PRODUCT MONOGRAPH

^{Pr}AZITHROMYCIN FOR INJECTION, USP
(azithromycin monohydrate USP)

Powder for Injection 500 mg azithromycin per vial
(100 mg azithromycin/mL solution after reconstitution)

Antibacterial agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous	500 mg/vial (100 mg/mL after reconstitution)	anhydrous citric acid 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**).

<u>Adults</u>

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 for Injection, USP is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin and in those with 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 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 for Injection, USP**. 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 intravenous 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 Market Adverse Drug Reactions**). 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 perforation 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

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 for Injection, USP** 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 for Injection, USP** 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 for Injection, USP** 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 mcg/mL (see **TOXICOLOGY**).

Nursing Women:
Azithromycin has been reported to have been secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk. In addition, 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. 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:
Acute Otitis Media: Safety and efficacy in the treatment of children with otitis media under 6 months of age have not been established.

Community-acquired pneumonia: Safety and efficacy in the treatment of children with community-acquired pneumonia under 6 months of age have not been established.

Pharyngitis and tonsillitis: Safety and efficacy in the treatment of children with pharyngitis and tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted. Safety data with the use of Azithromycin at doses higher than proposed and for durations longer than recommended are limited to a small number of immunocompromised children who underwent chronic treatment.

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

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

Prevention of Disseminated Mycobacterium Avium Complex (MAC) Disease:
Safety and efficacy of Azithromycin for the prevention of MAC in children have not been established.

Limited safety data are available for 24 children 5 months to 14 years of age (mean 4.6 years) who received Azithromycin for treatment of opportunistic infections. The mean duration of therapy was 186.7 days (range 13-710 days) at doses of < 5 to 20 mg/kg/day. Adverse events were similar to those observed in the adult population, most of which involved the gastrointestinal tract. While none of these children prematurely discontinued treatment due to a side effect, one child discontinued due to a laboratory abnormality (eosinophilia). Based on available pediatric pharmacokinetic data, a dose of 20 mg/kg in children would provide drug exposure similar to the 1200 mg adult dose but with a higher C_{max}.

Geriatrics:
The pharmacokinetics in elderly volunteers (age 65 to 85) were similar to those in younger volunteers (age 18 to 40) for the 5-day oral therapeutic regimen. Dosage adjustment does not appear to be necessary for elderly patients with normal renal and hepatic function receiving treatment with this dosage regimen. 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 **Azithromycin for Injection, USP** may be considered by the physician as appropriate.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The majority of side effects observed in controlled clinical trials involving patients (adults and children) treated with oral azithromycin were of a mild and transient nature. Approximately 0.7% of both adult patients (n=3812) and children (n=2878) from the 5-day multiple dose clinical trials discontinued azithromycin therapy because of drug related side effects. 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%. In clinical trials in children given 30 mg/kg, orally either as a single dose (n=487) or over 3 days, (n=1729) discontinuation from therapy due to treatment-related side effects was approximately 1%.

Most of the side effects leading to discontinuation in patients on oral or 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 intravenous/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 intravenous/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 intravenous/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 intravenous 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, hemolytic anemia, thrombocytopenia.
Cardiovascular:	Cardiac arrhythmias (including ventricular tachycardia), palpitations, hypotension. There have been rare reports of QT prolongation and *torsades 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 sternosis / infantile hypertrophic pyloric stenosis (IHPS);.
General:	Asthenia, paresthesia, fatigue, muscle pain;
Genitourinary:	Interstitial nephritis, acute renal failure, nephrotic syndrome, vaginitis.

Liver/Biliary:	Hepatic 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), and 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 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 who 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 coadministration 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_{0-8} 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 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 / P-glycoprotein substrates

Concomitant administration of some macrolide antibiotics with P-glycoprotein substrates, including digoxin, 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 azithromycin 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-Food Interactions
Azithromycin tablets and powder for oral suspension can be taken with or without food.

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:
Due to the lack of data, **Azithromycin for Injection, USP** should be used with caution in patients with hepatic impairment.

Renal Impairment:
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 intravenous 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 intravenous 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:

FLIPTOP VIAL

RECONSTITUTION OF AZITHROMYCIN FOR INJECTION				
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 monohydrate equivalent to 100 mg azithromycin. Reconstituted solution is stable for 24 hours when stored between 20 and 25°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 (20 to 25°C), or for 7 days if stored under refrigeration (5°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.

ADD-Vantage™ Vial

Dilution of reconstituted solution:

Azithromycin for Injection, USP, when reconstituted with the solutions listed below to 2 mg/mL concentration, is stable for 24 hours between 20 and 25°C and 7 days at 5°C conditions.

Admixture containers available

The ADD-Vantage vial should be joined with a 250 mL ADD-Vantage flexible diluent container (5% dextrose injection or 0.9% sodium chloride injection or 0.45% sodium chloride injection).
The diluted solution contains 2 mg/mL of azithromycin, on dilution with 250 mL of diluent.

INSTRUCTIONS FOR USE OF THE ADD-Vantage™ VIAL

To Open Diluent Container

Peel overwrap from the corner and remove container. Some opacity of the plastic is due to moisture absorption during the sterilization process and may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually.

