macrolide antibacterial drug, for oral administration. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.00. Azithromycin has the following structural formula:



Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}\cdot 2H_2O$ and a molecular weight of 785.0.

CLINICAL PHARMACOLOGY:

Mechanism of Action: Azithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible organisms and thus interfering with microbial protein synthesis and inhibition of peptide translocation. Nucleic acid synthesis is not affected.

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 C_{max} by 23% but had no effect on AUC. When azithromycin oral suspension was administered with food to 28 adult healthy male subjects, C_{max} 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 and excretion: 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.

Microbiology: Azithromycin is an azalide, derived from the macrolide class of antibiotics. Azithromycin demonstrates activity in vitro, against a wide range of gram-positive and gram- negative bacteria including Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes (Group A) and other Streptococcal species; Haemophilus influenzae and para- influenzae; Moraxella catarrhalis; anaerobes including Bacteroides fragilis; Escherichia coli; Bordetella pertussis; Bordetella parapertussis; Borrelia burgdorferi; Haemophilus ducreyi: Neisseria gonorrhoeae and Chlamydia trachomatis. Azithromycin also demonstrates in-vitro activity against Legionella pneumophila, Mycoplasma pneumoniae and hominis, Campylobacter Sp., Toxoplasma gondii and Treponema pallidum.

Special Populations:

Pregnancy: There are no adequate and well-controlled studies in pregnant women. Azithromycin should not be used during pregnancy unless the benefits outweigh the potential risks.

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

Renal insufficiency: Following a single oral dose of azithromycin 1g, mean C_{max} and AUC(0-120) increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80ml/min) compared with normal renal function (GFR > 80ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC (0-120) increased 61% and 33% respectively compared to normal.

Hepatic insufficiency: The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

Pediatric use: Safety and effectiveness in the treatment of pediatric patients with acute otitis media, acute bacterial sinusitis and community acquired pneumonia under 6 months of age have not been established. Use of azithromycin for the treatment of acute bacterial sinusitis and community acquired pneumonia in pediatric patients (6 months of age or greater) is supported by adequate and well controlled trials in adults. Pharyngitis/tonsillitis pediatric patients (2 years of age and older).

Geriatric use: No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out . Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients. Elderly patients may be more susceptible to drug-associated effects on the QT interval. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin.

INDICATIONS AND USAGE:

ACASIA is a macrolide antibacterial drug 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).
- ***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 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).

Usage: To reduce the development of drug-resistant bacteria and maintain the effectiveness of **ACASIA** (azithromycin) and other antibacterial drugs, **ACASIA** 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. **ACASIA** can be taken with or without food.

Dosage for 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	

Dosage for Pediatric patients:

Infection*	Recommended Dose/Duration of Therapy
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	One single 1 gram dose
Non-gonococcal urethritis and cervicitis	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

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Constituting instructions for Azythromycin Oral Suspension 300, 600, 900, 1200 mg bottles. The table below indicates the volume of water to be used for constitution:

Amount of water to be added	Total volume after constitution (azithromycin content)	Azithromycin concentration after constitution
9 mL (300 mg)	15 mL (300 mg)	100 mg/5 mL
9 mL (600 mg)	15 mL (600 mg)	200 mg/5 mL
12 mL (900 mg)	22.5 mL (900 mg)	200 mg/5 mL
15 mL (1200 mg)	30 mL (1200 mg)	200 mg/5 mL

Shake well before each use. Oversized bottle provides shake space. Keep tightly closed.

CONTRAINDICATIONS:

Hypersensitivity: **ACASIA** is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.

Hepatic dysfunction: **ACASIA** 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 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. 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 postmarketing 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, 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 has been reported with use of nearly all antibacterial agents, including ACASIA, and may range in severity from mild diarrhea to fatal colitis. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

Use in sexually transmitted infections:

ACASIA, 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 **ACASIA** 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.

ADVERSE REACTIONS:

Adults:

Multiple-dose regimens: Overall, the most common treatment-related adverse reactions in adult patients receiving multiple-dose regimens of **ACASIA** 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.

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.
Pediatric patients: Most frequent adverse reactions attributed to treatment were diarrhea/loose stools, abdominal pain, vomiting, nausea, and rash.
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 adverse events: 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, cholestatic 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 multiforme, 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.
Lab 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.

DRUG INTERACTIONS:

Nelfinavir: 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: Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Potential drug-Drug interactions with macrolides: interactions when digoxin or phenytoin are used concomitantly with azithromycin careful monitoring of patients is advised.

USE IN SPECIAL POPULATIONS:

Pregnancy teratogenic effects: Pregnancy Category B

Nursing mothers: 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.

Pediatric use: Safety and effectiveness in the treatment of pediatric patients with acute otitis media, acute bacterial sinusitis and community-acquired pneumonia under 6 months of age have not been established. Use of ACASIA for the treatment of acute bacterial sinusitis and community-acquired pneumonia in pediatric patients (6 months of age or greater) is supported by adequate and well-controlled trials in adults.

Pharyngitis/Tonsillitis: Safety and effectiveness in the treatment of pediatric patients with pharyngitis/tonsillitis under 2 years of age have not been established.

Geriatric use: Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients.

OVERDOSAGE:

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 overdosage, general symptomatic and supportive measures are indicated as required.

RECONSTITUTION: Add freshly boiled and cooled water in bottle and shake well to make 15 ml suspension up to the line on the bottle.

INSTRUCTIONS:

For Tablet, Capsule:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

For Suspension:
- Store below 30ºC.
- Protect from heat, sunlight & moisture.
- Shake well before use.
- Keep bottle tightly closed after use.
- Improper storage may deteriorate the medicine.
- Keep out of the reach of children.
- To be sold on the prescription of a registered medical practitioner only.

PRESENTATION:

ACASIA Tablet 500 mg	:	Pack of 1 x 6 tablets.
ACASIA Capsule 250 mg	:	Pack of 2 x 5 capsules.
ACASIA Suspension 200 mg / 5 ml	:	Pack of 15 ml.

ہدایات برائے ٹیبلیٹ، کیپسول:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

بنانے کا طریقہ:
تازہ اُبلا ہوا ٹھنڈا پانی مناسب مقدار میں بوتل میں ڈالیں اور اچھی طرح ہلالیں تا کہ
بوتل پر دی گئی لائن تک ۱۵ ملی لیٹر سسپنشن تیار ہو جائے۔

ہدایات برائے سسپنشن:
۳۰ درجہ سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، دھوپ اور نمی سے بچائیں۔
استعمال سے قبل بوتل کو اچھی طرح ہلالیں۔
استعمال کے بعد بوتل کو اچھی طرح بند کر کے رکھیں۔
غیر مناسب سٹوریج دوا کو خراب کر سکتی ہے۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

FOR FURTHER INFORMATION PLEASE CONTACT:

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