FRESENIUS KABI

45996G/Revised: September 2014

AZITHROMYCIN

FOR INJECTION, USP

For Intravenous infusion only

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Azithromycin for Injection, USP safely and effectively. See full prescribing information for Azithromycin for Injection, USP.

Azithromycin for Injection, USP, for intravenous infusion only
Initial U.S. Approval: 1991

INDICATIONS AND USAGE

Azithromycin for injection, USP 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 azithromycin for injection, USP and other antibacterial drugs, azithromycin for injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

DOSAGE AND ADMINISTRATION

- Community-acquired pneumonia: 500 mg as a single daily dose by the intravenous route for at least two days. (2.1)
- Pelvic inflammatory disease in adults: 500 mg as a single daily dose by the intravenous route for one or two days. (2.2)

DOSAGE FORMS AND STRENGTHS

- 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 ketolide 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 azithromycin and initiate appropriate therapy if reaction occurs. (5.1)
- Hepatotoxicity: Severe and sometimes fatal, hepatoxicity has been reported. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur. (5.2)
- 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 prorrhythmic conditions, and with other drugs that prolong the QT interval. (5.3)
- *Clostridium difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.4)
- Azithromycin may exacerbate muscle weakness in persons with myasthenia gravis. (5.5)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC, Vigilance & Medical Affairs at 1-800-551-7176 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.

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FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin for injection, USP and other antibacterial drugs, azithromycin for injection, USP 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.

Azithromycin for injection, USP 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 *Chlamydophila 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 azithromycin for injection, USP.

Azithromycin for injection, USP should be followed by azithromycin by the oral route as required *[see Dosage and Administration (2)].*

2 DOSAGE AND ADMINISTRATION

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

2.1 Community-Acquired Pneumonia
The recommended dose of azithromycin 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 azithromycin 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 azithromycin for injection should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour. Azithromycin for injection should not be given as a bolus or as an intramuscular injection.

Reconstitution

Prepare the initial solution of azithromycin 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 azithromycin 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 hours 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 to 2 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.

Final Infusion Solution Concentration (mg/mL)	Amount of Diluent (mL)
1 mg/mL	500 mL
2 mg/mL	250 mL

Other intravenous substances, additives, or medications should not be added to azithromycin for injection or infused simultaneously through the same intravenous line.

Storage

Store the white to off-white lyophilized cake at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. When diluted according to the instructions (1 mg/mL to 2 mg/mL), azithromycin for injection is stable for 24 hours 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

Azithromycin 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

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

4.2 Hepatic Dysfunction

Azithromycin for injection 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. 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 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.

5.4 *Clostridium Difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including 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.

5.5 Exacerbation of Myasthenia Gravis

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

5.6 Infusion Site Reactions

Azithromycin 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 hours (1 mg/mL as 500 mL infusion) *[see Adverse Reactions (6)]*. All volunteers who received infusate concentrations above 2 mg/mL experienced local IV site reactions and, therefore, higher concentrations should be avoided.

5.7 Development of Drug-Resistant Bacteria

Prescribing azithromycin for injection 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 azithromycin 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 azithromycin 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 azithromycin 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 and toxic epidermal necrolysis.

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 azithromycin (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 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 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 to 85 years old) were similar to those in younger volunteers (18 to 40 years old) for the 5 day therapeutic regimen.

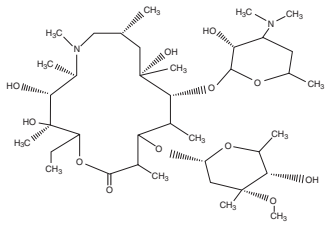
In multiple-dose clinical trials of intravenous azithromycin in the treatment of community-acquired pneumonia, 45% of patients (188/414) were at least 65 years of age and 22% of patients (91/414) were at least 75 years of age. No overall differences in safety were observed between these subjects and 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.

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 (5.3)]*.

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
Azithromycin for injection, USP 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-a-*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)-ß-*D*-*xylo*-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. Azithromycin has the following structural formula:



$C_{38}H_{72}N_2O_{12}$ **M.W. 749.00**

Azithromycin, as the monohydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12} \cdot H_2O$ and a molecular weight of 767.00.

Azithromycin for injection, USP consists of azithromycin monohydrate and the following inactive ingredients: citric acid and sodium hydroxide. Azithromycin for injection, USP 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 azithromycin for intravenous injection with each mL containing azithromycin monohydrate equivalent to 100 mg of azithromycin. After reconstitution each mL contains: azithromycin monohydrate equivalent to 100 mg of azithromycin, 76.9 mg of citric acid, and sodium hydroxide for pH adjustment.

