ZITHROMAX (azithromycin) for IV infusion only

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZITHROMAX safely and effectively. See full prescribing information for ZITHROMAX.

ZITHROMAX is a macrolide antibacterial drug indicated for mild to moderate infections caused by designated, susceptible bacteria:
• Community-acquired pneumonia in adults (1.1)
• Pelvic inflammatory disease (1.2)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX and other antibacterial drugs, ZITHROMAX should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. (1.3)

DOSE FORMS AND STRENGTHS
ZITHROMAX (azithromycin) for injection is supplied in lyophilized form in a 10 mL vial equivalent to 500 mg of azithromycin for intravenous administration. (3)

CONTRAINDICATIONS
• Patients with known hypersensitivity to azithromycin, erythromycin, any macrolide, or ketoconazole antibacterial drug. (4.1)
• Patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin. (4.2)

WARNINGS AND PRECAUTIONS
• Serious (including fatal) allergic reactions and skin reactions. Discontinue ZITHROMAX and initiate appropriate therapy if reaction occurs. (5.1)
• Hepatotoxicity: Severe and sometimes fatal, hepatotoxicity has been reported. Discontinue Zithromax immediately if signs and symptoms of hepatitis occur. (5.2)
• 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. (5.3)
• Prolongation of QT interval and cases of torsades de pointes have been reported. This risk which can be fatal should be considered in patients with certain cardiovascular disorders including known QT prolongation or history torsades de pointes, those with proarrhythmic conditions, and with other drugs that prolong the QT interval.(5.4)
• Clostridium difficile-Associated Diarrhea: Evaluate patients if diarrhea occurs. (5.5)
• Zithromax may exacerbate muscle weakness in persons with myasthenia gravis. (5.6)

ADVERSE REACTIONS
Most common adverse reactions are nausea (4%), diarrhea (4%), abdominal pain (3%), or vomiting (1%). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS
• Nelfinavir: Close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (7.1)
• Warfarin: Use with azithromycin may increase coagulation times; monitor prothrombin time. (7.2)

USE IN SPECIFIC POPULATIONS
• Pediatric use: Safety and effectiveness in the treatment of patients under 16 years of age have not been established. (8.4)
• Geriatric use: Elderly patients may be more susceptible to development of torsades de pointes arrhythmias. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.
1 INDICATIONS AND USAGE

ZITHROMAX (azithromycin) for injection is a macrolide antibacterial drug indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

1.1 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.

1.2 Pelvic Inflammatory Disease due to Chlamydia trachomatis, Neisseria gonorrhoeae, or Mycoplasma hominis in patients who require initial intravenous therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with ZITHROMAX.

ZITHROMAX for injection should be followed by ZITHROMAX by the oral route as required. [see Dosage and Administration (2)]

1.3 Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZITHROMAX (azithromycin) and other antibacterial drugs, ZITHROMAX (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.

2 DOSAGE AND ADMINISTRATION

[see Indications and Usage (1) and Clinical Pharmacology (12.3)]

2.1 Community-Acquired Pneumonia
The recommended dose of ZITHROMAX for injection for the treatment of adult patients with community-acquired pneumonia due to the indicated organisms is 500 mg as a single daily dose by the intravenous route for at least two days. Intravenous therapy should be followed by azithromycin by the oral route at a single, daily dose of 500 mg, administered as two 250 mg tablets to complete a 7- to 10-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

2.2 Pelvic Inflammatory Disease
The recommended dose of ZITHROMAX for injection for the treatment of adult patients with pelvic inflammatory disease due to the indicated organisms is 500 mg as a single daily dose by the intravenous route for one or two days. Intravenous therapy should be followed by azithromycin by the oral route at a single, daily dose of 250 mg to complete a 7-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

2.3 Preparation of the Solution for Intravenous Administration
The infusate concentration and rate of infusion for ZITHROMAX for injection should be either 1 mg/mL over 3 hr or 2 mg/mL over 1 hr. ZITHROMAX for injection should not be given as a bolus or as an intramuscular injection.

Reconstitution
Prepare the initial solution of ZITHROMAX for injection by adding 4.8 mL of Sterile Water for Injection to the 500 mg vial, and shaking the vial until all of the drug is dissolved. Since ZITHROMAX for injection is supplied under vacuum, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of Sterile Water is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin. Reconstituted solution is stable for 24 hr when stored below 30°C (86°F).

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.
Dilute this solution further prior to administration as instructed below.

Dilution
To provide azithromycin over a concentration range of 1.0-2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:

Normal Saline (0.9% sodium chloride)
1/2 Normal Saline (0.45% sodium chloride)
5% Dextrose in Water
Lactated Ringer’s Solution
5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride) with 20 mEq KCl
5% Dextrose in Lactated Ringer’s Solution
5% Dextrose in 1/3 Normal Saline (0.3% sodium chloride)
5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride)
Normosol®-M in 5% Dextrose
Normosol®-R in 5% Dextrose

When used with the Vial-Mate® drug reconstitution device, please reference the Vial-Mate® instructions for assembly and reconstitution.

<table>
<thead>
<tr>
<th>Final Infusion Solution Concentration (mg/mL)</th>
<th>Amount of Diluent (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mg/mL</td>
<td>500 mL</td>
</tr>
<tr>
<td>2.0 mg/mL</td>
<td>250 mL</td>
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Other intravenous substances, additives, or medications should not be added to ZITHROMAX for injection, or infused simultaneously through the same intravenous line.

Storage
When diluted according to the instructions (1.0 mg/mL to 2.0 mg/mL), ZITHROMAX for injection is stable for 24 hr at or below room temperature 30°C (86°F), or for 7 days if stored under refrigeration 5°C (41°F).

3 DOSAGE FORMS AND STRENGTHS
ZITHROMAX for injection is supplied in lyophilized form in a 10 mL vial equivalent to 500 mg of azithromycin for intravenous administration.

4 CONTRAINDICATIONS

4.1 Hypersensitivity
ZITHROMAX is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drugs.

4.2 Hepatic Dysfunction
ZITHROMAX is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

5 WARNINGS AND PRECAUTIONS

5.1 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. [see Contraindications (4.1)]

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 unknown at present.
If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that the allergic symptoms may reappear after symptomatic therapy has been discontinued.

5.2 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.

5.3 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.

5.4 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, bradycardias 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.

5.5 Clostridium difficile-Associated Diarrhea
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ZITHROMAX (azithromycin for injection), 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 antibacterial 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 antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

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

5.7 Infusion Site Reactions
ZITHROMAX for injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. [see Dosage and Administration (2)]

Local IV site reactions have been reported with the intravenous administration of azithromycin. The incidence and severity of these reactions were the same when 500 mg azithromycin was given over 1 hour (2 mg/mL as 250 mL infusion) or over 3 hr (1 mg/mL as 500 mL infusion) [see Adverse Reactions (6)]. All volunteers who received infusate concentrations above 2.0 mg/mL experienced local IV site reactions and, therefore, higher concentrations should be avoided.

5.8 Development of Drug-Resistant Bacteria
Prescribing ZITHROMAX 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.
6 ADVERSE REACTIONS

6.1 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 of intravenous azithromycin for community-acquired pneumonia, in which 2 to 5 IV doses were given, the reported adverse reactions were mild to moderate in severity and were reversible upon discontinuation of the drug. The majority of patients in these trials had one or more co-morbid diseases and were receiving concomitant medications. Approximately 1.2% of the patients discontinued intravenous ZITHROMAX therapy, and a total of 2.4% discontinued azithromycin therapy by either the intravenous or oral route because of clinical or laboratory side effects.

In clinical trials conducted in patients with pelvic inflammatory disease, in which 1 to 2 IV doses were given, 2% of women who received monotherapy with azithromycin and 4% who received azithromycin plus metronidazole discontinued therapy due to clinical side effects.

Clinical adverse reactions leading to discontinuations from these studies were gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), and rashes; laboratory side effects leading to discontinuation were increases in transaminase levels and/or alkaline phosphatase levels.

Overall, the most common adverse reactions associated with treatment in adult patients who received IV/Oral ZITHROMAX in studies of community-acquired pneumonia were related to the gastrointestinal system with diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%) being the most frequently reported. Approximately 12% of patients experienced a side effect related to the intravenous infusion; most common were pain at the injection site (6.5%) and local inflammation (3.1%).

The most common adverse reactions associated with treatment in adult women who received IV/Oral ZITHROMAX in trials of pelvic inflammatory disease were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most commonly reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was co-administered with metronidazole in these trials, a higher proportion of women experienced adverse reactions of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), infusion site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).

Adverse reactions that occurred with a frequency of 1% or less included the following:

**Gastrointestinal:** Dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis.

**Nervous system:** Headache, somnolence.

**Allergic:** Bronchospasm.

**Special senses:** Taste perversion.

6.2 Postmarketing 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 (including fatalities).

**Genitourinary:** Interstitial nephritis and acute renal failure and vaginitis.

**Hematopoietic:** Thrombocytopenia.

**Liver/biliary:** Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure. [see Warnings and Precautions (5.2)]

**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.

6.3 Laboratory Abnormalities
Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:
- Elevated ALT (SGPT), AST (SGOT), creatinine (4 to 6%)
- Elevated LDH, bilirubin (1 to 3%)
- Leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase (less than 1%)

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 750 patients treated with ZITHROMAX (IV/Oral), less than 2% of patients discontinued azithromycin therapy because of treatment-related liver enzyme abnormalities.

7 DRUG INTERACTIONS

7.1 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. [see Adverse Reactions (6)]

7.2 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.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Teratogenic Effects. Pregnancy Category B: Reproductive and development studies have not been conducted using IV administration of azithromycin to animals. Reproduction studies have been performed in rats and mice using oral administration at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These daily doses in rats and mice based on body surface area, are estimated to be 4 and 2 times, respectively, an adult daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. 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.

8.3 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.

8.4 Pediatric Use
Safety and effectiveness of azithromycin for injection in children or adolescents under 16 years have not been established. In controlled clinical studies, azithromycin has been administered to pediatric patients (age 6 months to 16 years) by the oral route. For information regarding the use of ZITHROMAX (azithromycin for oral suspension) in the treatment of pediatric patients, [see Indications and Usage (1), and Dosage and Administration (2)] of the prescribing information for ZITHROMAX (azithromycin for oral suspension) 100 mg/5 mL and 200 mg/5 mL bottles.
8.5 Geriatric Use
Pharmacokinetic studies with intravenous azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen.

In multiple-dose clinical trials of intravenous azithromycin in the treatment of community-acquired pneumonia, 45% of patients (188/414) were at least 65 years of age and 22% of patients (91/414) were at least 75 years of age. No overall differences in safety were observed between these subjects and younger subjects in terms of adverse reactions, laboratory abnormalities, and discontinuations. Similar decreases in clinical response were noted in azithromycin- and comparator-treated patients with increasing age.

ZITHROMAX (azithromycin for injection) contains 114 mg (4.96 mEq) of sodium per vial. At the usual recommended doses, patients would receive 114 mg (4.96 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. The total sodium content from dietary and non-dietary sources may be clinically important with regard to such diseases as congestive heart failure.

Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients. [see Warnings and Precautions (5.4)]

10 OVERDOSAGE
Adverse reactions experienced in 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.

11 DESCRIPTION
ZITHROMAX for injection contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibacterial drug, for intravenous injection. 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-hepta-methyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xoyo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is C_{38}H_{72}N_{2}O_{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_{2}O_{12}·2H_{2}O and a molecular weight of 785.0.
ZITHROMAX for injection consists of azithromycin dihydrate and the following inactive ingredients: citric acid and sodium hydroxide. ZITHROMAX for injection is supplied in lyophilized form in a 10 mL vial equivalent to 500 mg of azithromycin for intravenous administration. Reconstitution, according to label directions, results in approximately 5 mL of ZITHROMAX for intravenous injection with each mL containing azithromycin dihydrate equivalent to 100 mg of azithromycin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Azithromycin is a macrolide antibacterial drug [see Microbiology (12.4)]

12.2 Pharmacodynamics
Based on animal models of infection, the antibacterial activity of azithromycin appears to correlate with the ratio of area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for certain pathogens (S. pneumoniae and S. aureus). The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with azithromycin.