To Assemble Vial and Flexible Diluent Container: (Use Aseptic Technique)

1. Remove the protective covers from the top of the vial and the vial port on the diluent container as follows:
    a. To remove the breakaway vial cap, swing the pull ring over the top of the vial and pull down far enough to start the opening (see Figure 1), pull the ring approximately half way around the cap and then pull straight up to remove the cap (see Figure 2).

       NOTE: Do not access vial with syringe.
    b. To remove the vial port cover, grasp the tab on the pull ring, pull up to break the three tie strings, then pull back to remove the cover. (See Figure 3.)

2. Screw the vial into the vial port until it will go no further. THE VIAL MUST BE SCREWED IN TIGHTLY TO ASSURE A SEAL. This occurs approximately 1/2 turn (180°) after the first audible click. (See Figure 4.) The clicking sound does not assure a seal, the vial must be turned as far as it will go.

   NOTE: Once vial is sealed, do not attempt to remove. (See Figure 4.)

3. Recheck the vial to assure that it is tight by trying to turn it further in the direction of assembly.

4. Label appropriately.

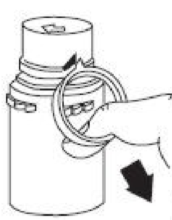


Fig. 1


Fig. 2


Fig. 3

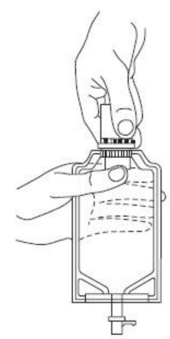


Fig. 4

To Prepare Admixture

1. Squeeze the bottom of the diluent container gently to inflate the portion of the container surrounding the end of the drug vial.

2. With the other hand, push the drug vial down into the container telescoping the walls of the container. Grasp the inner cap of the vial through the walls of the container. (See Figure 5.)

3. Pull the inner cap from the drug vial. (See Figure 6.) Verify that the rubber stopper has been pulled out, allowing the drug and diluent to mix.

4. Mix container contents thoroughly and use within the specified time.

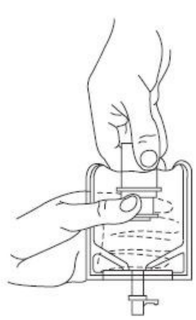


Fig. 5

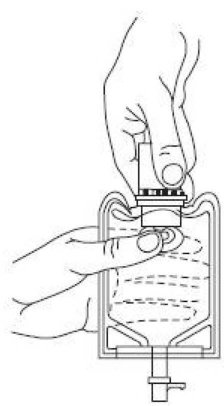


Fig. 6

5. Look through the bottom of the vial to verify that the stopper has been removed and complete mixing has occurred (See Figure 7.) If the rubber stopper is not removed from the vial and medication is not released on the first attempt, the inner cap may be manipulated back into the rubber stopper without removing the drug vial from the diluent container. Repeat step 3 through 5.

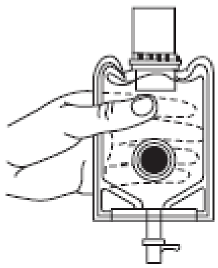


Fig. 7

Preparation for Administration:

1. Confirm the activation and admixture of vial contents.
2. Check for leaks by squeezing container firmly. If leaks are found, discard unit as sterility may be impaired.
3. Close flow control clamp of administration set.
4. Remove cover from outlet port at bottom of container.
5. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton.
6. Lift the free end of the hanger loop on the bottom of the vial, breaking the two tie strings. Bend the loop outward to lock it in the upright position, then suspend container from hanger.
7. Squeeze and release drip chamber to establish proper fluid level in chamber.
8. Open flow control clamp and clear air from set. Close clamp.
9. Attach set to venipuncture device. If device is not indwelling, prime and make venipuncture.
10. Regulate rate of administration with flow control clamp.

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 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 for Injection, USP (azithromycin monohydrate), 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 Cmax values for the 500, 1000 and 1500 mg azithromycin dose regimens were 0.536 (33), 0.957 (31), and 1.54 (28) mcg/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.

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 mcg/mL (range: 1.70 -6.00 mcg/mL) while the 24-hour trough level was 0.18 mcg/mL (range: 0.07 -0.60 mcg/mL) and the AUC_{24} was 8.50 mcg•h/mL (range: 5.10-19.60 mcg•h/mL).

The median C_{max}, 24-hour trough and AUC_{24} values were 1.20 mcg/mL (range: 0.89-1.36 mcg/mL), 0.18 mcg/mL (range: 0.15-0.21 mcg/mL) and 7.98 mcg•h/mL (range: 6.45-9.80 mcg•h/mL), respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/mL. Similar pharmacokinetic values were obtained in patients hospitalized with CAP that received the same 3-hour dosage regimen for 2-5 days.

Plasma concentrations (mcg/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:
The serum protein binding of azithromycin is concentration dependent, decreasing from 51% at 0.02 mcg/mL to 7% at 2.0 mcg/mL. Following oral administration, azithromycin is widely distributed throughout the body with a steady-state apparent volume of distribution of 31.1 L/kg.

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**).

Special Populations and Conditions

Pediatric Pharmacokinetics:
Pharmacokinetics in children receiving a total dose of 30 mg/kg:
The table below shows mean pharmacokinetic parameters on day 5 in children 1 to 5 years and 5 to 15 years of age when azithromycin oral suspension was dosed in the absence of food at a total dose of 30 mg/kg delivered as 10 mg/kg on day 1 and 5 mg/kg on days 2-5.

Pharmacokinetics in children given a total dose of 30 mg/kg delivered as a single dose have not been studied.

Pharmacokinetic parameters on day 5 at dosage 10 mg/kg (day 1) and 5 mg/kg (days 2-5)					
Ages 1-5			Ages 5-15		
C_{max} (mcg/mL)	T_{max} (hrs)	AUC_{0-24} (mcg•hr/mL)	C_{max} (mcg/mL)	T_{max} (hrs)	AUC_{0-24} (mcg•hr/mL)
0.216	1.9	1.822	0.383	2.4	3.109

Pharmacokinetics in children receiving a 60 mg/kg total dose:
Two clinical studies enrolled 35 and 33 children respectively aged 3-16 years with pharyngitis/tonsillitis to determine the pharmacokinetics and safety of azithromycin for oral suspension in children when given 60 mg/kg in divided doses delivered as 20 mg/kg/day over 3 days or 12mg/kg/day over 5 days with a maximum daily dose of 500 mg.

The following table shows pharmacokinetic data in the subset of children who received a total dose of 60 mg/kg. In both studies azithromycin concentrations were determined over a 24 hour period following the last daily dose.

Similarity of overall exposure ($AUC_{0-\infty}$) between the 3 and 5 day regimen is unknown.

	3-Day Regimen	5-Day Regimen
N	11[B]	17[B]
C_{max} (mcg/mL)	1.05 ± 0.44[a]	0.534 ± 0.361[a]
T_{max} (hr)	3 ± 2.0[a]	2.2 ± 0.8[a]
AUC_{0-24}(mcg × hr/mL)	7.92 ± 2.87[a]	3.94 ± 1.90[a]

[a] Arithmetic means

[B] Maximum weight for 3 day regimen was ≤ 25 kg and for 5 day regimen was ≤ 41.7 kg

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 conditions (20 to 25°C)

Flip Top Vial:
Reconstituted Solution: Stable for 24 hours stored at controlled room temperature (20 to 25°C).

Diluted solution: Stable for 24 hours between 20 to 25°C, or for 7 days if stored under refrigeration (5°C). For single-use only. Discard any unused portion after use.

ADD-Vantage Vial:
Reconstituted Solution: Stable for 24 hours at controlled room temperature (20 to 25°C), or 7 days if stored under refrigeration (5°C).

DOSAGE FORMS, COMPOSITION AND PACKAGING

Azithromycin for Injection, USP 500 mg: Each vial contains azithromycin monohydrate in a lyophilized form equivalent to 500 mg azithromycin. The non-medicinal ingredients include: 392 mg (ADD Vantage) and 384.6 mg (Flip Top) of anhydrous citric acid and sodium hydroxide for pH adjustment. After reconstitution, each mL contains azithromycin monohydrate equivalent to 100 mg azithromycin (see **DOSAGE AND ADMINISTRATION, Reconstitution Directions**).

Flip Top Vial:
Cartons of 10 single dose vials.

Provides 500 mg/5 mL (100 mg/mL) azithromycin when reconstituted as directed.

ADD-Vantage Vial

Carton of 10 Single Use ADD-Vantage™ vials of 500 mg. Provides 500 mg/250 mL (2 mg/mL) azithromycin when reconstituted as directed in a 250 mL ADD-Vantage flexible diluant container.

PART II: SCIENTIFIC INFORMATION

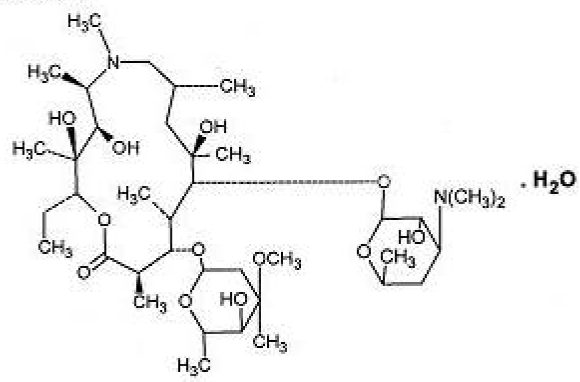
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name:	azithromycin monohydrate
Chemical Name:	9-deoxo-9α-aza-9α-methyl-9α-homoerythromycin A monohydrate.
Molecular Formula:	$C_{38}H_{72}N_{2}0_{12}\cdot H_{2}O$
Molecular Weight:	767.02 g/mol
Structural Formula:	

STRUCTURE

Chemical structure



Phisiochemical properties:	Azithromycin monohydrate is a white to off-white crystalline powder of uniform appearance. pH is between 9.0 and 11.0. The powder is non-hygroscopic.
pK_a:	8.74
Melting point:	133°C-135°C

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.

Pediatric Patients:

Otitis Media:

Efficacy using azithromycin 30 mg/kg given over 5 days

Protocol 1

In a double-blind, controlled clinical study of acute otitis media performed in North America, azithromycin (10 mg/kg on day 1 followed by 5 mg/kg on days 2-5) was compared to amoxicillin/clavulanate potassium (4:1). For the 553 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the day 11 visit was 88% for azithromycin and 88% for the control agent. For the 528 patients who were evaluated at the day 30 visit, the clinical success rate was 76% for azithromycin and 76% for the control agent.

Protocol 2

In a non-comparative clinical and microbiologic trial performed in North America and in which significant numbers of β-lactamase producing organisms were identified (35%), the combined clinical success rate (i.e., cure plus improvement) was 84% at the day 11 visit (n=131) and 70% at the day 30 visit (n=122).

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. The following presumptive bacterial/clinical cure outcomes (i.e., clinical success) were obtained from the evaluable group:

Presumed Bacteriologic Eradication Clinical Success	Day 11	Day 30
	Azithromycin	Azithromycin
S. pneumoniae	61/74 (82%)	40/56 (71%)
H. influenzae	43/54 (80%)	30/47 (64%)
M. catarrhalis	28/35 (80%)	19/26 (73%)
S. pyogenes	11/11 (100%)	7/7
Overall	177/217 (82%)	97/137 (73%)

From the perspective of evaluating clinical trials in patients using the 3 day or 1 day accelerated regimen of azithromycin, the analysis of efficacy was based on a Modified Intent to Treat population with efficacy assessments at approximately Day 11-16 and Day 28-32. Since peak age incidence for acute otitis media is 6-18 months of age, stratified data is provided for clinical guidance in this age group.

Efficacy using azithromycin 30 mg/kg given over 3 days

Protocol 3

In a double-blind, controlled, randomized clinical study of acute otitis media in North American children from 6 months to 12 years of age, azithromycin (10 mg/kg per day for 3 days) was compared to amoxicillin/clavulanate potassium (7:1) in divided doses q12h for 10 days. Each child received active drug and placebo matched for the comparator. For the 366 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the day 12 visit was 83% for azithromycin and 88% for the control agent. For the 362 patients who were evaluated at the day 24-28 visit, the clinical success rate was 74% for azithromycin and 69% for the control agent.

Protocol 3 MITT Subjects ≤ 2years of age	Azithromycin 3 day 10mg/kg/day N (%)	Comparator N (%)
Evaluable at Day 12	60	52
Cure	23 (38%)	29 (56%)
Improvement	22 (37%)	15 (29%)
Failure	15 (25%)	8 (15%)
Evaluable at Day 24-28	58	52
Cure	35 (60%)	30 (58%)
Improvement	0 (0%)	0 (0%)
Failure	23 (40%)	22 (42%)

Efficacy using azithromycin 30 mg/kg given as a single dose

Protocol 4

In a double-blind, controlled, randomized clinical study of acute otitis media in North American children from 6 months to 12 years of age, azithromycin (given at 30mg/kg as a single dose on day 1) was compared to amoxicillin/clavulanate potassium (7:1) in divided doses q12h for 10 days. Each child received active drug, and placebo matched for the comparator. For the 321 subjects who were evaluated at Day 12-16, the clinical success rate (cure plus improvement) was 87% for azithromycin, and 88% for the comparator. For the 305 subjects who were evaluated at Day 28-32, the clinical success rate was 75% for both azithromycin and the comparator.

Protocol 4 MITT subjects ≤ 2 years	Azithromycin 1 day N (%)	Comparator N (%)
Evaluable at Day 12-16	68	56
Cure	36 (53%)	39 (70%)
Improvement	17 (25%)	6 (11%)
Failure	15 (22%)	11 (20%)

Evaluable at Day 28-32	64	53
Cure	40 (63%)	27 (51%)
Improvement	1 (1.5%)	3 (6%)
Failure	23 (36%)	23 (43%)

Protocol 5

Protocol 5 MITT subjects ≤ 2 years	Azithromycin 1 day N (%)
Evaluable at Day 10	82
Cure	50 (61%)
Improvement	19 (23%)
Failure	13 (16%)
Evaluable at Day 24-28	83
Cure	64 (77%)
Improvement	0 (0%)
Failure	19 (23%)

	Day 10		Day 24-28	
Presumed Bacteriologic Eradication/ Clinical Success	MITT	MITT < =2years	MITT	MITT <=2years
S. pneumoniae	70/76 (92%)	23/25 (92%)	67/76 (88%)	20/25 (80%)
H. influenzae	30/42 (71%)	11/18 (61%)	28/44 (64%)	10/19 (53%)
M. catarrhalis	10/10 (100%)	6 /6 (100%)	10/10 (100%)	6/6 (100%)
Overall	110/128 (86%)	40/49 (82%)	105/130 (81%)	36/50 (72%)

In a non-comparative clinical and microbiological trial enrolling 70% North American children and 30% South American children, 248 patients from 6 months to 12 years of age with documented acute otitis media were dosed with a single oral dose of azithromycin (30 mg/kg on day 1). For the 240 evaluable patients, the clinical success rate (i.e., cure plus improvement) at day 10 was 89% and for the 242 patients evaluable at Day 24-28, the clinical success rate (cure) was 85%. Of the 76 S. pneumoniae isolates, 16% exhibited resistance to azithromycin at baseline. No bacterial eradication data is available for the azithromycin 3 day regimen.

Pharyngitis and Tonsillitis:

Efficacy using azithromycin 60 mg/kg over 5 days

In three double-blind North American controlled studies, azithromycin (12 mg/kg once a day for 5 days) was compared to penicillin V (250 mg three times a day for 10 days) in the treatment of pharyngitis due to documented group A β-hemolytic streptococci (GAβHS or *S. pyogenes*). Azithromycin was clinically and microbiologically statistically superior to penicillin at day 14 and day 30 with the following clinical success (i.e., cure and improvement) and bacteriologic efficacy rates (for the combined evaluable patients with documented GaβHS):

3 Combined Streptococcal Pharyngitis Studies
5-Day Dosing Regimen
Azithromycin vs. Penicillin V
EFFICACY RESULTS

	Day 14	Day 30
Bacteriologic Eradication		
Azithromycin Penicillin V	323/340 (95%) 242/332 (73%)	261/329 (79%) 214/304 (71%)
Clinical Success (Cure plus improvement)		
Azithromycin Penicillin V	336/343 (98%) 284/338 (84%)	313/328 (95%) 240/303 (79%)

Approximately 1% of azithromycin-susceptible *S. pyogenes* isolates were resistant to azithromycin following therapy.

Adult Patients

Acute Bacterial Exacerbations of Chronic Bronchitis:

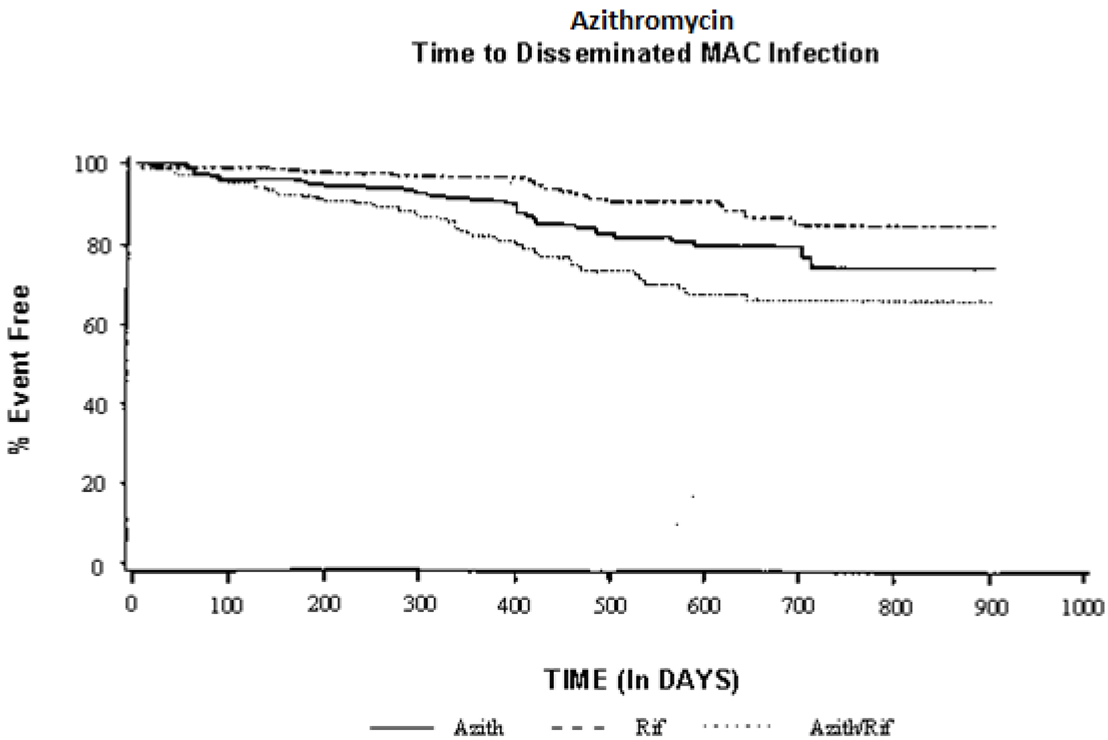
Efficacy using azithromycin 500 mg over 3 days
In a randomized, double-blind controlled clinical trial of acute exacerbation of chronic bronchitis (AECB) in 404 adult patients, azithromycin (500 mg once daily for 3 days) was compared with clarithromycin (500 mg twice daily for 10 days). The primary endpoint 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/mcL. The first study compared azithromycin (1200 mg once weekly) to placebo and enrolled 182 patients with a mean CD4 count of 35 cells/mcL. 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/mcL. Endpoints included disseminated MAC disease, the incidence of clinically significant disseminated MAC disease and discontinuations from therapy for drug-related side effects.



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

Following oral administration, azithromycin is rapidly absorbed (T_{max} = 2-3 hours) and distributed widely throughout the body. 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). The absolute bioavailability is approximately 37%.

Adults:

Following administration of a 500 mg oral dose, the maximum serum concentration (C_{max}) is 0.4 mcg/mL and is attained 2-3 hours after dosing with areas under the curve of 2.6 mcg•hr/mL (AUC 0-24) and 3.7 mcg•hr/mL (AUC 0-48) and trough levels of 0.05 mcg/mL. These oral values are approximately 38%, 83% and 52% of the values observed following a single 500 mg intravenous 3 -hour infusion: C_{max} 1.08 mcg/mL, trough level 0.06 mcg/mL, and AUC24 5.0 mcg•hr/mL. Thus, plasma concentrations are higher following the intravenous regimen throughout the 24-hour interval. Also refer to tabulated pharmacokinetic data reported in adults under **ACTION AND CLINICAL PHARMACOLOGY, Adult Pharmacokinetics** section. 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} (mcg/mL)	0.41	0.24
T_{max} (h)	2.5	3.2
AUC_{0-24} (mcg • h/mL)	2.6	2.1
C_{min} (mcg/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, mcg/mL)	0.310	0.446	0.383	0.290	0.182
Serum $AUC_{0-\infty}$ (mcg.hr/mL)	15.2			14.5	
Kel (hr^{-1})	0.0101			0.0105	
Serum $T_{1/2}$	68.6 hr			66.0 hr	

Mean $AUC_{0\infty}$ for both regimens were similar, with a ratio of $AUC_{0\infty}$(3-day)/$AUC_{0\infty}$(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 intravenous 3-hour infusion.

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

	C_{max} (mcg/mL)	trough level (mcg/mL)	AUC_{0-24} (mcg• h/mL)
500 mg single oral dose	0.41	0.05	2.5
500 mg intravenous 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 mcg/g or mcg/mL	Plasma/Serum mcg/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 mcg/g tissue or greater. However, only very low concentrations are noted in cerebrospinal fluid (less than 0.01 mcg/mL) of noninflamed meninges. High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy.

When azithromycin oral suspension as the 200 mg/5mL dose was administered with food to 28 adult healthy male subjects, the rate of absorption (C_{max}) was increased by 56% while the extent of absorption (AUC) was unchanged.

The extent of 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 mcg/mL to 7% at 2 mcg/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 mcg/mL) than those in serum (< 0.1 mcg/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.

Following oral administration of a single Azithromycin 1200 mg dose (two 600 mg tablets), the mean maximum concentration of azithromycin in peripheral leukocytes was 140 ng/mL. Concentrations remained above 32 ng/mL for approximately 60 hr.

The absolute bioavailability of two 600 mg Azithromycin tablets was 34%. Administration of two 600 mg tablets with food increased C_{max} by 31% while the extent of absorption (AUC) was unchanged.

Children:

When azithromycin was dosed at 10 mg/kg day 1, followed by 5 mg/kg days 2 through 5 in children 1 to 15 years old, the mean pharmacokinetic parameters on day 5 were:

Pharmacokinetic parameters in pediatric subjects on day 5
at dosage 10 mg/kg (day 1) and 5 mg/kg (days 2-5)*

Age 1-5			Age 5-15		
C_{max} (mcg/mL)	T_{max} (hrs)	AUC_{0-24} (mcg•hr/mL)	C_{max} (mcg/mL)	T_{max} (hrs)	AUC_{0-24} (mcg•hr/mL)
0.216	1.9	1.822	0.383	2.4	3.109

* Dose administered as Powder for Oral Suspension

Two clinical studies were conducted in 68 children aged 3-16 years with pharyngitis/tonsillitis to determine the pharmacokinetics and safety of azithromycin for oral suspension in children when given 60 mg/kg in divided doses over either 3 or 5 days.

Both studies were open, non-comparative trials. Drug was administered following a low-fat breakfast in order to assess the effect of food on absorption and safety.

The first study consisted of 35 pediatric subjects treated with 20 mg/kg/day (maximum daily dose of 500 mg) for 3 days of whom 34 subjects were evaluated for pharmacokinetics.

In the second study, 33 pediatric subjects received doses of 12 mg/kg/day (maximum daily dose of 500 mg) for 5 days of whom 31 subjects were evaluated for pharmacokinetics.

In both studies, azithromycin levels were determined over a 24-hour period following the last daily dose. Subjects weighing above 25.0 kg in the 3-day study or 41.7 kg in the 5-day study received the maximum adult daily dose of 500 mg. Eleven subjects (weighing 25.0 kg or less) in the first study and 17 subjects (weighing 41.7 kg or less) in the second study received a total dose of 60 mg/kg. The following table shows pharmacokinetic data in the subset of children who received a total dose of 60 mg/kg.

	3-Day Regimen (20mg/kg x 3 days)	5-Day Regimen (12 mg/kg x 5 days)
n	11	17
C_{max} (mcg/mL)	1.05 ± 0.44[a]	0.534 ± 0.361[a]
T_{max} (hr)	3 ± 2.0[a]	2.2 ± 0.8[a]
AUC_{0-24} (mcg_hr/mL)	7.92 ± 2.87[a]	3.94 ± 1.90[a]
a Arithmetic means		

Single dose pharmacokinetics in children given doses of 30 mg/kg has not been studied.

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

	Minimum Inhibitory Concentrations (mcg/mL)			**Disk Diffusion (zone diameters in mm)**		
Pathogen	S	I	R	S	I	R
Haimophilus influenzaea[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**	**LD50** (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
ORAL in Adult Animals					
Rat (Adult)	Oral (gavage)	50100200	10/sex	36 days + reversibility	Cecal enlargement was dose-related. Elevated serum hepatic enzyme (SGPT, SGOT, SDH, and 5'NT) levels were dose- and time-related at high and mid levels; marginal SGPT elevations only were observed in 2 rats at the low dose. Histological examination of tissues from 6/sex of mid-and high-dose and 10/sex of low-dose rats revealed evidence of phospholipidosis in bile ducts (8/20, 12/12, 12/12 low-, mid-, and high-dose rats, respectively) and hepatocytes (10/12 high dose only), fatty change (4/20, 10/12, 11/12 in low-, mid-, and high-doses, respectively), and necrosis of single hepatocytes (6/12 and 11/12, respectively, in mid- and high-dose only). Phospholipidosis also occurred in high-dose rats in the tubular cells of the renal medulla 12/12, spleen 2/12, thymus 2/12, and choroid plexus 10/12; 3/12 rats at 100 mg/kg and 10/12 at 200 mg/kg exhibited mesenteric sinusoidal lymph node phospholipidosis. Phospholipidosis is characterized by accumulation of drug-lipid complexes in lysosomes where they form ultramicroscopic lamellated structures typified at the microscopic level by vacuolated macrophage or tissue cells. The remaining animals (4/sex in control, mid- and high-dose groups) were sacrificed 20 days after termination of treatment. Phospholipidosis was still observable in the renal tubules of 7/8 high dose animals

					and in 1/8 mid-dose animals and in the bile duct of 1/8 high-dose animals. Fatty change was still detectable in livers of 5/8 and 6/8 mid- and high-dose animals, respectively. Megaceca also regressed following drug withdrawal.

SPECIES	**ROUTE**	**DOSE mg/kg/day**	**ANIMALS PER DOSE LEVEL**	**DURATION**	**FINDINGS**
Dog (Adult)	Oral (gavage)	2550100	3/sex	36 days	Transaminase levels (SGPT, SGOT) were elevated in a dose-related pattern at the 2 higher doses. ALP (alkaline phosphatase), gamma-GTP, and SDH elevations occurred only at the high dose. Histological examination of tissues revealed the presence of phospholipidosis in all treated animals. It occurred in six or more organs in all 100 mg/kg/day animals. These included kidney, liver, spleen, gallbladder, thymus, mesenteric lymph node, esophagus, uterus and cervix as well as lymphatic nodules of gastrointestinal tissues. At the low dose of 25 mg/kg phospholipidosis was confined to the spleen, gallbladder, thymus, mesenteric lymph node and the lymphatic nodules of the ileum and colon.
Rat (Adult)	Oral (gavage)	40 (10 days on 10 days off) 0 continuous 10 " 20 "	15/sex 25/sex	190-193 days + reversibility	Sporadic mild elevations in SGOT and SGPT occurred in all dose groups during and after the treatment period. There was no evidence of phospholipidosis.

Dog (Adult)	Oral (gavage)	40 (10 days on 10 days off) 0 10 20	4/sex 4/sex + 2/sex+ 2/sex	190 days + reversibility 1 month 2 months	Sporadic elevations in SGPT levels occurred at 20 and 40 mg/kg only. Phospholipidosis, was minimal to mild in the kidney, liver, gallbladder, spleen, mesenteric lymph node, esophagus and prostate of almost all 40 and 20 mg/kg dogs. In dogs dosed for 6 months at 20 mg/kg/day complete reversibility of phospholipidosis of the kidney, liver, and spleen with minimal phospholipidosis still present in the gallbladder and esophagus was demonstrated in the animals sacrificed 2 months after the end of treatment.

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Dog (Adult)	Oral (gavage)	30100	6/sex	6 months 2 months + reversibility	Selected animals were sacrificed at end of treatment; sacrifices (1/sex/dose level) were also performed 1 month (100 mg/kg), 2 months (30 mg/kg) and 4 months (100 mg/kg) post-treatment. Necropsies of the remaining animals were performed 7 months (30 mg/kg) and 11 months (100 mg/kg) post treatment. Drug treatment of high dose dogs was terminated at 2 months (61 doses) due to intolerance. Serum chemistry changes including substantial increases in liver enzymes (SGPT, SGOT, ALP, SDH, gamma-GPT) and BUN as well as mild decreases in erythrocytic parameters (RBC, Hb, Hct) and the presence of atypical eosinophil and vacuolated lymphocytes returned to normal range within 2 months of withdrawal from treatment. The low dose was well tolerated. Dose-related effects on tapetum lucidum reflectivity ranged from trace (low dose) to moderate (high dose) decoloration, dulled reflectivity and loss of the tapetum-choroid junctional zone. Following cessation of treatment, most animals showed improvements in these ocular changes. Normal junctional tissue was evident in high dose animals 4 months after withdrawal. At no time was there ophthalmoscopic evidence of an effect on vision. Histological examination at the end of treatment showed phospholipidosis. In the eye it included the tapetum, neurons of the retinal ganglion cell, inner nuclear, inner and outer plexiform layers, and mural pericytes of the superficial retinal vasculature. The rod and cone segments and retinal pigmented epithelium were generally spared. Also affected were dorsal root ganglion, liver, gallbladder, kidneys, spleen and pancreas and, at the high dose only gastrointestinal tract, mesenteric lymph nodes, thymus, aorta, heart, salivary gland and lung. Dose-related degenerative changes were observed only in the liver (focal necrosis of hepatocytes and bile duct epithelium), gallbladder (hyperplasia) and kidneys (glomerulonephrosis). All of the above effects, with the exception of those on the retina, dorsal root ganglion and gallbladder which all abated in severity, were completely reversible on drug withdrawal from both low and high dose animals. In general, these changes were consistent with the relative drug/tissue concentrations attained and their decline following withdrawal. Biochemical measurements

