AZITHROMYCIN CONCENTRATIONS FOLLOWING TWO - 250 mg (500 mg) CAPSULES IN ADULTS (continued)

<table>
<thead>
<tr>
<th>TISSUE/FLUID</th>
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* Sample was obtained 2 to 4 hours after the first dose.
** Sample was obtained 10 to 12 hours after the first dose.
*** Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.
**** Sample was obtained 19 hours after a single 500 mg dose.

**Azithromycin is variable in the concentration range approximating human exposure decreasing from 6 to 0.02 mcg/mL to 7% at 2 mcg/mL.**

**Microbiology**

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

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 in inflamed tissues.

Azithromycin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in INDICATIONS AND USAGE:

**Aerobic gram-positive microorganisms**

*Staphylococcus aureus*
*Streptococcus pneumoniae*  

**Aerobic gram-negative microorganisms**

*Moraxella catarrhalis*  
*Neisseria gonorrhoeae*  
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**“Other” microorganisms**

*Chlamydia pneumoniae*  
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Azithromycin has been shown to be active against most strains of the following microorganisms, both in vitro and in clinical infections as described in INDICATIONS AND USAGE section of the package insert for azithromycin tablets and azithromycin for oral suspension.

**AZITHROMYCIN CONCENTRATIONS FOLLOWING TWO - 250 mg (500 mg) CAPSULES IN ADULTS**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Azithromycin for injection and other bacterial drugs, Azithromycin for injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**AZITHROMYCIN**

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Aerobic gram-positive microorganisms
Staphylococcus aureus
Streptococcus pyogenes
Streptococcus pneumoniae
Streptococcus agalactiae

Aerobic gram-negative microorganisms
Haemophilus ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

“Other” microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

The following in vitro data are available, but their clinical significance is unknown.

Azithromycin exhibits in vitro minimum inhibitory concentrations (MICs) of ≤0.5 mcg/mL (≥minimal inhibitory concentration (MIC) of 15 mcg/mL) against most (≥90%) strains of streptococci listed below and MIC of ≤2 mcg/mL (≥MIC of 32 mcg/mL) against most of other listed microorganisms. However, the safety and effectiveness of azithromycin in vitro data are available in well-controlled and monitoring clinical trials.

Aerobic resistant microorganisms
Streptococcus (Groups C, F, G)

Vulval infections

Aerobic gram-negative microorganisms
Bordetella pertussis

Anaerobic microorganisms
Peptostreptococcus species
Prevotella bivia

“Other” anaerobic organisms
Ureaplasma urealyticum

Susceptibility Tests
Antimicrobial compounds are usually used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure1 (broth or agar) with a methodology that includes well-characterized quality control strains. Standardized procedures are based on a dilution method1 (broth or agar) or equivalent dilution techniques, with inoculum concentrations that approximate those of clinical specimens.

Interpretation of susceptibility test results should be as stated above for results of dilution techniques. Interpretation involves correlation of the zone diameter obtained in the disk test with the MIC for azithromycin.

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the minimum inhibitory concentrations (MIC’s) of 0.5 mcg/mL or less against most strains of S. pneumoniae due to these microorganisms have not been established in adequate and well-controlled trials.

Azithromycin powder should provide the following MIC values:

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Zone Diameter (mm)</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATCC 49247</td>
<td>≤17</td>
<td>Susceptible (S)</td>
</tr>
<tr>
<td>ATCC 49619</td>
<td>≥18</td>
<td>Resistant (R)</td>
</tr>
</tbody>
</table>

*These zone diameter standards for streptococci apply only to tests conducted with Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO2.

For testing Haemophilus species:

MIC (mcg/mL)

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<tbody>
<tr>
<td>Intermediate (I)</td>
<td>≤2</td>
</tr>
<tr>
<td>Intermediate (I)</td>
<td>≤4</td>
</tr>
<tr>
<td>Sensitive (S)</td>
<td>≤0.5</td>
</tr>
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<td>Resistant (R)</td>
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</tr>
<tr>
<td>Intermediate (I)</td>
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INDICATIONS AND USAGE:

Azithromycin is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed in Table 1 below. As recommended dosages, durations of therapy, and interpretive standards in these infections, please see DOSAGE AND ADMINISTRATION.