Cardiac Electrophysiology
QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with oral azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

Since the mean $C_{\text{max}}$ of azithromycin following a 500 mg IV dose given over 1 hr is higher than the mean $C_{\text{max}}$ of azithromycin following the administration of a 1500 mg oral dose, it is possible that QTc may be prolonged to a greater extent with IV azithromycin at close proximity to a one hour infusion of 500 mg.

12.3 Pharmacokinetics
In patients hospitalized with community-acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean $C_{\text{max}}$ ± S.D. achieved was 3.63 ± 1.60 mcg/mL, while the 24-hour trough level was 0.20 ± 0.15 mcg/mL, and the AUC$_{24}$ was 9.60 ± 4.80 mcg·hr/mL.

The mean $C_{\text{max}}$, 24-hour trough and AUC$_{24}$ values were 1.14 ± 0.14 mcg/mL, 0.18 ± 0.02 mcg/mL, and 8.03 ±0.86 mcg·hr/mL, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/mL. Similar pharmacokinetic values were obtained in patients hospitalized with community-acquired pneumonia who received the same 3-hour dosage regimen for 2-5 days.

<table>
<thead>
<tr>
<th>Infusion, Duration</th>
<th>Time after starting the infusion (hr)</th>
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<tbody>
<tr>
<td></td>
<td>0.5</td>
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<tr>
<td>2 mg/mL, 1 hr$^a$</td>
<td>2.98 ±1.12</td>
</tr>
<tr>
<td>1 mg/mL, 3 hr$^b$</td>
<td>0.91 ±0.13</td>
</tr>
</tbody>
</table>

$^a$500 mg (2 mg/mL) for 2-5 days in community-acquired pneumonia patients.

$^b$500 mg (1 mg/mL) for 5 days in healthy subjects.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg intravenous azithromycin showed only an 8% increase in $C_{\text{max}}$ but a 61% increase in AUC$_{24}$ reflecting a threefold rise in $C_{24}$ trough levels.

Following single-oral doses of 500 mg azithromycin (two 250 mg capsules) to 12 healthy volunteers, $C_{\text{max}}$, trough level, and AUC$_{24}$ were reported to be 0.41 mcg/mL, 0.05 mcg/mL, and 2.6 mcg·hr/mL, respectively. These oral values are approximately 38%, 83%, and 52% of the values observed following a single 500-mg I.V. 3-hour infusion ($C_{\text{max}}$: 1.08 mcg/mL, trough: 0.06 mcg/mL, and AUC$_{24}$: 5.0 mcg·hr/mL). Thus, plasma concentrations are higher following the intravenous regimen throughout the 24-hour interval.
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.

Tissue concentrations have not been obtained following intravenous infusions of azithromycin, but following oral administration in humans azithromycin has been shown to penetrate into tissues, including skin, lung, tonsil, and cervix. Tissue levels were determined following a single oral dose of 500 mg azithromycin in 7 gynecological patients. Approximately 17 hr after dosing, azithromycin concentrations were 2.7 mcg/g in ovarian tissue, 3.5 mcg/g in uterine tissue, and 3.3 mcg/g in salpinx. Following a regimen of 500 mg on the first day followed by 250 mg daily for 4 days, concentrations in the cerebrospinal fluid were less than 0.01 mcg/mL in the presence of non-inflamed 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 with 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.

In a multiple-dose study in 12 normal volunteers utilizing a 500 mg (1 mg/mL) one-hour intravenous-dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hr was about 11% after the 1st dose and 14% after the 5th dose. These values are greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin. Biliary excretion is a major route of elimination for unchanged drug, following oral administration.

Specific Populations
Renal Insufficiency
Azithromycin pharmacokinetics were investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1,000 mg dose of azithromycin, mean Cmax and AUC0-120 increased by 5.1% and 4.2%, respectively in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean Cmax and AUC0-120 increased 61% and 35%, respectively in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min).

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

Gender
There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

Geriatric Patients
Pharmacokinetic studies with intravenous azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen. [see Geriatric Use 8.5].

Pediatric Patients
Pharmacokinetic studies with intravenous azithromycin have not been performed in children.

Drug-drug Interactions
Drug interaction studies were performed with oral azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 1 and the effects of other drugs on the pharmacokinetics of azithromycin are shown in Table 2.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 1. No dosage adjustment of drugs listed in Table 1 is recommended when co-administered with azithromycin.

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the Cmax and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 2 [see Drug Interactions (7.3)].
Table 1. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin

<table>
<thead>
<tr>
<th>Co-administered Drug</th>
<th>Dose of Co-administered Drug</th>
<th>Dose of Azithromycin</th>
<th>n</th>
<th>Ratio (with/without azithromycin) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00</th>
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<tr>
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<td></td>
<td>Mean $C_{max}$</td>
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<tr>
<td>Atorvastatin</td>
<td>10 mg/day for 8 days</td>
<td>500 mg/day orally on days 6-8</td>
<td>12</td>
<td>0.83 (0.63 to 1.08)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>200 mg/day for 2 days, then 200 mg twice a day for 18 days</td>
<td>500 mg/day orally for days 16-18</td>
<td>7</td>
<td>0.97 (0.88 to 1.06)</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>20 mg/day for 11 days</td>
<td>500 mg orally on day 7, then 250 mg/day on days 8-11</td>
<td>14</td>
<td>1.03 (0.93 to 1.14)</td>
</tr>
<tr>
<td>Didanosine</td>
<td>200 mg orally twice a day for 21 days</td>
<td>1,200 mg/day orally on days 8-21</td>
<td>6</td>
<td>1.44 (0.85 to 2.43)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>400 mg/day for 7 days</td>
<td>600 mg orally on day 7</td>
<td>14</td>
<td>1.04* (0.98 to 1.11)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200 mg orally single dose</td>
<td>1,200 mg orally single dose</td>
<td>18</td>
<td>1.04 (0.98 to 1.11)</td>
</tr>
<tr>
<td>Indinavir</td>
<td>800 mg three times a day for 5 days</td>
<td>1,200 mg orally on day 5</td>
<td>18</td>
<td>0.96 (0.86 to 1.08)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>15 mg orally on day 3</td>
<td>500 mg/day orally for 3 days</td>
<td>12</td>
<td>1.27 (0.89 to 1.81)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>750 mg three times a day for 11 days</td>
<td>1,200 mg orally on day 9</td>
<td>14</td>
<td>0.90 (0.81 to 1.01)</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>100 mg on days 1 and 4</td>
<td>500 mg/day orally for 3 days</td>
<td>12</td>
<td>1.16 (0.86 to 1.57)</td>
</tr>
<tr>
<td>Triazolam</td>
<td>0.125 mg on day 2</td>
<td>500 mg orally on day 1, then 250 mg/day on day 2</td>
<td>12</td>
<td>1.06* (0.92 to 1.29)</td>
</tr>
<tr>
<td>Trimethoprim/</td>
<td>160 mg/800 mg/day orally</td>
<td>1,200 mg orally on day 7</td>
<td>12</td>
<td>0.85 (0.75 to 0.97)/0.90 (0.78 to 1.03)</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>for 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>500 mg/day orally for 21 days</td>
<td>600 mg/day orally for 14 days</td>
<td>5</td>
<td>1.12 (0.42 to 3.02)</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>500 mg/day orally for 21 days</td>
<td>1,200 mg/day orally for 14 days</td>
<td>4</td>
<td>1.31 (0.43 to 3.97)</td>
</tr>
</tbody>
</table>
Table 2. Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs [see Drug Interactions (7.3)].

<table>
<thead>
<tr>
<th>Co-administered Drug</th>
<th>Dose of Co-administered Drug</th>
<th>Dose of Azithromycin</th>
<th>n</th>
<th>Ratio (with/without co-administered drug) of Azithromycin Pharmacokinetic Parameters (90% CI); No Effect = 1.00</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean $C_{\text{max}}$</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>400 mg/day for 7 days</td>
<td>600 mg orally on day 7</td>
<td>14</td>
<td>1.22 (1.04 to 1.42)</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200 mg orally single dose</td>
<td>1,200 mg orally single dose</td>
<td>18</td>
<td>0.82 (0.66 to 1.02)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>750 mg three times a day for 11 days</td>
<td>1,200 mg orally on day 9</td>
<td>14</td>
<td>2.36 (1.77 to 3.15)</td>
</tr>
</tbody>
</table>

* - 90% Confidence interval not reported

12.4 Microbiology

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 the following microorganisms, both in vitro and in clinical infections. [see Indications and Usage (1)]

Gram-positive Bacteria

*Staphylococcus aureus*  
*Streptococcus pneumoniae*

Gram-negative Bacteria

*Haemophilus influenzae*  
*Moraxella catarrhalis*  
*Neisseria gonorrhoeae*  
*Legionella pneumophila*

Other Bacteria

*Chlamydophila pneumoniae*  
*Chlamydia trachomatis*  
*Mycoplasma hominis*  
*Mycoplasma pneumoniae*

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for azithromycin against isolates of similar genus or organism group. However, the efficacy of azithromycin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Aerobic Gram-Positive Bacteria

Streptococci (Groups C, F, G)  
Viridans group streptococci
Gram-Negative Bacteria
Bordetella pertussis

Anaerobic Bacteria
Peptostreptococcus species
Prevotella bivia

Other Bacteria
Ureaplasma urealyticum

Susceptibility Testing Methods
When available, the clinical microbiology laboratory should provide cumulative reports of in vitro susceptibility test results for antibacterial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug for treatment.

Dilution techniques
Quantitative methods are used to determine antimicrobial MICs. These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth, and/or agar). The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques
Quantitative methods that require measurement of zone diameters can provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using standardized methods. This procedure uses paper disk impregnated with 15 mcg azithromycin to test the susceptibility of bacteria to azithromycin. The disk diffusion breakpoints are provided in Table 3.

Table 3. Susceptibility Interpretive Criteria for Azithromycin

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (mcg/mL)</th>
<th>Disk Diffusion (zone diameters in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>Haemophilus influenzae.*</td>
<td>≤ 4</td>
<td>--</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>≤ 2</td>
<td>4</td>
</tr>
<tr>
<td>Streptococci including S. pneumoniae</td>
<td>≤ 0.5</td>
<td>1</td>
</tr>
<tr>
<td>Moraxella catarrhalis*</td>
<td>≤ 0.25</td>
<td>-</td>
</tr>
</tbody>
</table>

* Insufficient information is available to determine Intermediate or Resistant interpretive criteria

A report of Susceptible (S) indicates that the antimicrobial drug is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of Intermediate (I) indicates that the result should be considered equivocal and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant (R) indicates that the antimicrobial drug is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control
Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard azithromycin powder should provide the following range of MIC values provided in Table 4. For the diffusion technique using the 15-mcg azithromycin disk the criteria provided in Table 4 should be achieved.
Table 4: Acceptable Quality Control Ranges for Susceptibility Testing

<table>
<thead>
<tr>
<th>Quality Control Organism</th>
<th>Minimum Inhibitory Concentrations (mcg/mL)</th>
<th>Disk Diffusion (zone diameters in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus ATCC 25923</td>
<td>Not Applicable</td>
<td>21-26</td>
</tr>
<tr>
<td>Staphylococcus aureus ATCC 29213</td>
<td>0.5-2</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Haemophilus Influenzae ATCC 49247</td>
<td>1-4</td>
<td>13-21</td>
</tr>
<tr>
<td>Streptococcus pneumoniae ATCC 49619</td>
<td>0.06-0.25</td>
<td>19-25</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae ATCC 49226</td>
<td>0.25-1</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

ATCC = American Type Culture Collection

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found in rats given daily doses up to 10 mg/kg (approximately 0.2 times an adult daily dose of 500 mg based on body surface area).

13.2 Animal Toxicology and/or Pharmacology
Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple oral doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) in dogs and rats treated with azithromycin at doses which, expressed on the basis of body surface area, are similar to or less than the highest recommended adult human dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (50 mg/kg/day dose) at the observed maximal plasma concentration of 1.3 mcg/mL (1.6 times the observed Cmax of 0.821 mcg/mL at the adult dose of 2 g.). Similarly, it has been shown in the dog (10 mg/kg/day dose) at the observed maximal serum concentration of 1 mcg/mL (1.2 times the observed Cmax of 0.821 mcg/mL at the adult dose of 2 g.).

Phospholipidosis was also observed in neonatal rats dosed for 18 days at 30 mg/kg/day, which is less than the pediatric dose of 60 mg/kg based on body surface area. It was not observed in neonatal rats treated for 10 days at 40 mg/kg/day with mean maximal serum concentrations of 1.86 mcg/mL, approximately 1.5 times the Cmax of 1.27 mcg/mL at the pediatric dose. Phospholipidosis has been observed in neonatal dogs (10 mg/kg/day) at maximum mean whole blood concentrations of 3.54 mcg/mL, approximately 3 times the pediatric dose Cmax. The significance of the findings for animals and for humans is unknown.

14 CLINICAL STUDIES

14.1 Community-Acquired Pneumonia
In a controlled trial of community-acquired pneumonia performed in the U.S., azithromycin (500 mg as a single daily dose by the intravenous route for 2 to 5 days, followed by 500 mg/day by the oral route to complete 7 to 10 days therapy) was compared to cefuroxime (2250 mg/day in three divided doses by the intravenous route for 2 to 5 days followed by 1000 mg/day in two divided doses by the oral route to complete 7 to 10 days therapy), with or without erythromycin. For the 291 patients who were evaluable for clinical efficacy, the clinical outcome rates, i.e., cure, improved, and success (cure + improved) among the 277 patients seen at 10 to 14 days post-therapy were as follows:

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>Azithromycin</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>46%</td>
<td>44%</td>
</tr>
<tr>
<td>Improved</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td>Success (Cure + Improved)</td>
<td>78%</td>
<td>74%</td>
</tr>
</tbody>
</table>

In a separate, uncontrolled clinical and microbiological trial performed in the U.S., 94 patients with community-acquired pneumonia who received azithromycin in the same regimen were evaluable for clinical efficacy. The clinical outcome rates, i.e., cure, improved, and success (cure + improved) among the 84 patients seen at 10 to 14 days post-therapy were as follows:

Reference ID: 4051690
Microbiological determinations in both trials were made at the pre-treatment visit and, where applicable, were reassessed at later visits. Serological testing was done on baseline and final visit specimens. The following combined presumptive bacteriological eradication rates were obtained from the evaluable groups:

Combined Bacteriological Eradication Rates for Azithromycin:

<table>
<thead>
<tr>
<th>(at last completed visit)</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>64/67 (96%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>41/43 (95%)</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>9/10 (90%)</td>
</tr>
<tr>
<td>S. aureus</td>
<td>9/10 (90%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Nineteen of twenty-four patients (79%) with positive blood cultures for S. pneumoniae were cured (intent-to-treat analysis) with eradication of the pathogen.

The presumed bacteriological outcomes at 10 to 14 days post-therapy for patients treated with azithromycin with evidence (serology and/or culture) of atypical pathogens for both trials were as follows:

<table>
<thead>
<tr>
<th>Evidence of Infection</th>
<th>Total</th>
<th>Cure</th>
<th>Improved</th>
<th>Cure + Improved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>18</td>
<td>11 (61%)</td>
<td>5 (28%)</td>
<td>16 (89%)</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>34</td>
<td>15 (44%)</td>
<td>13 (38%)</td>
<td>28 (82%)</td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td>16</td>
<td>5 (31%)</td>
<td>8 (50%)</td>
<td>13 (81%)</td>
</tr>
</tbody>
</table>

### References


### How Supplied/Storage and Handling

ZITHROMAX is supplied in lyophilized form under a vacuum in a 10 mL vial equivalent to 500 mg of azithromycin for intravenous administration. Each vial also contains sodium hydroxide and 413.6 mg citric acid.

These are packaged as follows:

- 10 vials of 500 mg NDC 0069-3150-83
- 10 vials of 500 mg with 1 Vial-Mate® Adaptor each NDC 0069-3150-14

### Patient Counseling Information

Patients should be informed of the following serious and potentially serious adverse reactions that have been associated with ZITHROMAX.
Diarrhea: Inform patients that diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial. If this occurs, patients should notify their physician as soon as possible.

Rx only

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