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 (1,000 mg) alone or in combination with oral azithromycin (500 mg, 1,000 mg, and 1,500 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, 1,000 mg and 1,500 mg azithromycin, respectively.

Since the mean C_{max} of azithromycin following a 500 mg IV dose given over 1 hour is higher than the mean C_{max} of azithromycin following the administration of a 1,500 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_{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•h/mL.

The mean C_{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•h/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 to 5 days.

Infusion Concentration, Duration	Time after starting the infusion (hr)			
	0.5	1	2	3
2 mg/mL, 1 hr[a]	2.98 ± 1.12	3.63 ± 1.73	0.60 ± 0.31	0.40 ± 0.23
1 mg/mL, 3 hr[b]	0.91 ± 0.13	1.02 ± 0.11	1.14 ± 0.13	1.13 ± 0.16

Infusion Concentration, Duration	Time after starting the infusion (hr)				
	4	6	8	12	24
2 mg/mL, 1 hr[a]	0.33 ± 0.16	0.26 ± 0.14	0.27 ± 0.15	0.20 ± 0.12	0.20 ± 0.15
1 mg/mL, 3 hr[b]	0.32 ± 0.05	0.28 ± 0.04	0.27 ± 0.03	0.22 ± 0.02	0.18 ± 0.02

[a] 500 mg (2 mg/mL) for 2 to 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_{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_{max}, trough level, and AUC_{24} were reported to be 0.41 mcg/mL, 0.05 mcg/mL, and 2.6 mcg•h/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_{max}: 1.08 mcg/mL, trough: 0.06 mcg/mL, and AUC_{24}: 5 mcg•h/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 hours 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 hours. 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 hours 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 C_{max} and AUC_{0-120} 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 C_{max} and AUC_{0-120} 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 to 85 years old) were similar to those in younger volunteers (18 to 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 C_{max} 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

Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (with/without azithromycin) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1	
				Mean C_{max}	Mean AUC
Atorvastatin	10 mg/day for 8 days	500 mg/day orally on days 6 to 8	12	0.83 (0.63 to 1.08)	1.01 (0.81 to 1.25)
Carbamazepine	200 mg/day for 2 days, then 200 mg twice a day for 18 days	500 mg/day orally for days 16 to 18	7	0.97 (0.88 to 1.06)	0.96 (0.88 to 1.06)
Cetirizine	20 mg/day for 11 days	500 mg orally on day 7, then 250 mg/day on days 8 to 11	14	1.03 (0.93 to 1.14)	1.02 (0.92 to 1.13)
Didanosine	200 mg orally twice a day for 21 days	1,200 mg/day orally on days 8 to 21	6	1.44 (0.85 to 2.43)	1.14 (0.83 to 1.57)
Efavirenz	400 mg/day for 7 days	600 mg orally on day 7	14	1.04*	0.95*
Fluconazole	200 mg orally single dose	1,200 mg orally single dose	18	1.04 (0.98 to 1.11)	1.01 (0.97 to 1.05)
Indinavir	800 mg three times a day for 5 days	1,200 mg orally on day 5	18	0.96 (0.86 to 1.08)	0.90 (0.81 to 1.00)
Midazolam	15 mg orally on day 3	500 mg/day orally for 3 days	12	1.27 (0.89 to 1.81)	1.26 (1.01 to 1.56)
Nelfinavir	750 mg three times a day for 11 days	1,200 mg orally on day 9	14	0.90 (0.81 to 1.01)	0.85 (0.78 to 0.93)
Sildenafil	100 mg on days 1 and 4	500 mg/day orally for 3 days	12	1.16 (0.86 to 1.57)	0.92 (0.75 to 1.12)
Theophylline	4 mg/kg IV on days 1, 11, 25	500 mg orally on day 7, 250 mg/day on days 8 to 11	10	1.19 (1.02 to 1.40)	1.02 (0.86 to 1.22)
Theophylline	300 mg orally BID ×15 days	500 mg orally on day 6, then 250 mg/day on days 7 to 10	8	1.09 (0.92 to 1.29)	1.08 (0.89 to 1.31)
Triazolam	0.125 mg on day 2	500 mg orally on day 1, then 250 mg/day on day 2	12	1.06*	1.02*
Trimethoprim/ Sulfamethoxazole	160 mg/800 mg/day orally for 7 days	1,200 mg orally on day 7	12	0.85 (0.75 to 0.97)/ 0.90 (0.78 to 1.03)	0.87 (0.80 to 0.95/ 0.96 (0.88 to 1.03)
Zidovudine	500 mg/day orally for 21 days	600 mg/day orally for 14 days	5	1.12 (0.42 to 3.02)	0.94 (0.52 to 1.70)
Zidovudine	500 mg/day orally for 21 days	1,200 mg/day orally for 14 days	4	1.31 (0.43 to 3.97)	1.30 (0.69 to 2.43)

***** - 90% Confidence interval not reported

Table 2. Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs *[see Drug Interactions (7.3)]*.

Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (with/without co-administered drug) of Azithromycin Pharmacokinetic Parameters (90% CI); No Effect = 1	
				Mean C_{max}	Mean AUC
Efavirenz	400 mg/day for 7 days	600 mg orally on day 7	14	1.22 (1.04 to 1.42)	0.92*
Fluconazole	200 mg orally single dose	1,200 mg orally single dose	18	0.82 (0.66 to 1.02)	1.07 (0.94 to 1.22)
Nelfinavir	750 mg three times a day for 11 days	1,200 mg orally on day 9	14	2.36 (1.77 to 3.15)	2.12 (1.80 to 2.50)

***** - 90% Confidence interval not reported

12.4 Microbiology

Mechanism of Action

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.

Cross Resistance
Azithromycin demonstrates cross-resistance with erythromycin-resistant Gram-positive isolates.

Azithromycin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in *[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. Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 mcg/mL or less against most (≥ 90%) isolates of the following bacteria; however, the safety and effectiveness of azithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled 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, clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial products used in resident hospitals 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 product for treatment.

Dilution techniques
Quantitative methods are used to determine minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method[1,2] (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 provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using standardized methods[2,3]. This procedure uses paper disk impregnated with 15 mcg azithromycin to test the susceptibility of bacteria to azithromycin. The disk diffusion interpretive criteria are provided in Table 3.

Table 3: Susceptibility Interpretive Criteria for Azithromycin

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)		
	S	I	R
Haemophilus influenzae*	≤ 4	--	--
Staphylococcus aureus	≤ 2	4	≥ 8
Streptococci including *S. pneumoniae*	≤ 0.5	1	≥ 2

Table 3: Susceptibility Interpretive Criteria for Azithromycin (cont'd.)

Pathogen	Disk Diffusion (zone diameters in mm)		
	S	I	R
Haemophilus influenzae*	≥ 12	--	--
Staphylococcus aureus	≥ 18	14 to 17	≤ 13
Streptococci including *S. pneumoniae*	≥ 18	14 to 17	≤ 13

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

A report of "Susceptible" indicates that the pathogen is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentration at the infection site necessary to inhibit growth of the pathogen. A report of "Intermediate" 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. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound 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[1,2,3]. 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

Quality Control Organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Staphylococcus aureus **ATCC 25923**	Not Applicable	21 to 26
Staphylococcus aureus **ATCC 29213**	0.5 to 2	Not Applicable
Haemophilus Influenzae **ATCC 49247**	1 to 4	13 to 21
Streptococcus pneumoniae **ATCC 49619**	0.06 to 0.25	19 to 25

ATCC = American Type Culture Collection

The ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues *[see Clinical Pharmacology (12)]*.

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 C_{max} 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 C_{max} 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 C_{max} 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 C_{max}. 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 (2,250 mg/day in three divided doses by the intravenous route for 2 to 5 days followed by 1,000 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:

Clinical Outcome	Azithromycin	Comparator
Cure	46%	44%
Improved	32%	30%
Success (Cure + Improved)	78%	74%

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:

Clinical Outcome	Azithromycin
Cure	60%
Improved	29%
Success (Cure + Improved)	89%

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:

(at last completed visit)	Azithromycin
S. pneumonia	64/67 (96%)[a]
H. influenzae	41/43 (95%)
M. catarrhalis	9/10 (90%)
S. aureus	9/10 (90%)

[a] 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:

Evidence of Infection	Total	Cure	Improved	Cure + Improved
Mycoplasma pneumoniae	18	11 (61%)	5 (28%)	16 (89%)
Chlamydia pneumoniae	34	15 (44%)	13 (38%)	28 (82%)
Legionella pneumophila	16	5 (31%)	8 (50%)	13 (81%)

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI) *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically: Approved Standard-Ninth Edition.* CLSI Document M07-A9. CLSI, 950 West Valley Rd., Suite 2500, Wayne, PA 19087, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-third Informational Supplement,* CLSI document M100-S23. CLSI document M100-S23, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2013.
3. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition* CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

16 HOW SUPPLIED/STORAGE AND HANDLING

Azithromycin for injection, USP 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.

Product No.	NDC No.	
309810	63323-398-10	500 mg per vial in packages of 10.

This container closure is not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

Patients should be informed of the following serious and potentially serious adverse reactions that have been associated with azithromycin for injection, USP.

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.

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Revised: September 2014