Community-acquired pneumonia due to Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus, or Streptococcus pneumoniae in patients who require initial intravenous therapy.

Pelvic inflammatory disease due to Chlamydia trachomatis, Neisseria gonorrhoeae, or Mycoplasma hominis in patients who require initial intravenous therapy.

TRAINDICATIONS:

Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic reaction was not reoccurred soon thereafter in some patients without further treatment. Physicians should be alert to the possibility of a serious reaction to azithromycin and should monitor patients for serious allergic reactions after administration of the drug.
azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised. Discontinue or adjust the doses of other drugs with a narrow therapeutic index, especially in older patients. Do not give azithromycin to patients with known QT interval prolongation, including those with congenital long QT syndrome and those taking drugs known to cause QT interval prolongation.

Pharmacokinetics: Azithromycin is rapidly absorbed after oral administration, with peak plasma concentrations occurring approximately 2-3 hours after a single dose. The bioavailability of azithromycin is increased in patients with reduced renal function due to the reduced clearance of the drug. Azithromycin is extensively metabolized by the liver and a minor fraction is excreted unchanged in the urine. The half-life of azithromycin is approximately 60 hours in adults, which allows for once-a-day dosing.

Adverse Effects: The most common adverse effects associated with azithromycin are gastrointestinal (e.g., diarrhea, abdominal pain) and dermatological (e.g., rash, pruritus). Other less common adverse effects include headache, nausea, and vomiting. Azithromycin is associated with rare cases of Stevens-Johnson syndrome and toxic epidermal necrolysis.

Interactions: Azithromycin may interact with other drugs, particularly those that are substrates of cytochrome P450 3A4 (CYP3A4) or are renally excreted. Azithromycin should be used with caution in patients taking drugs that are highly dependent on hepatic metabolism or renal excretion.

Pediatric Use: Azithromycin is generally well tolerated in children and adolescents, with the most common adverse effects being diarrhea, vomiting, and abdominal pain. Azithromycin is not recommended for use in children younger than 6 months of age due to limited data availability.

Geriatric Use: Azithromycin is generally well tolerated in the elderly, with the most common adverse effects being diarrhea and abdominal pain. Azithromycin is not recommended for use in patients over 75 years of age due to a lack of specific data on the use of azithromycin in this age group.

Contraindications: Azithromycin should be used with caution in patients with a history of QT interval prolongation or a family history of QT interval prolongation. Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin or to other macrolides.

Dilution: After reconstitution, azithromycin should be used within 24 hours. It is recommended that only aseptic technique be used when administering azithromycin. Azithromycin should be administered by intravenous infusion over at least 2 hours.

Store: Store the oral suspension at room temperature (20° to 25°C) [68° to 77°F] or below 30°C [86°F]. Store the injectable suspension at room temperature (68° to 77°F) or below 30°C [86°F]. Store the injectable suspension in the refrigerator [5°C or 41°F]. Azithromycin should not be frozen.

Microbial Resistance: There is a concern for the development of resistance to azithromycin, particularly in regions where azithromycin is overused. It is important to monitor antimicrobial resistance patterns and to use azithromycin only for indications where it is clinically indicated.
ANIMAL TOXICOLOGY:
Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on a mg/kg basis, are only 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_max value of 1.3 mcg/mL (6 times greater than the observed C_max of 0.216 mcg/mL at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_max value of 1.5 mcg/mL (7 times greater than the observed same C_max and drug dose in the studied pediatric population). On mg/m^2 basis, 30 mg/kg dose in the rat (135 mg/m^2) and 10 mg/kg dose in the dog (79 mg/m^2) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

REFERENCES: