PRODUCT MONOGRAPH

[Pr]AZITHROMYCIN FOR INJECTION USP

azithromycin dihydrate

*Azithromycin for Injection, 500 mg/vial, 100 mg/mL when reconstituted
(*as azithromycin dihydrate)

Antibacterial Agent

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[Pr]AZITHROMYCIN FOR INJECTION USP
(azithromycin dihydrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous	Azithromycin for injection, 500 mg/vial, (100 mg/mL after reconstitution) (as azithromycin dihydrate)	Citric acid anhydrous, and sodium hydroxide for pH adjustment

INDICATIONS AND CLINICAL USE

Azithromycin for Injection USP is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Azithromycin for Injection USP should be followed by oral administration of azithromycin as required (see **DOSAGE AND ADMINISTRATION**).

Adults

Lower Respiratory Tract:
Community-acquired pneumonia (CAP) due to *Chlamydia pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Legionella pneumophila, Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients who require initial intravenous therapy.

Genitourinary Tract:
Pelvic inflammatory disease (PID) due to *Chlamydia trachomatis, Neisseria gonorrhoeae* or *Mycoplasma hominis* in patients who require initial intravenous therapy. If anaerobic organisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with **Azithromycin for Injection USP**.

Patients should have a serologic test for syphilis performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for this disease should be initiated if infection is confirmed.

Because some strains are resistant to azithromycin, appropriate culture and susceptibility tests should be initiated before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with **Azithromycin for Injection USP** may be initiated before results of these tests are known; once the results become available, antibiotic treatment should be adjusted accordingly.

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.

CONTRAINDICATIONS

Azithromycin dihydrate is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin and in those with a hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibacterial agent, or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

General

Serious allergic reactions, including angioedema, anaphylaxis, and dermatological reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermolysis, toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic symptoms (DRESS) have been reported rarely (with rare reports of fatalities), in patients on azithromycin dihydrate therapy (see **CONTRAINDICATIONS**). Allergic reactions may occur during and soon after treatment with **Azithromycin for Injection USP**. 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. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

The use of azithromycin with other drugs may lead to drug-drug interactions. For established or potential drug interactions, see **DRUG INTERACTIONS** section of the product monograph.

In the absence of data on the metabolism and pharmacokinetics in patients with lysosomal lipid storage diseases (e.g., Tay-Sachs disease, Niemann-Pick disease) the use of **Azithromycin for Injection USP** in these patients is not recommended.

Azithromycin and ergot derivatives should not be co-administered due to the possibility that ergot toxicity may be precipitated by macrolide antibiotics. Acute ergot toxicity is characterized by severe peripheral vasospasm, including ischemia of the extremities, along with dysesthesia and possible central nervous system effects.

As with any antibacterial preparation, observation for signs of superinfection with nonsusceptible organisms, including fungi is recommended.

Intramuscular use of azithromycin is not recommended; extravasation of drug into the tissues may cause tissue injury.

Intravenous Administration

Azithromycin for Injection USP should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. Do not administer as an intravenous bolus

or an intramuscular injection (see **DOSAGE AND ADMINISTRATION**).

Local injection 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) (see **ADVERSE REACTIONS**). All volunteers who received infusate concentrations above 2.0 mg/mL experienced local I.V. site reactions, therefore, higher concentrations should be avoided.

Carcinogenesis and Mutagenesis
Long term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no genotoxic or mutagenic potential in standard laboratory tests (see **TOXICOLOGY**).

Cardiovascular
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and *torsade de pointes*, have been seen in treatment with macrolides including azithromycin (see **ADVERSE REACTIONS**). Prescribers should consider the risk of QT prolongation which can lead to fatal events when weighing the risks and benefits of azithromycin. Risk factors for *torsade de pointes* include patients:

- With a history of *torsade de pointes*
- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly may be more susceptible to drug-associated effects on the QT interval
- Exposed to higher plasma levels of azithromycin (e.g. receiving intravenous azithromycin, hepatobiliary impaired)

There is information that 'QT Related Adverse Events' may occur in some patients receiving azithromycin. There have been spontaneous reports from post-marketing experience of prolonged QT interval and *torsade de pointes* (see **ADVERSE REACTIONS, Post-Marketing Experience**). These include but are not limited to: one AIDS patient dosed at 750 mg to 1 g daily experienced prolonged QT interval and *torsade de pointes*; a patient with previous history of arrhythmias who experienced *torsade de pointes* and subsequent myocardial infarction following a course of azithromycin therapy; and a pediatric case report of prolonged QT interval experienced at a therapeutic dose of azithromycin which reversed to normal upon discontinuation (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology).**

Gastrointestinal
A higher incidence of gastrointestinal adverse events (8 of 19 subjects) was observed when azithromycin was administered to a limited number of subjects with GFR<10 mL/min.

Clostridium difficile-associated disease
Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents including azithromycin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis,

pseudomembranous colitis, toxic megacolon, or performation of colon subsequent to the administration of any antibacterial agents. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *Clostridium difficile* produces toxins A and B which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see **ADVERSE REACTIONS**).

Hematologic

Severe neutropenia (WBC < 1000/mm^3) may adversely affect the distribution of azithromycin and its transport to the site of infection. Antibacterials with proven efficacy in this population should be used, as outlined by the relevant guidelines for treatment of patients with severe neutropenia. Efficacy and safety of azithromycin have not been studied in patients with severe neutropenia.

Hepatic/Biliary/Pancreatic

Azithromycin has not been studied in patients with severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**). Due to the lack of data, **Azithromycin for Injection USP** should be used with caution in patients with hepatic impairment.

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 (see **ADVERSE REACTIONS**).

Musculoskeletal and connective tissue disorders

Myasthenia gravis

Exacerbations of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy. The use of azithromycin in patients with a known history of myasthenia gravis is not recommended.

Renal

The safety, efficacy and pharmacokinetics of azithromycin in patients with renal impairment have not been established. No dose adjustment is recommended for patients with GFR 10-80 mL/min. Caution should be exercised when azithromycin is administered to patients with GFR <10 mL/min. This precaution is based on a clinical study of azithromycin immediate-release tablets, in which patients with GFR <10 mL/min showed a significant (61%) increase in mean C_{max} and a significant (35%) increase in systemic exposure to azithromycin, and experienced a high incidence of gastrointestinal adverse events (8 of 19 clinical study subjects). Patients with GFR 10-80 mL/min showed only slightly increased serum azithromycin levels compared to patients with normal renal

function.

Due to the lack of data, **Azithromycin for Injection USP** should be used with caution in patients with renal impairment (including patients on dialysis).

Sexual Function/Reproduction

There are no adequate and well-controlled studies in humans. In fertility studies conducted in the rat, reduced pregnancy rates were noted following administration of azithromycin. The predictive value of these data to the response in humans has not been established (see **TOXICOLOGY**).

Susceptibility/Resistance

Development of drug resistant bacteria

Prescribing azithromycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug- resistant bacteria.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies in pregnant women. **Azithromycin for Injection USP** should not be used during pregnancy unless the expected benefit to the mother outweighs any potential risk to the fetus. In animal reproduction studies in mice and rats, at azithromycin doses up to 200 mg/kg/day (moderately maternally toxic), effects were noted in the rat at 200 mg/kg/day, during the prenatal development period (delayed ossification) and during the postnatal development period (decreased viability, delayed developmental landmarks, differences in performance of learning task). The 200 mg/kg/day dose in mice and rats, is approximately 0.5-fold and 1-fold, respectively, the single adult oral dose of 2 g, based on mg/m^2 (body surface area). Pharmacokinetic data from the 200 mg/kg/day dose level in these studies showed that azithromycin crossed the placenta and distributed to fetal tissue at 5 to 9-fold the maternal plasma C_{max} of 2 ug/mL (see **TOXICOLOGY**).

Nursing Women:

Limited information available from published literature indicated that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed, However, the safety of azithromycin has not been studied in infants less than 6 months of age. Therefore, **Azithromycin for Injection USP** should not be used in the treatment of nursing women unless the expected benefit to the mother outweighs any potential risk to the infant. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Because azithromycin may accumulate in breast milk over time with continued **Azithromycin for Injection USP** therapy, if the lactating mother is treated with **Azithromycin for Injection USP**, the breast milk should be expressed and discarded during treatment.

Pediatrics:

The safety and effectiveness of azithromycin in children or adolescents under 16 years have not been established.

Geriatrics:

Pharmacokinetic studies with intravenous azithromycin have not been performed in the elderly. Based on clinical trials, there appear to be no significant differences in safety or tolerance of intravenous azithromycin between elderly (age ≥65) and younger subjects (ages 16 to ≤64).

Monitoring and Laboratory Tests
Monitoring of QT/QTc intervals during treatment with **Azithromcyin for Injection USP** may be considered by the physician as appropriate.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Among adults receiving azithromycin intravenously, 1.2% of CAP, and 2% of PID patients discontinued treatment. Discontinuation rates were slightly higher for PID patients receiving concomitant metronidazole therapy (4%).

In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.4%.

Most of the side effects leading to discontinuation in patients on intravenous therapy were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, along with abdominal pain, rashes and increases in aminotransferases and/or alkaline phosphatase levels in adult patients receiving intravenous azithromycin. Potentially serious treatment-related side effects including angioedema and cholestatic jaundice occurred in less than 1% of patients.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Intravenous/Oral Regimen: Adults
The most common side effects (greater than 1%) in adult patients who received sequential I.V./oral azithromycin in studies of **community-acquired pneumonia** were related to the gastrointestinal system: diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%). Approximately 12% of patients experienced a side effect related to the intravenous infusion; most common were pain at the site and/or during the infusion (6.5%) and local inflammation (3.1%).

In adult women who received sequential I.V./oral azithromycin in studies of **pelvic inflammatory disease**, the most common side effects (greater than 1%) were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most frequently 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 studies, a higher proportion of women experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%) and application site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).

Side effects that occurred with a frequency of 1% or less included:
Gastrointestinal: dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis
Nervous System: headache, somnolence

Allergic: bronchospasm
Special Senses: taste perversion

Abnormal Hematologic and Clinical Chemistry Findings

Intravenous Therapy
Adults:
With an incidence of 4-6%, elevated ALT, AST, and creatinine.
With an incidence of 1-3%, elevated LDH and bilirubin.
With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase.

In multiple dose clinical trials involving more than 750 patients treated with sequential I.V./oral azithromycin less than 2% of patients discontinued therapy because of treatment-related liver enzyme abnormalities.

When follow-up was provided, changes in laboratory tests appeared to be reversible for both oral and I.V. dosing.

Post-Market Adverse Drug Reactions
The following adverse experiences have been reported in patients under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain or in patients treated with significantly higher than the recommended doses for prolonged periods. -

In addition, because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency is not always possible.

Allergic:	Arthralgia, edema, anaphylaxis (with rare reports of fatalities) (see **WARNINGS AND PRECAUTIONS**), serum sickness, urticaria, vasculitis, angioedema, pruritus;
Blood and the lymphatic system disorders:	Agranulocytosis, haemolytic anaemia, thrombocytopenia;
Cardiovascular:	Cardiac arrhythmias (including ventricular tachycardia), palpitations, hypotension. There have been rare reports of QT prolongation and *torsade de pointes* in patients receiving therapeutic doses of azithromycin, including a pediatric case report of QT interval prolongation which reversed to normal upon discontinuation (see **WARNINGS AND PRECAUTIONS**).
Gastrointestinal:	Anorexia, constipation, hypoglycaemia, dehydration, vomiting/diarrhea rarely resulting in dehydration, pancreatitis, pseudomembranous colitis, rare reports of tongue discoloration, pyloric stenosis / infantile hypertrophic pyloric stenosis (IHPS);
General:	Asthenia, paresthesia, fatigue, musclepain;
Genitourinary:	Interstitial nephritis, acute renal failure, nephrotic syndrome, vaginitis;
Liver/Biliary:	Hepatitis fulminant. Abnormal liver function including drug-induced hepatitis and cholestatic jaundice have been reported. There have also been rare cases of hepatic

	necrosis and hepatic failure, which have resulted in death (see **WARNINGS AND PRECAUTIONS**);
Musculoskeletal and connective tissue disorders:	myasthenia gravis;
Nervous System:	Dizziness, hyperactivity, hypoaesthesia, seizure, convulsions, and syncope;
Psychiatric Disorders:	Aggressive reaction, anxiety, nervousness, agitation, delirium,hallucinations;
Skin/Appendages:	Serious skin reactions including erythema multiforme, exfoliative dermatitis, Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) (see **WARNINGS and PRECAUTIONS**).
Special Senses:	Hearing disturbances including hearing loss, hearing impaired, deafness and / or tinnitus, vertigo, taste/smell perversion and/or loss, abnormal vision.

DRUG INTERACTIONS

Overview

Caution is warranted when azithromycin is administered to a patient with a history of a significant cardiac repolarization disorder or who is taking other medicinal products that cause a prolonged QT interval (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular** and **ADVERSE REACTIONS**, **Post-Marketing Experience**).

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the cytochrome P450-related drug interactions seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inhibition via cytochrome metabolite complex does not occur with azithromycin.

Concomitant administration of azithromycin with P-glycoprotein substrates may result in increased serum levels of P-glycoprotein substrates. Concomitant administration of P- glycoprotein inhibitors with azithromycin sustained-release form had minimal effect on the pharmacokinetics of azithromycin.

Drug-Drug Interactions

Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Antacids Aluminum and magnesium containing antacids (Maalox®)	CT	Reduce the peak serum levels but not the extent of azithromycin absorption	Azithromycin and these drugs should not be taken simultaneously

Carbamazepine	CT	In a Pharmacokinetic interaction study in healthy volunteers no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin	
Cetirizine	CT	In healthy male volunteers, co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.	
Cimetidine	CT	Administration of a single-dose of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption or on azithromycin pharmacokinetics.	
Coumarin-Type Oral Anticoagulants	CT	In a pharmacokinetic interaction study of 22 healthy men, a 5-day course of azithromycin did not affect the prothrombin time from a subsequently administered single 15 mg dose of warfarin Spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants	Prothrombin times should be carefully monitored while patients are receiving azithromycin and concomitantly-administered oral anticoagulants.
Cyclosporine	CT	In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporine, the resulting cyclosporine C_{max} and AUC_{0-5} were found to be significantly elevated	Caution should be exercised before considering concurrent administration of these drugs. If co administration of these drugs is necessary, cyclosporine levels should be monitored and the dose adjusted accordingly.
Didanosine	CT	Daily doses of 1200 mg azithromycin had no effect on the pharmacokinetics of didanosine	
Efavirenz	CT	Efavirenz, when administered at a dose of 400 mg for seven days produced a 22% increase in the C_{max} of azithromycin administered as a 600 mg single dose. AUC was not affected. Administration of a single 600 mg dose of azithromycin immediate-release had no effect on the pharmacokinetics of efavirenz given at 400 mg doses for seven days.	
Fluconazole	CT	A single dose of 1200 mg azithromycin immediate-release did not alter the pharmacokinetics of a single 800 mg oral dose of fluconazole. Total exposure and half-life of 1200 mg azithromycin were unchanged and C_{max} had a clinically insignificant decrease (18%) by coadministration with 800 mg fluconazole.	

HMG-CoA Reductase Inhibitors	CT	In healthy volunteers, co-administration of atorvastatin (10 mg daily) and azithromycin immediate-release (500 mg daily) did not alter plasma concentrations of atorvastatin (based on HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.	
Indinavir	CT	A single dose of 1200 mg azithromycin immediate-release had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir three times daily for 5 days).	
Midazolam	CT	In healthy volunteers (N=12), co-administration of azithromycin immediate-release 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.	
Nelfinavir	CT	Coadministration of a single dose of 1200 mg azithromycin immediate-release with steady-state nelfinavir (750 mg three times daily) produced an approximately 16% decrease in mean AUC_{0-8} of nelfinavir and its M8 metabolite. C_{max} was not affected. Coadministration of nelfinavir (750 mg three times daily) at steady-state with a single dose of 1200 mg azithromycin immediate-release increased the mean $AUC_{0-\infty}$ of azithromycin by 113% and mean C_{max} by 136%.	Dose adjustment of azithromycin is not recommended. However, close monitoring for known side effects of azithromycin, when administered in conjunction with nelfinavir, is warranted.
P-glycoprotein inhibitors	CT	Co-administration of P-glycoprotein inhibitors (Vitamin E, Poloxamer 407, or Poloxamer 124) with azithromycin sustained release form (1 gram dose) had minimal effect on the pharmacokinetics of azithromycin.	
Rifabutin	CT	Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment with azithromycin and rifabutin.	Neutropenia has been associated with the use of rifabutin, but it has not been established if concomitantly-administered azithromycin potentiates that effect (see **ADVERSE REACTIONS**).
Sildenafil	CT	In normal healthy male volunteers, there was no evidence of a statistically significant effect of azithromycin immediate-release (500 mg daily for 3 days) on the AUC, C_{max}, T_{max}, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite.	

Theophylline	CT	Concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Azithromycin did not affect the pharmacokinetics of theophylline administered either as a single intravenous infusion or multiple oral doses at a recommended dose of 300 mg every 12 hours. There is one post-marketing report of supraventricular tachycardia associated with an elevated theophylline serum level that developed soon after initiation of treatment with azithromycin**.**	Until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving Azithromycin and theophylline concomitantly.
Trimethoprim/ Sulfamethoxazole	CT	Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin immediate-release 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.	
Zidovudine	CT	Single 1 g doses and multiple 1200 mg or 600 mg doses of azithromycin did not affect the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite in peripheral blood mononuclear cells.	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; UNK=Unknown

Concomitant Therapy

The following drug interactions have not been reported in clinical trials with azithromycin and no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. Nonetheless, they have been observed with macrolide products, and there have been rare spontaneously reported cases with azithromycin and some of these drugs, in post marketing experience. Until further data are developed regarding drug interactions, when **Azithromycin for Injection USP** and these drugs are used concomitantly, careful monitoring of patients is advised both during and for a short period following therapy:

Antihistamines

Prolongation of QT intervals, palpitations or cardiac arrhythmias have been reported with concomitant administration of azithromycin and astemizole or terfenadine.

Cisapride, Hexobarbital, Phenytoin

Increased serum levels of hexobarbital, cisapride or phenytoin have been reported.

Digoxin and colchicine / P-glycoprotein substrates

Concomitant administration of some macrolide antibiotics with P-glycoprotein substrates, including digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered

concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycn and after its discontinuation are necessary.

Disopyramide
Azithromycin may increase the pharmacologic effect of disopyramide.

Ergot (ergotamine or dihydroergotamine)
Azithromycin and ergot derivatives should not be co-administered due to the possibility that ergot toxicity may be precipitated by some macrolide antibiotics. Acute ergot toxicity is characterized by severe peripheral vasospasm including ischemia of the extremities, along with dysesthesia and possible central nervous system effects.

Gentamicin
No data are available on the concomitant clinical use of azithromycin and gentamicin or other amphiphilic drugs which have been reported to alter intracellular lipid metabolism.

Triazolam
Azithromycin may decrease the clearance of triazolam and increase the pharmacologic effect of triazolam.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

General

Hepatic Impairment:
Azithromycin has not been studied in patients with severe hepatic impairment. Due to the lack of data, **Azithromycin for Injection USP** should be used with caution in patients with hepatic impairment.

Renal Impairment:
Caution should be exercised when azithromycin is administered to subjects with severe renal impairment. No studies have been conducted in patients requiring hemodialysis (see **ACTIONS AND CLINICAL PHARMACOLOGY and WARNINGS AND PRECAUTIONS**). Due to the lack of data, **Azithromycin for Injection USP** should be used with caution in patients with renal impairment (including patients on dialysis).

Recommended Dose and Dosage Adjustment

Adults:
Azithromycin for Injection USP must be reconstituted and diluted as directed, and administered as an intravenous infusion over at least 60 minutes. **Do not administer as an intravenous bolus or an intramuscular injection (**see **WARNINGS AND PRECAUTIONS).** Intravenous therapy should

be followed by oral azithromycin**.** The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

The infusate concentration and rate of infusion for **Azithromycin for Injection USP** should be either 1 mg/mL over 3 hours, or 2 mg/mL over 1 hour.

Community-Acquired Pneumonia in patients who require initial intravenous therapy:
The recommended dose is 500 mg I.V. as a single daily infusion for at least 2 days followed by oral therapy at 500 mg daily to complete a 7-10 day course of therapy.

Pelvic Inflammatory Disease:
The recommended dose is 500 mg I.V. as a single daily infusion for at least 1 day followed by oral therapy at 250 mg daily to complete a 7 day course of therapy. Note: If anaerobic organisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with **Azithromycin for Injection USP**.

Administration

Reconstitution:

RECONSTITUTION OF AZITHROMYCIN FOR INJECTION USP				
Strength	Reconstitution Solution	Volume to be Added	Approximate Volume Available	Nominal Concentration
500 mg	Sterile Water for Injection	4.8 mL	5 mL	100 mg/mL

Prepare the initial solution of **Azithromycin for Injection USP** by adding 4.8 mL of Sterile Water for Injection to the 500 mg vial. Shake the vial until all of the drug is dissolved. Since the vial is evacuated, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact volume of 4.8 mL is dispensed. Each mL of reconstituted solution contains azithromycin dihydrate equivalent to 100 mg azithromycin. Reconstituted solution is stable for 24 hours when stored at room temperature (15°C-30°C). **The reconstituted solution must be further diluted prior to administration.**

Dilution of reconstituted solution:
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 the following diluents:

Final Infusion Concentration (mg/mL)	Amount of Diluent (mL)
1.0 mg/mL	500 mL
2.0 mg/mL	250 mL

Appropriate Diluents
0.9% Sodium Chloride Injection 5% Dextrose in Water for Injection 0.45% Sodium Chloride Injection Lactated Ringer's Injection 5% Dextrose in 0.45% Sodium Chloride Injection with 20 mEq Potassium Chloride 5% Dextrose in Lactated Ringer's Injection 5% Dextrose in 0.3% Sodium Chloride Injection 5% Dextrose in 0.45% Sodium Chloride Injection Normosol-M in 5% Dextrose

Diluted solutions prepared in this manner are stable for 24 hours at room temperature (15°C-30°C) or for 72 hours refrigerated (2°C-8°C). As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discoloration or leakage should be discarded.

Only limited data are available on the compatibility of **Azithromycin for Injection USP** with other intravenous substances, therefore additives or other medications should not be added to **Azithromycin for Injection USP** or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of **Azithromycin for Injection USP** with an infusion solution compatible with **Azithromycin for Injection USP** and with any other drug(s) administered via the common line. If **Azithromycin for Injection USP** is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

OVERDOSAGE

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

Ototoxicity and gastrointestinal adverse events may occur with an overdose of azithromycin.

Up to 15 grams cumulative dose of azithromycin dihydrate over 10 days has been administered in clinical trials without apparent adverse effect.

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Azithromycin dihydrate, a macrolide antibiotic of the azalide subclass, exerts its antibacterial action by binding to the 23S rRNA of the 50s ribosomal subunits of susceptible bacteria. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Pharmacodynamics

Cardiac Electrophysiology:

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial. A total of 119 healthy subjects were enrolled (mean age of 35.5 years; range 18-55 years), of which 116 subjects (97 males) completed the study and were included in the analysis. Subjects were randomized to one of 5 treatments and received orally once daily for 3 days: placebo, chloroquine 600 mg base only, or chloroquine 600 mg base in combination with azithromycin 500 mg, 1000 mg, and 1500 mg. On Day 3, the azithromycin mean (%CV) plasma C_{max} values for the 500, 1000 and 1500 mg azithromycin dose regimens were 0.536 (33), 0.957 (31), and 1.54 (28) µg/mL, respectively. Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the day 3 maximum mean (90% 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.

Pharmacokinetics

No data exist in humans in regard to the extent of accumulation, duration of exposure, metabolism or excretory mechanisms of azithromycin in neural tissue such as the retina and the cochlea.

Adult Pharmacokinetics:

Plasma concentrations of azithromycin decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. The prolonged half-life is likely due to *extensive* uptake and subsequent release of drug from tissues. Over the dose range of 250 to 1000 mg orally, the serum concentrations are *related* to dose.

Intravenous Administration:

In patients hospitalized with community-acquired pneumonia (CAP) receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the median maximum concentration (C_{max}) achieved was 3.00 µg/mL (range: 1.70-6.00 µg/mL) while the 24-hour trough level was 0.18 µg/mL (range: 0.07-0.60 µg/mL) and the AUC_{24} was 8.50 µg·h/mL (range: 5.10-19.60 µg·h/mL).

The median C_{max}, 24-hour trough and AUC_{24} values were 1.20 µg/mL (range: 0.89-1.36 µg/mL), 0.18 µg/mL (range: 0.15-0.21 µg/mL) and 7.98 µg·h/mL (range: 6.45-9.80 µg·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 CAP that received the same 3-hour dosage regimen for 2-5 days.

Plasma concentrations (μg/mL) after the last daily intravenous infusion of 500 mg azithromycin [median (range)]									
Conc. + Duration	Time after starting infusion (hr)								
	0.5	1	2	3	4	6	8	12	24
2 mg/mL, 1 hr[a]	2.42 (1.71-5.12)	2.65 (1.94-6.03)	0.63 (0.21-1.07)	0.34 (0.18-0.87)	0.32 (0.16-0.69)	0.19 (0.12-0.58)	0.22 (0.10-0.61)	0.16 (0.09-0.46)	0.18 (0.07-0.60)
1 mg/mL, 3 hr[b]	0.87 (0.76-1.16)	1.03 (0.83-1.19)	1.16 (0.87-1.36)	1.17 (0.86-1.35)	0.32 (0.26-0.47)	0.29 (0.23-0.35)	0.27 (0.23-0.34)	0.22 (0.17-0.26)	0.18 (0.15-0.21)

[a] 500 mg (2 mg/mL) for 2-5 days in CAP patients

[b] 500 mg (1 mg/mL) for 5 days in healthy subjects

The average Cl_t and Vd values were 10.18 mL/min/kg and 33.3 L/kg, respectively, in 18 normal volunteers receiving 1000 to 4000 mg doses given as 1 mg/mL over 2 hours.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg intravenous azithromycin shows only an 8% increase in C_{max} but a 61% increase in AUC_{24} reflecting the three-fold rise in C_{24} trough levels.

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

Distribution:
Rapid movement of azithromycin from blood into tissue results in significantly higher azithromycin concentrations in tissue than in plasma (up to 50 times the maximum observed concentration in plasma), (see **DETAILED PHARMACOLOGY**).

The long tissue half-life and large volume of distribution result from intracytoplasmic uptake and storage in lysosomal phospholipid complexes.

Metabolism:
The majority of systemically available azithromycin is excreted unchanged in the bile. Metabolites of azithromycin were identified in bile but have not been studied further, (see **DETAILED PHARMACOLOGY**).

Excretion:
Biliary excretion of azithromycin, predominantly as unchanged drug, is a main route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in the urine, (see **DETAILED PHARMACOLOGY**).

Geriatrics:
When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women,

although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

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

Hepatic Insufficiency:
In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of oral azithromycin compared to those with normal hepatic function. In these patients urinary recovery of azithromycin appears to increase. Hence no dose adjustment is recommended for patients with mild to moderate hepatic impairment.

Azithromycin has not been studied in patients with severe hepatic impairment.

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).

STORAGE AND STABILITY

Dry powder: Store at controlled room temperature (15°C to 30°C).
Diluted solution: Stable for 24 hours at room temperature (15°C-30°C) or for 72 hours refrigerated (2°C-8°C). For single-use only. Discard any unused portion after use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Each vial contains azithromycin dihydrate in a lyophilized form equivalent to 500 mg azithromycin for injection. The non-medicinal ingredients include: 384.6 mg citric acid anhydrous and sodium hydroxide for pH adjustment. After reconstitution, each mL contains azithromycin dihydrate equivalent to 100 mg azithromycin (500 mg/5 mL) (see **DOSAGE AND ADMINISTRATION, Reconstitution Directions**).

Azithromycin for Injection USP is supplied in 10 mL USP type-I glass vials with 20 mm rubber stoppers and 20 mm aluminum seal with plastic flip-off caps. Each carton contains 10 single dose vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: azithromycin dihydrate

Chemical name: 1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-, [2*R*-(2*R**,3*S**,4*R**,5*R**,8*R**,10*R**,11*R**,12*S**,13*S**,14*R**)], dihydrate

OR

(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one, dihydrate

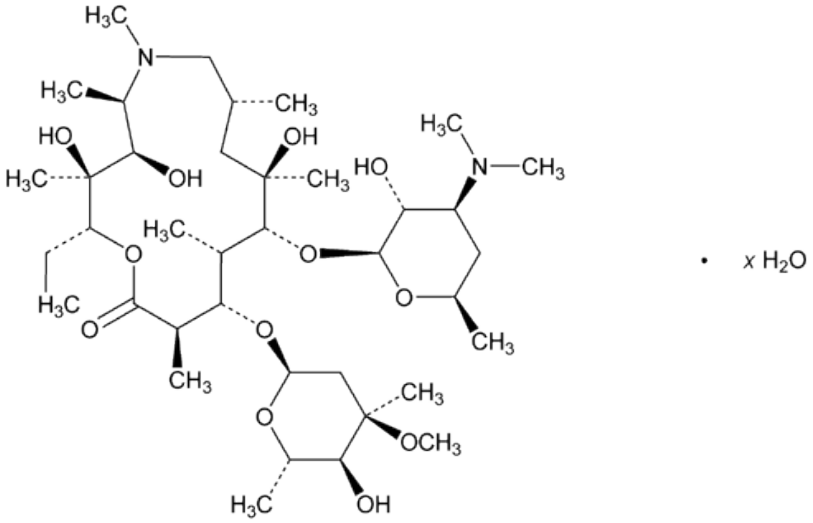
OR

9-deoxo-9α-aza-9α-methyl-9α-homoerythromycin A, dihydrate.

Molecular formula: $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$

Molecular mass: 785.02 g/mol

Structural formula:



Physicochemical properties:	Azithromycin dihydrate is a white to almost white powder or crystal. It is practically insoluble in water, freely soluble in anhydrous ethanol, acetone, and methylene chloride
Melting point:	124.168°C
pK_a:	8.48

CLINICAL TRIALS

From the perspective of evaluating clinical trials because of the extended half-life of azithromycin, days 11-14 (10-13 days after completion of the one-day regimen, 8-11 days after completion of the three-day regimen or 6-9 days after completion of the five-day regimen) were considered on-therapy evaluations and are provided for clinical guidance. Day 21-30 evaluations were considered the primary test of cure endpoint. For patients with community-acquired pneumonia, Days 15-19 were considered as on-therapy evaluations. Days 28-42 were the cure endpoint.

Adult Patients

Acute Bacterial Exacerbations of Chronic Bronchitis:

Efficacy using azithromycin 500 mg over 3 days

In a randomized, double-blind controlled clinical trial of acute exacerbation of chronic bronchitis (AECB) in 404 adult patients, azithromycin (500 mg once daily for 3 days) was compared with clarithromycin (500 mg twice daily for 10 days). The primary endpoint of this trial was the clinical cure rate at Day 21- 24. For the 377 patients analyzed in the MITT analysis at the Day 21-24 visit, the clinical cure rate for 3 days of azithromycin was 87% (162/186) compared to 85% (162/191) for 10 days of clarithromycin (95% CI for azithromycin-clarithromycin cure rate = -5.3, 9.8).

The following outcomes were the clinical cure rates at the Day 21-24 visit for the bacteriologically evaluable patients by pathogen:

Clinical Outcome by Baseline Pathogen

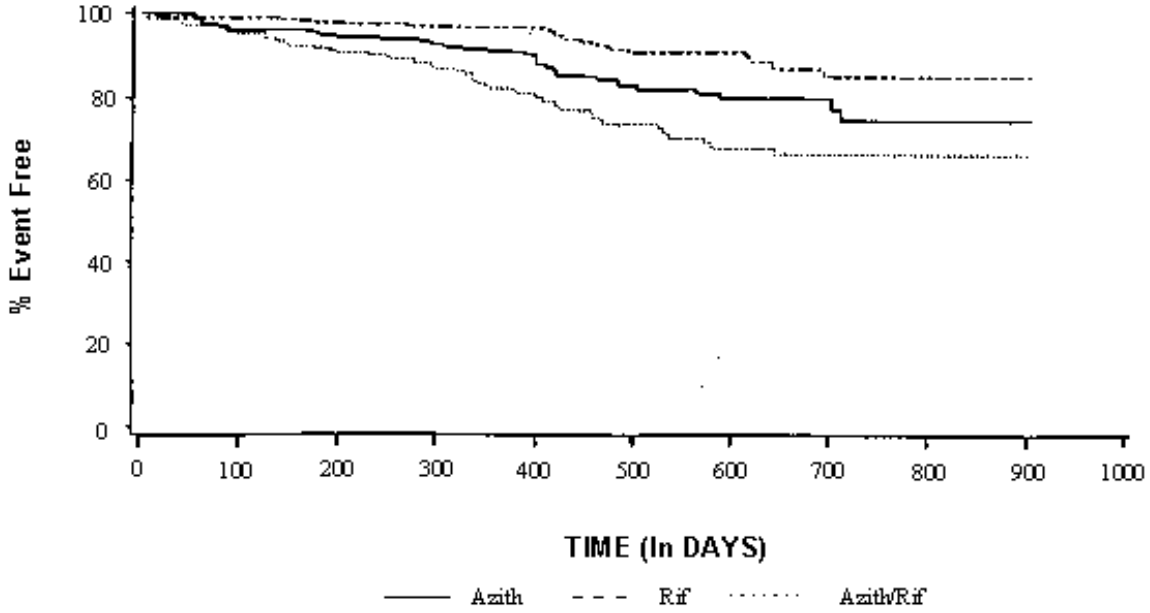
Pathogen	Azithromycin (3 days)	Clarithromycin (10 days)
S. pneumonia	29/32 (91%)	21/27 (78%)
H. influenza	12/14 (86%)	14/16 (88%)
M. catarrhalis	11/12 (92%)	12/15 (80%)

In patients with advanced HIV infection for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease (see **INDICATIONS AND CLINICAL USE):**

Two randomized, double-blind clinical trials were performed in patients with CD4 counts <100 cells/µL. The first study compared azithromycin (1200 mg once weekly) to placebo and enrolled 182 patients with a mean CD4 count of 35 cells/µL. The second study randomized 723 patients to either azithromycin (1200 mg once weekly), rifabutin (300 mg daily) or the combination of both. The mean CD4 count was 51 cells/µL. Endpoints included disseminated MAC disease, the

incidence of clinically significant disseminated MAC disease and discontinuations from therapy for drug-related side effects.

Azithromycin dihydrate
Time to Disseminated MAC Infection
MAC Bacteremia:



In the first study, in the intent-to-treat analysis comparing azithromycin to placebo, patients randomized to azithromycin were one-half as likely to develop MAC as those who received placebo (p=0.004). The one year cumulative incidence rate of disseminated MAC disease was 8.25% on azithromycin and 20.22% on placebo.

In the second study, in the intent-to-treat analysis comparing azithromycin, rifabutin and the combination of azithromycin/rifabutin, the risk of developing MAC bacteremia for patients assigned to azithromycin was also reduced by one-half relative to rifabutin (p=.005). Patients on the combination of azithromycin and rifabutin experienced a risk reduction of approximately two-thirds compared to rifabutin alone (p<0.001). The one year cumulative incidence rate of MAC infection was 7.62% on azithromycin, 15.25% on rifabutin and 2.75% on the combination.

In the placebo-controlled first study, all MAC isolates recovered within 30 days of the last dose of drug from patients randomized to azithromycin were sensitive to azithromycin. In the second study, 2 of 23 (8.7%) isolates received from patients randomized to azithromycin were resistant to azithromycin while none of the isolates received from patients randomized to rifabutin were resistant to azithromycin (p=0.14). None of the isolates recovered from patients randomized to the combination of azithromycin and rifabutin were resistant to azithromycin.

Clinically Significant Disseminated MAC Disease:
In association with the decreased incidence of bacteremia, patients in the groups randomized to either azithromycin alone or azithromycin in combination with rifabutin showed reductions in the signs and symptoms of disseminated MAC disease, including fever or night sweats, weight loss and anemia.

Discontinuations from Therapy for Drug-Related Side Effects:
In the first study, discontinuations for drug-related toxicity occurred in 8.2% of subjects treated with azithromycin and 2.3% of those given placebo (p=0.121). In the second study, more subjects discontinued from the combination of azithromycin and rifabutin (22.7%) than from azithromycin alone (13.5%; p=0.026) or rifabutin alone (15.9%).

DETAILED PHARMACOLOGY

Rapid movement of azithromycin from blood into tissue results in significantly higher azithromycin concentrations in tissue than in plasma (up to 50 times the maximum observed concentration in plasma).

Adults:
Following administration of a 500 mg oral dose, the maximum serum concentration (C_{max}) is 0.4 µg/mL and is attained 2-3 hours after dosing with areas under the curve of 2.6 µg·hr/mL (AUC 0-24) and 3.7 µg·hr/mL (AUC 0-48) and trough levels of 0.05 µg/mL. 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 µg/mL, trough level 0.06 µg/mL, and AUC24 5.0 µg·hr/mL. Thus, plasma concentrations are higher following the intravenous regimen throughout the 24-hour interval. When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

The pharmacokinetic parameters of azithromycin in plasma, after a loading dose of 500 mg on day 1 followed by 250 mg q.d. on days 2 through 5 in healthy young adults (age 18-40 years old) are presented in the following table:

Pharmacokinetic Parameters (Mean) in Adult Subjects (Total n=12) on Days 1 and 5*

	Day 1	**Day 5**
C_{max} (µg/mL)	0.41	0.24
T_{max} (h)	2.5	3.2
AUC_{0-24} (µg • h/mL)	2.6	2.1
C_{min} (µg/mL)	0.05	0.05
Urinary Excret. (% dose)	4.5	6.5

2 x 250 mg on Day 1 followed by one 250 mg on Days 2 through 5

In this study, there was no significant difference in the disposition of azithromycin between male

and female subjects. Plasma concentrations of azithromycin declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. With this regimen, C_{min} and C_{max} remained essentially unchanged from day 2 through day 5 of therapy. However, without a loading dose, azithromycin C_{min} levels required 5 to 7 days to reach steady-state.

In a two-way crossover study, 12 adult normal volunteers (6 males; 6 females) received 1500 mg of azithromycin, administered in single daily doses over either 5 days (two 250 mg tablets on day 1, followed by one 250 mg tablet on days 2-5) or 3 days (500 mg per day). Mean peak serum concentrations were similar on day 1 for both regimens and slightly higher on days 2 and 3 for the 3-day regimen, suggesting that there is minimal serum accumulation of azithromycin on days 2 and 3 of the 3-day regimen.

Pharmacokinetic Parameter (mean)	3-Day Regimen			5-Day Regimen	
	Day 1	Day 2	Day 3	Day 1	Day 5
C_{max} (serum, µg/mL)	0.310	0.446	0.383	0.290	0.182
Serum $AUC_{0-\infty}$ (µg.hr/mL)	15.2			14.5	
Kel (hr^{-1})	0.0101			0.0105	
Serum $T_{1/2}$	68.6 hr			66.0 hr	

Mean AUC0-∞ for both regimens were similar, with a ratio of AUC0-∞(3-day)/AUC0-∞(5-day) of 105% (90% CI=93, 120). Serum concentrations of azithromycin declined in a polyphasic pattern resulting in average terminal half-life of 68.6 hours for the 3-day regimen and about 66 hours for the 5-day regimen.

Median azithromycin exposure (AUC_{0-288}) in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following either the 5-day or 3-day regimen was more than 1000-fold and 800-fold greater than in serum, respectively. Administration of the same total dose with either the 5-day or 3-day regimen may be expected to provide comparable concentrations of azithromycin with MN and PMN leukocytes.

The table below compares pharmacokinetic parameters following single oral doses of 500 mg azithromycin with those obtained after a single 500 mg I.V. 3-hour infusion.

Pharmacokinetic parameters in adults
after oral and intravenous administration of 500 mg azithromycin

	C_{max} (µg/mL)	trough level (µg/mL)	AUC_{0-24} (µg·h/mL)
500 mg single oral dose	0.41	0.05	2.5
500 mg I.V. infusion over 3 hours	1.08	0.06	5

Thus, plasma concentrations are higher following the intravenous regimen throughout the 24- hour interval. Although tissue levels have not been obtained following intravenous infusions of azithromycin, these data suggest that they would be substantially greater than those observed

following oral administration.

After oral administration, serum concentrations of azithromycin decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours.

The high values for apparent steady-state volume of distribution (31.1 L/kg) and plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues. The tissue (or fluid) to plasma concentration ratios for key sites of infection are shown in the following table:

Azithromycin Concentrations Following the Recommended Clinical Dosage Regimen of 500 mg (2 x 250 mg) on Day 1 Followed by 250 mg Daily for Four Additional Days

Tissue or Fluid	Sample Time after Final Dose (hrs)	Tissue or Fluid µg/g or µg/mL	Plasma/Serum µg/mL	Concentration Ratio
Skin	72	0.42	0.011	38.2
Lung	72	4.05	0.011	368.2
Sputum*	15	3.7	0.1	37
Tonsil**	9-18 180	4.5 0.93	0.03 0.006	150 155
Cervix ***	19	2.8	0.04	70

* Samples were obtained 2-24 hours after the first dose
** Dosing regimen of 2 doses of 250 mg each, separated by 12 hours
*** Sample was obtained 19 hours after a single 500 mg dose

The extensive tissue distribution is confirmed by examination of other tissues (prostate; ovary, uterus and salpinx; stomach; liver and gallbladder), in which azithromycin is present in concentrations of 2 µg/g tissue or greater. However, only very low concentrations are noted in cerebrospinal fluid (less than 0.01 µg/mL) of noninflamed meninges. High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy.

The extent of azithromycin absorption is unaffected by co-administration with antacid; however, the C_{max} is reduced by 24%. Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption. There is no evidence of any pharmacokinetic interaction when azithromycin and theophylline are administered to healthy volunteers.

Azithromycin did not affect the prothrombin time response to a single dose of warfarin (15 mg). However, prudent medical practice dictates careful monitoring of prothrombin time in all patients.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 2 µg/mL. These values are not likely to be high enough to influence the protein binding of other drugs or to cause significant protein binding interactions with other drugs.

Following a five-day dosing regimen, human bile contains concentrations of azithromycin much greater (approximately 200 µg/mL) than those in serum (<0.1 µg/mL), indicating that biliary

excretion of azithromycin is a major route of elimination. The major portion of the drug-related material in bile is unchanged drug. Approximately 6% of the administered dose appears in urine.

In patients with mild to moderate hepatic impairment, there is no evidence of marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase.

MICROBIOLOGY

Mechanism of Resistance:
The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

Spectrum of Activity:
Azithromycin has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS SECTION**.

Gram-positive bacteria
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-negative bacteria
Haemophilus ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

"Other" bacteria
Chlamydophila pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

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

At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration MIC) less than or equal to the azithromycin susceptible breakpoint of ≤ 4mcg/mL. However, safety and effectiveness of azithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

Gram-positive bacteria
Beta-hemolytic streptococci (Groups C, F, G)
Viridans group streptococci

Gram-negative bacteria
Bordetella pertussis

Anaerobic bacteria
Peptostreptococcus species
Prevotella bivia

"Other" bacteria
Ureaplasma urealyticum
Legionella pneumophila
Mycoplasma hominis

Activity of Azithromycin against Mycobacterium avium complex (MAC)
In vitro azithromycin has demonstrated activity against Mycobacterium avium complex (MAC) bacteria. Azithromycin has also been shown to be active against phagocytized MAC bacteria in mouse and human macrophage cell cultures.

Susceptibility Testing Methods:
When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports may differ from susceptibility data obtained from outpatient use, but could aid the physician in selecting the most effective antimicrobial.

Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[54,52] (broth or agar) or equivalent with standardized inoculum concentration and standardized concentration of azithromycin powder. The MIC values should be interpreted according to criteria provided in Table 1.

Diffusion Techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[52, 53] requires the use of standardized inoculum concentration. This procedure uses paper disks impregnated with 15-mcg azithromycin to test the susceptibility of bacteria to azithromycin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1. Susceptibility Interpretive Criteria for Azithromycin
Susceptibility Test Result Interpretive Criteria

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
Haemophilus influenzae[a].	≤ 4	--	--	≥ 12	--	--
Staphylococcus aureus	≤ 2	4	≥ 8	≥ 18	14 – 17	≤ 13
Streptococci including *S. pneumoniae*	≤ 0.5	1	≥ 2	≥ 18	14 – 17	≤ 13

Susceptibility to azithromycin must be tested in ambient air.
[a]Insufficient information is available to determine Intermediate or Resistant interpretive criteria
The ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues.

A report of "susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. 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 or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; 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 individual performing the test. Standard azithromycin powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the azithromycin 15 mcg disk, the criteria in Table 2 should be achieved.

Table 2. Acceptable Quality Control Ranges for Azithromycin

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Haemophilus influenza ATCC* 49247	1.0 – 4.0	13 – 21
Staphylococcus aureus ATCC 29213	0.5 – 2.0	---
Staphylococcus aureus ATCC 25923	---	21 – 26
Streptococcus pneumonia ATCC 49619	0.06 – 0.25	19 – 25

Susceptibility to azithromycin must be tested in ambient air.

*ATCC = American Type Culture Collection

TOXICOLOGY

Acute Toxicity: Mice and Rats

Oral and Intraperitoneal Toxicity Studies in Mice and Rats			
Route	**Species**	**Sex**	**LD_{50}** (mg of free base/kg)
Oral	Mice	M	3000
Oral	Mice	F	4000
Oral	Rats	M	>2000
Oral	Rats	F	>2000
Oral	Neonatal Rats	M	>1000
Oral	Neonatal Rats	F	>1000
I/P	Mice	M	>400 <600
I/P	Mice	F	NA*

I/P	Rats	M	>500 <900
I/P	Rats	F	NA*

* NA = not available

Adult animals (Mice and Rats)
Most mortality occurred within 1 to 2 hours and generally within 48 hours of dosing. At higher doses in mice, symptomatology included clonic convulsive activity, loss of righting reflex, gasping, and blanching prior to death.

Gross necropsy of mice or rats which died following intraperitoneal doses revealed yellowish or clear fluid in the pleural and peritoneal cavities. At necropsy on day 14 there were no gross pathological changes in either species aside from a few liver adhesions to the diaphragm.

Neonatal animals (Rats)
No deaths or remarkable clinical signs were observed in any animal during the 14-day observation period. All animals gained weight during the trial. At sacrifice on day 15, no remarkable gross findings were observed in any surviving rat.

Subacute Toxicity:
Phospholipidosis has been observed in animals administered high doses of azithromycin. This effect is reversible after cessation of azithromycin treatment in animals. Despite light- and electron-microscopic correlates of phospholipidosis (myeloid figures and intracytoplasmic vacuoles) in many organs, only in dogs receiving 100 mg/kg/day for at least 2 months have kidney, liver, and gallbladder toxicity been seen. This dose in dogs results in tissue levels greater than 5000 mg/g. Minimal increases in serum transaminase levels in rats and dogs at 20 mg/kg/day and above have also been seen, but are consistent with findings previously reported for erythromycin. Special attention has been given to the effects of phospholipidosis in the retina, including studies of azithromycin, 30 and 100 mg/kg/day for 6 and 2 months, respectively, in dogs. No evidence was elicited of deleterious effects of azithromycin on vision, pupillary reflex or retinal vasculature. The detection of phospholipidosis in the choroid plexus and dorsal root ganglion was not associated with degenerative or functional changes.

In animal studies, treatment with azithromycin is associated with accumulation in various tissues, including the extra-cranial neural ganglia (i.e., retina and sympathetic nervous system). Tissue accumulation is both dose and time dependent, and is associated microscopically with the development of phospholipidosis (intra-lysosomal drug phospholipid complexes). The only evidence in animals that azithromycin is associated with alterations of intracellular phospholipid metabolism has been the documentation of small increases in phospholipid content after prolonged treatment (6 months) or exaggerated doses. Phospholipidosis has been observed at total cumulative doses only 2 multiples of the clinical dose. One month after withdrawal of treatment the concentration of azithromycin and the presence of phospholipidosis in tissue, including the retina, is at or near predose levels.

Subacute and Chronic Toxicity:

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
INTRAVENOUS In Adult Animals					
Rat (Adult)	IV	10 20 20 (every other day)	10/sex	14 days	No untoward effects.
Dog (Adult)	IV	10 20 10 (every other day)	3/sex	14 days	No untoward effects with 3 exceptions in the former two groups. Sporadic elevated serum liver enzyme levels in 2/3 females at the high-dose level; serum alkaline phosphatase levels gradually increased in one 10 mg/kg/day female; phospholipidosis by accumulation of vacuolated macrophages within the lamina propria of the gallbladder and germinal centers of the mesenteric lymph nodes of dogs receiving 20 mg/kg/day.
Rat (Adult)	IV	5 10 20	10/sex	1 month (36-39 days)	Minimal phospholipidosis in the epithelium of the large bile ducts was observed in all high dose and in 13/20 mid-dose animals and at the injection site in the tail of one high dose rat.
Dog (Adult)	IV	5 10 20	3/sex	1 month (36 days)	Slight SGPT elevations occurred in 4/6 high dose animals together with a slight increase in serum alkaline phosphatase activity. Slight SGPT elevations were also noted in 1 low dose and 1 control animal. Histological changes at the high dose were limited to the presence of phospholipidosis. One 10 mg/kg dog also showed minimal phospholipidosis in the large bile ducts. There was no evidence of phospholipidosis at 5 mg/kg/day.
SPECIAL TOXICOLOGY					
Rabbit	IM	0 200 400 (single dose)	3/sex	3 days and 7 days (observation)	Signs indicative of considerable pain upon injection were produced by both volumes of the azithromycin test solution. These changes subsided within 2 to 4 days of dosing. At sacrifice 3 or 7 days post dose, substantial changes were observed in the subcutaneous tissue and the muscle. At 7 days, these changes were much smaller at 1 mL than they were at 2 mL dose.
Rabbit	IV	0 10 (single dose)	3/sex	1 and 2 days (observation)	There were no obvious signs of pain or discomfort upon injection of normal saline with or without azithromycin in the marginal ear vein of six albino rabbits. The gross and microscopic tissue changes indicated that this solution was only minimally irritating.

Reproductive Studies:

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
FERTILITY AND REPRODUCTIVE PERFORMANCE					
Rat	Oral (gavage)	0 10 20	15M/dose 30F/dose	64-66 days	In females the drug given for 14 days prior to and during cohabitation (1M:2F) and to all females throughout gestation, parturition, and lactation until Day 21 postpartum resulted in a lower pregnancy rate of 63% for the high-dose group compared to 83% and 87% for the low-dose and control groups, respectively.
Rat	Oral (gavage)	30	15M/dose 15F/dose	64-66 days	In females the drug was given 15 days prior to mating and continuously throughout the 3 weeks of mating. A lower pregnancy rate for the drug-treated group (67% compared to 100% in the concurrent control group) was also found here.
FERTILITY EFFECT ON MALES OR FEMALES					
Rat	Oral	0 30	40M/dose 80F/dose (Fertile animals only)	64 days (males) See text (females)	In females the drug was given 15 days prior to mating and continuously throughout the 3 weeks of mating. Groups were mated as follows: Group 1: Drug treated males mated with drug treated females. Group 2: Drug treated males mated with control females. Group 3: Control males mated with drug treated females. Group 4: Control males mated with control females. Pregnancy rates were: Group 1, 84%; Group 2, 89%; Group 3, 90%; and Group 4, 96%. The pregnancy rate was statistically significantly lower than control when the males and females were both treated with azithromycin (Group 1). The pregnancy rate of 84% in that group was, however, higher than in the two previous studies and well within our historical control range. The nearly identical pregnancy rates in Groups 2 and 3 (89% and 90%, respectively) do not indicate an effect on either sex alone as being the cause for the apparently reduced pregnancy rate.

Fetotoxicity Teratology

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE	DURATION	FINDINGS
Mice	Oral (gavage)	0 10 20 40	20	days 6-13 of gestation	Azithromycin was not toxic to the dams or their fetuses nor was there evidence of teratogenicity.

Mice	Oral (gavage)	0 50 100 200	20	days 6-13 of gestation	Azithromycin was not toxic to the dams or their fetuses nor was there evidence of teratogenicity.
Rat	Oral (gavage)	0 10 20 40	20	days 6-15 of gestation	Azithromycin was not toxic to the dams or to their fetuses nor was there evidence of teratogenicity.
Rat	Oral (gavage)	0 50 100 200	20	days 6-15 of gestation	Azithromycin was not toxic to the dams or fetuses. Dose levels of 100 and 200 mg/kg induced slight delays in maternal body weight gain and in ossification process of fetuses. The compound was neither embryotoxic nor teratogenic at the three dose levels. The 50 mg/kg dose can be considered as the no-observable-effect-level.
PERI/POSTNATAL					
Rat	Oral (gavage)	102040	15	See text	Azithromycin administered from day 15 p.i. through end of gestation and for the whole period of lactation was not toxic to the dams. The pre- and post-natal developments of pups were not affected.
Rat	Oral (gavage)	0 50 100 200	20	See text	Azithromycin administered from day 15 p.i. through end of gestation and for the whole period of lactation was not toxic to the dams. A slight reduction in weight gain of pups and their post-natal development was related to the litter size and not to drug administration. No drug-related external or visceral anomalies were observed.

Neonatal Studies

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 10 20 40	10/sex	18 days (4-21 days postpartum) 10 days (4-13 days postpartum)	There was no evidence of toxicity and no observation of phospholipidosis.
Rat	Oral (gavage)	0 40 60 80	5/sex	18 days (4-21 days postpartum)	Azithromycin induced dose-related microscopic evidence of phospholipidosis only in the bile duct epithelium of both males and females.

Rat	Oral (gavage)	0 100 120 140	5/sex	18 days (4-21 days postpartum)	Azithromycin in addition to affecting the gallbladder epithelium of all animals, induced microscopic evidence of myocardial phospholipidosis in a majority of high and intermediate dose pups as well as in a single low dose male. Hepatocellular vacuolation, apparent in some animals at each dose level, more pronounced than that of vehicle treated rats, appeared to be a manifestation of drug-induced phospholipidosis.
Rat	Oral (gavage)	30700140	10/sex 20/sex	18 days (4-21 days postpartum) + reversibility	Animals (treated and controls) exhibited normal growth and development. All animals at each dose were systemically exposed to azithromycin, as evidenced by the concentration of the compound in the rats' serum, liver and brain at 24 hours after the last dose. At this time point, the concentration of azithromycin in brain and especially liver greatly exceeded that in serum. At 31 days after the last dose, azithromycin is still detectable in the liver and brain of all rats in the high dose (140 mg/kg/day) reversibility group, but the serum concentrations were generally below the limit of detection (<0.01 µg/mL) and the concentration of azithromycin in the liver, brain, and serum was substantially lower than that found one day after the last dose. In spite of the high azithromycin concentrations detected in both the liver and brain at 24 hours after the last dose, the phospholipid levels in these tissues from rats given azithromycin were generally no greater than those of the vehicle-treated controls at both the end of the dosing period and after the one-month reversibility period. In the animals sacrificed the day after the last dose, i.e. on day 22 postpartum, light microscopic evidence of phospholipidosis was apparent in bile duct epithelium, hepatocyte cytoplasm, cardiac muscle, smooth muscle of the duodenum and uterus, and in the choroid plexus. The only evidence of phospholipidosis at the low dose was in the bile ducts of a single male. No light microscopic evidence of phospholipidosis remained in high dose animals examined after a 30-day reversibility period.

Carcinogenicity

Long-term toxicology studies to assess the carcinogenicity potential have not been conducted.

Genetic Toxicology

Azithromycin was examined in several genetic toxicology assays for induction of gene mutations in microbial and mammalian cells and for chromosomal mutations *in vivo* and *in vitro*. No evidence of genotoxic activity was observed in any of the following assays:

Microbial Assay: Tests were conducted on strains TA 1535, TA 1537, TA 98 and TA 100 of *Salmonella typhimurium* at concentrations up to 2 µg/plate (higher concentrations cause bacterial growth inhibition) in the presence and absence of Aroclor-stimulated rat or mouse liver microsomal enzymes. Additional tests were performed using the same strains of *Salmonella* spp. and urine from mice treated orally with up to 200 mg/kg of azithromycin.

Mammalian Cell Gene Mutation Assay: The L5178Y Mouse Lymphoma Assay for gene mutations at the thymidine kinase locus was conducted at concentrations of 36-360 μg/mL to cytotoxicity in the presence and absence of rat liver microsomal enzymes.

In Vitro **Cytogenetics Assay:** The clastogenic activity of azithromycin was evaluated in human lymphocytes *in vitro* exposed up to toxic concentrations of 40 μg/mL in the presence and 7.5 μg/mL in the absence of rat liver microsomal enzymes.

In Vivo **Cytogenetics Assay:** Azithromycin was examined for clastogenic activity in the bone marrow cells of male and female CD-1 mice treated orally at 200 mg/kg, and sacrificed at 6, 24 or 48 hours post-treatment.

Antigenicity Studies

Azithromycin was tested for the induction of a systemic anaphylaxis reaction in guinea pigs and in rabbits. Azithromycin did not have antigenic potential under the conditions used in the studies.

REFERENCES

1. Arguedas A, Loaiza C, Herrera ML, et al. Comparative trial of 3-day azithromycin versus 10-day amoxicillin/clavulanate potassium in the treatment of children with acute otitis media with effusion. Int J Antimicrob Agents 1996;6:233-8.

2. Arguedas A, Loaiza C, Perez A, et al. Microbiology of acute otitis media in Costa Rican children. Pediatr Infect Dis J 1998;17(8):680-9.

3. Arguedas A, Loaiza C, Rodriguez F, et al. Comparative trial of 3 days of azithromycin versus 10 days of clarithromycin in the treatment of children with acute otitis media with effusion. J Chemother 1997;9(1):44-50.

4. Blondeau JM, Suter M, Borsos S et al. Determination of the antimicrobial susceptibilities of Canadian isolates of *haemophilus influenza*, *streptococcus pneumoniae* and *moraxella catarrhalis*. J Antimicrob Chemother 1999;43:25-30

5. Bright GM, Nagel AA, Bordner J, Desai KA, Dibrino JN, Nowakowska J, Vincent L, Watrous RM, Sciavolino FC, English AR, et al. Synthesis, *in vitro* and *in vivo* activity of novel 9-deoxo-9a-AZA-9a- homoerythromycin A derivatives; a new class of macrolide antibiotics, the azalides. J Antibiot (Tokyo) 1988;41(8):1029-47.

6. Cooper MA, Nye K, Andrews JM, Wise R. The pharmacokinetics and inflammatory fluid penetration of orally administered azithromycin. J Antimicrob Chemother 1990;26(4):533-8.

7. Dagan R, Leibovitz E, Fliss DM, *et al*. Bacteriologic efficacies of oral Azithromycin and oral Cefaclor in treatment of acute otitis media in infants and young children. *Antimicrob Agents Chemother* 2000;44(1):43- 50.

8. Dagan R, Leibovitz E, Greenberg D, *et al*. Early eradication of pathogens from middle ear fluid during antibiotic treatment of acute otitis media is associated with improved clinical outcome. *Pediatr Infect Dis J* 1998;17(9):776-82.

9. Dagan R, Johnson CE, McLinn S et al. Bacteriologic and clinical efficacy of ammoxicillin/ clavulanate vs. azithromycin in acute otitis media. Pediatr Infect Dis J 2000;19:95-104

10. Daniel RR. Comparison of azithromycin and co-amoxiclav in the treatment of otitis media in children. J ntimicrob Chemother 1993;31(SupplE):65-71.

11. Davies BI, Maesen FP, Gubbelmans R. Azithromycin (CP-62,993) in acute exacerbations of chronic bronchitis: an open clinical, microbiological and pharmacokinetic study. J Antimicrob Chemother 1989;23(5):743-51.

12. Dunkin KT, Jones S, Howard AJ. The in-vitro activity of CP-62,993 against Haemophilus influenzae, Branhamella catarrhalis, staphylococci and streptococci. J Antimicrob Chemother 1988;21(4):405-11.

13. Edelstein PH, Edelstein MAC. *In vitro* activity of azithromycin against clinical isolates of Legionella species. Antimicrob Agents Chemother 1991;35(1):180-1.

14. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. J Antimicrob Chemother 1990;25(Suppl A):73-82.

15. Gary KW, Amsden GW. Intravenous azithromycin. Ann Pharmacotherapy 1999;33:218-228

16. Girard AE, Girard D, English AR, Gootz TD, Cimochowski CR, Faiella JA, Haskell SL, Retsema JA. Pharmacokinetic and *in vivo* studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. Antimicrob Agents Chemother 1987;31(12):1948-54.

17. Girard AE, Girard D, Retsema JA. Correlation of the extravascular pharmacokinetics of azithromycin with in-vivo efficacy in models of localized infection. J Antimicrob Chemother 1990;25(Suppl A):61-71.

18. Gladue RP, Bright GM, Isaacson RE, Newborg MF. *In vitro* and *in vivo* uptake of azithromycin (CP- 62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. Antimicrob Agents Chemother 1989;33(3):277-82.

19. Gladue RP, Snider ME. Intracellular accumulation of azithromycin by cultured human fibroblasts. Antimicrob Agents Chemother 1990;34(6):1056-60.

20. Goldstein FW, Emirian MF, Coutrot A, Acar JF. Bacteriostatic and bactericidal activity of azithromycin against Haemophilus influenzae. J Antimicrob Chemother 1990;25(Suppl A):25-8.

21. Hamill J. Multicentre evaluation of azithromycin and penicillin V in the treatment of acute streptococcal pharyngitis and tonsillitis in children. J Antimicrob Chemother 1993;31(Suppl E):89-94.

22. Handsfield HH, Dalu ZA, Martin DH, Douglas JM, McCarty JM, Schlossberg D, and the azithromycin gonorrhea study group. Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. Sex Transm Dis 1994;21(2):107-11.

23. Hopkins S. Clinical toleration and safety of azithromycin. Am J Med 1991:91(Suppl 3A):40S-45S.

24. Hopkins S. Clinical safety and tolerance of azithromycin in children. J Antimicrob Chemother 1993;31(Suppl E):111-7.

25. Issoire C, Casin I, Perenet F, Brunat N, Janier M, Perol Y, Morel P. Pilot study of azithromycin in the treatment of chancroid caused by *Haemophilus ducreyi*. In: Abstracts of the International Congress for Infectious Diseases. 15-19 July 1990:90. (Abstract #152).

26. Johnson RC, Kodner C, Russell M, Girard D. In-vitro and in-vivo susceptibility of Borrelia burgdorferi to azithromycin. J Antimicrob Chemother 1990;25(Suppl A):33-8.

27. Jones K, Felmingham D, Ridgway G. *In vitro* activity of azithromycin (CP-62,993), a novel macrolide, against enteric pathogens. Drugs Exp Clin Res 1988;14(10):613-5.

28. Kitzis MD, Goldstein FW, Miegi M, Acar JF. In-vitro activity of azithromycin against various gram- negative bacilli and anaerobic bacteria. J Antimicrob Chemother 1990;25(Suppl A):15-8.

29. Manfredi E, Jannuzzi C, Mantero E, Longo L, Schiavone R, Tempesta A, Pavesio D, Pecco P, Chiodo F. Clinical comparative study of azithromycin versus erythromycin in the treatment of acute respiratory tract infections in children. J Chemother 1992;4(6):364-70.

30. Martin DH, Sargent S, Wendel GD, Armentor BA, Cammarata CL, Hopkins SJ, Johnson RB. Azithromycin (A) versus ceftriaxone (C) for the treatment of chancroid. In: Program and Abstracts of the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy; 1992 Oct 11-14; Anaheim. American Society for Microbiology, 1992:265. (Abstract #931)

31. Maskell JP, Sefton AM, Williams JD. Comparative *in vitro* activity of azithromycin and erythromycin against Gram-positive cocci, Haemophilus influenzae and anaerobes. J Antimicrob Chemother 1990;25(Suppl A):19-24.

32. Metchock B. In-vitro activity of azithromycin compared with other macrolides and oral antibiotics against Salmonella typhi. J Antimicrob Chemother 1990;25(Suppl A):29-31.

33. Mohs E, Rodriguez-Solares A, Rivas E, El Hoshy Z. A comparative study of azithromycin and amoxycillin in paediatric patients with acute otitis media. J Antimicrob Chemother 1993;31(Suppl E):73-9.

34. Nahata MC, Koranyi KI, Gadgil SD, Hilligos DM, Fouda HG, Gardner MJ. Pharmacokinetics of azithromycin in pediatric patients after oral administration of multiple doses of suspension. Antimicrob Agents Chemother 1993;37(2):314-6.

35. Neu HC, Chin NX, Saha G, Labthavikul P. Comparative *in vitro* activity of the new oral macrolide azithromycin. Eur J Clin Microbiol Infect Dis 1988;7(4):541-4.

36. O'Doherty B, The Paediatric Azithromycin Study Group. Azithromycin versus Penicillin V in the treatment of paediatric patients with acute streptococcal pharyngitis/tonsillitis. *Eur J Clin Microbiol Infect Dis* 1996;15(9):718-24.

37. Pestalozza G, Cioce C, Facchini M. Azithromycin in upper respiratory tract infections: a clinical trial in children with otitis media. Scand J Infect Dis 1992;(Suppl 83):22-5.

38. Plouffe J, Schwartz DB, Kolokathis A, et al. Clinical efficacy of intravenous followed by oral azithromycin monotherapy in hospitalized patients with community-acquired pneumonia. Antimicrob Agents Chemother 2000;44(7):1796-1802.

39. Rapp R. Pharmacokinetics and pharmacodynamics of intravenous and oral azithromycin: enhanced tissue activity and minimal drug interactions. Ann Pharmacotherapy 1998;32:785-793.

40. Retsema JA, Girard AE, Girard D, Milisen WB. Relationship of high tissue concentrations of azithromycin to bactericidal activity and efficacy *in vivo*. J Antimicrob Chemother 1990;25(Suppl A):83-9.

41. Retsema J, Girard A, Schelkly W, Manousos M, Anderson M, Bright G, Borovoy R, Brennan L, Mason R. Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. Antimicrob Agents Chemother 1987;31(12):1939- 47.

42. Rylander M, Hallander HO. *In vitro* comparison of the activity of doxycycline, tetracycline, erythromycin and a new macrolide, CP-62,993, against Mycoplasma pneumoniae, Mycoplasma hominis and Ureaplasma urealyticum. Scand J Infect Dis Suppl 1988;53:12-7.

43. Schaad UB. Multicentre evaluation of azithromycin in comparison with co-amoxiclav for the treatment of acute otitis media in children. J Antimicrob Chemother 1993;31(Suppl E):81-8.

44. Schonwald S, Gunjaca M, Kolacny-Babic L, Car V, Gosev M. Comparison of azithromycin and erythromycin in the treatment of atypical pneumonias. J Antimicrob Chemother 1990;25(Suppl A):123-6.

45. Shepard RM, Falkner FC. Pharmacokinetics of azithromycin in rats and dogs. J Antimicrob Chemother 1990;25(Suppl A):49-60.

46. Stamm WE, Workowski K, Hicks CB, Cooper R, Martin DH, Leone PA, Batterger BE, Johnson RB and the Pfizer NGU Study Group. Azithromycin in the treatment of nongonococcal urethritis; a multicenter, double-blind, double-dummy study employing doxycycline as a comparative agent (abstract). In: Program and Abstracts of the 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 1993 Oct 17-20; New Orleans. American Society for Microbiology 1993:120. (Abstract #10)

47. Steingrimsson O, Olafsson JH, Thorarinsson H, Ryan RW, Johnson RB, Tilton RC. Azithromycin in the treatment of sexually transmitted disease. J Antimicrob Chemother 1990;25(Suppl A):109-14.

48. Steingrimsson O, Olafsson JH, Thorarinsson H, Ryan RW, Johnson RB, Tilton RC. Single dose azithromycin treatment of gonorrhea and infections caused by *C. trachomatis* and *U. urealyticum* in men. Sex Transm Dis 1994;21(1):43-6.

49. Vergis EN, Indorf A, File TM Jr, et al. Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients. Arch Intern Med 2000;160:1294-1300.

50. Weippl G. Multicentre comparison of azithromycin versus erythromycin in the treatment of paediatric pharyngitis or tonsillitis caused by group A streptococci. J Antimicrob Chemother 1993;31(Suppl E):95- 101.

51. Wildfeuer A, Laufen H, Muller-Wening D, Haferkamp O. Interaction of azithromycin and human phagocytic cells. Uptake of the antibiotic and the effect on the survival of ingested bacteria in phagocytes. Arzneimittelforschung 1989;39(7):755-8.

52. Clinical and Laboratory Standards Institute. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently isolated or Fastidious bacteria, 3rd ed. CLSI guideline M45. Wayne, PA: Clinical and Laboratory Standards Institute; 2015.

53. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard - Eleventh Edition. CLSI document M02-A11. CLSI, Wayne, PA 19087, 2012.

54. 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 250, Wayne, PA 19087, 2012.

55. Pfizer Canada Inc., ZITHROMAX® Product Monograph. Date of Revision: 11 September 2018. Control No. 218645.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

AZITHROMYCIN FOR INJECTION USP
Azithromycin for injection

Read this carefully before you start taking **Azithromycin for Injection USP** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **Azithromycin for Injection USP**.

What is Azithromycin for Injection USP used for?

Azithromycin for Injection USP is an antibiotic medicine used to treat the following types of **mild to moderate** infections **by certain microorganisms** in adults: genitourinary infections and pneumonia.

Antibacterial drugs like **Azithromycin for Injection USP** treat only bacterial infections. They do not treat viral infections such as the common cold. Although you may feel better early in treatment, **Azithromycin for Injection USP** should be taken exactly as directed. Misuse or overuse of **Azithromycin for Injection USP** could lead to the growth of bacteria that will not be killed by **Azithromycin for Injection USP** (resistance). This means that **Azithromycin for Injection USP** may not work for you in the future. Do not share your medicine.

How does Azithromycin for Injection USP work?
Azithromycin for Injection USP helps stop the growth of the bacteria that cause infection. It gets into infected tissue where it is released slowly over time so the medicine keeps fighting bacteria for many days after the last dose is taken. This is why **Azithromycin for Injection USP** may be taken for as short a time as one day.

What are the ingredients in Azithromycin for Injection USP?
Medicinal ingredients: Azithromycin dihydrate.
Non-medicinal ingredients: citric acid anhydrous; sodium hydroxide

Azithromycin for Injection USP comes in the following dosage forms:
Azithromycin for injection (as azithromycin dihydrate), 500 mg/vial or 500 mg/5 ml when reconstituted

Do not use Azithromycin for Injection USP if you:
- have a history of liver problems when you have used azithromycin.
- are hypersensitive (allergic) to azithromycin, or any macrolide or ketolide antibiotic (including erythromycin) or any other ingredient of **Azithromycin for Injection USP** (see **What are the ingredients in Azithromycin for Injection USP?**).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take Azithromycin for Injection USP. Talk about any health conditions or problems you may have, including if you:
- have a known prolonged heart cycle (interval) (QT prolongation)

- are currently taking medication known to prolong QT interval (prolong your heart cycle) such as antiarrhythmics (drugs to regulate your heart beat such as class IA: quinidine, procainamide and class III; dofetilide, amiodarone, sotalol); antipsychotic agents; antidepressants; and fluoroquinolones (a class of antibiotics)
- have a history of life-threatening irregular heart beat
- have constantly low levels of potassium or magnesium in your blood
- have a history for heart problems such as slow heart rate, irregular heart beat or cardiac insufficiency (your heart has a hard time pumping blood to your body)
- are pregnant or think you are pregnant,
- are breastfeeding or planning to breastfeed. Azithromycin is excreted in human breast milk. It is not known if **Azithromycin for Injection USP** could affect your baby. Discuss with your doctor.
- have ever had any liver or kidney problems
- have a weak immune system
- have ever had an allergic reaction to any medicines, including antibiotics such as erythromycin
- have myasthenia gravis (a chronic autoimmune neuromuscular disease which causes muscle weakness).

Other warnings you should know about:
If you develop diarrhea during or after treatment with **Azithromycin for Injection USP**, tell your doctor at once. Do not use any medicine to treat your diarrhea without first checking with your doctor.

Your healthcare professional will ensure that **Azithromycin for Injection USP** is administered for the full number of days prescribed. If **Azithromycin for Injection USP** is stopped too soon, your infection could come back. The next infection may be worse and be more difficult to treat.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with Azithromycin for Injection USP:

- Warfarin (or other anticoagulant medicine);
- Cyclosporin (used to suppress the immune system to prevent and treat rejection in organ or bone marrow transplants);
- Digoxin (used for treatment of heart problems);
- Colchicine (used for treatment of gout);
- Nelfinavir (used for treatment of HIV infections);
- Ergotamine and ergot derivatives (used for migraine treatment). Ergotamine and ergot derivatives should not be used with **Azithromycin for Injection USP**.

Some medicines may affect how well **Azithromycin for Injection USP** works. Check with your doctor before starting any new prescription or over-the-counter medicines, including natural/herbal remedies or antacids, while on **Azithromycin for Injection USP**.

How to take Azithromycin for Injection USP:
Azithromycin for Injection USP for Injection will always be prepared and given to you by a doctor or a healthcare professional.

Azithromycin for Injection USP for Injection must be reconstituted and diluted as directed, and administered as an intravenous infusion over at least 60 minutes.

Overdose:

If you think you have been given too much **Azithromycin for Injection USP**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

What are possible side effects from using Azithromycin for Injection USP?
These are not all the possible side effects you may feel when taking **Azithromycin for Injection USP**. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

- Diarrhea/loose stools
- Stomach pain
- Nausea and vomiting
- Headache

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON **Clostridium difficile colitis (bowel inflammation):** severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness			√
Vaginitis (inflammation of the vagina): change in colour, odor or amount of discharge, itching or irritation, pain during intercourse, painful urination, light vaginal bleeding or spotting	√		
Injection site reaction: pain, redness and/or swelling at the injection site		√	
UNCOMMON **Abnormal heart rhythm:** feel your heart beating in your chest, abnormal heartbeat, dizziness or feeling faint			√

Severe allergic reaction: trouble breathing, swelling of the face, mouth, throat, neck, severe skin rash or blisters			√
Liver disorder: abdominal pain, nausea, vomiting, yellowing of skin and eyes, dark urine			√
Myasthenia gravis: muscle weakness, drooping eyelid, vision changes, difficulty chewing and swallowing, trouble breathing		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
The healthcare professional will store the product under appropriate conditions.

Keep out of reach and sight of children.

If you want more information about Azithromycin for Injection USP:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (www.healthcanada.gc.ca); the manufacturer's website (www.sterimaxinc.com); or by calling 1-800-881-3550.

This leaflet was prepared by SteriMax Inc.

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