					of spleen, liver, kidney and retinal phospholipids of animals treated with 30 mg/kg drug for 6 months showed a difference from control only for the spleen, the tissue with the highest drug concentration. This experiment demonstrates that drug-induced phospholipidosis, although dose-dependent in tissue distribution and intensity, does not represent a toxic end point per se but is responsible for the cumulative tissue deposition of azithromycin.

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Dog (Adult)	Oral (gavage)	30100	6/sex	6 months + reversibility	Intermittent dosing: (10 days on, 10 days off drug) for: 5 months (100 mg), 6 months (30 mg). This experiment demonstrates that intermittent administration (to mimic a hypothetical clinical dose regime) produced less phospholipidosis than azithromycin administered continuously.
ORAL in Neonatal Animals Oral Subacute/Neonatal RATS					
Rat (Neonatal 4 days)	Oral (gavage)	102040	10/sex 10/sex	18 days (day 4 to day 21 postpartum) 10 days(day 4 to day 13 postpartum)	No treatment-related clinical signs were observed. Males given the dose of 20 mg/kg weighed significantly more than the vehicle controls on day 7 and from day 13 to sacrifice on day 22 postpartum. A slight increase in the incidence and prominence of periportal vacuolization appeared treatment related. However, the vacuolization observed in the treated animals was qualitatively no different from that seen in the vehicle-treated controls. There was no histologic evidence of phospholipidosis.
Rat (Neonatal 4 days)	Oral (gavage)	406080	10/sex	18 days (day 4 to day 21 postpartum)	The purpose of this study was to determine the dose at which there was evidence of phospholipidosis. There were no clinical signs of toxicity or effects on body weight. The administration of azithromycin to neonatal rats by gavage for 18 days produced clear evidence of phospholipidosis of bile duct epithelium in a dose related manner in males and females at all dose levels. Hepatocellular vacuolation, which may also be a manifestation of phospolipidosis, was apparent in most males given azithromycin but was not observed in the vehicle-treated males. However, in the female rats, hepatocellular vacuolation was seen in the azithromycin treated animals as well as in those given the vehicle, suggesting that it does not represent phospholipidosis in this study.

Rat (Neonatal 4 days)	Oral (gavage)	100120140	10/sex	18 days (day 4 to day 21 postpartum)	In the previous study, evidence of dose-related phospholipidosis was observed in only the bile duct epithelium of males and females at each dose. The purpose of the present study was to attempt to identify doses at which phospholipidosis is produced in more than one organ and/or tissue. There were no clinical signs of toxicity. The administration of azithromycin to neonatal rats by gavage for 18 days produced clear evidence of phospholipidosis of bile duct epithelium in all males and females at each dose. The hepatocellular vacuolation apparent in some animals from each dose was above that seen in the vehicle-treated animals and also appeared to be a manifestation of phospholipidosis. In addition, myocardial phospholipidosis was evident in a majority of high and intermediate dose males and females and in a single low dose male.
Rat (Neonatal 4 days)	Oral (gavage)	3070140	20/sex 10/sex 10/sex 20/sex	18 days (day 4 to day 21 postpartum) and 30 Day Reversibility Period for 10/sex in groups treated by 0 and 140 mg/kg.	The purpose of this study was to determine whether phospholipidosis, previously diagnosed by light and electron microscopic examination in neonatal animals treated with azithromycin could be confirmed biochemically by measurement of tissue phospholipid levels. All low and intermediate dose animals, plus one half of the high dose and vehicle-treated control animals were sacrificed on Day 22 postpartum. The remaining rats were sacrificed on Day 52 postpartum after a 30-day reversibility period. Assays for drug in serum, liver and brain samples obtained from pups sacrificed 24 hours after the last dose revealed that the azithromycin concentrations increased with dose and were highest in the liver, lower in the brain and lowest in serum. The concentration of azithromycin in the serum, liver and brain had declined substantially when next measured 31 days after cessation of dosing of the high dose group. Azithromycin was still detectable in the liver and brain, but serum concentrations were generally below the limit of detection. Despite 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 no greater than those of the vehicle-treated controls at both the end of the dosing period and after the one month reversibility period. The administration of azithromycin to neonatal Long-Evans rats for 18 days produced light microscopic evidence (vacuolation) of phospholipidosis in bile duct epithelium, hepatocyte cytoplasm, cardiac muscle, smooth muscle of the duodenum and uterus and in the choroid plexus. These changes, seen in the rats sacrificed on the day after the last dose (i.e., Day 22 postpartum), were

					evident primarily in high dose animals, and, except for the bile ducts, at a much reduced incidence in intermediate dose animals. The only histological evidence of phospholipidosis at the low dose was in the bile ducts of a single male. No light microscopic evidence of phospholipidosis was visible in the high dose animals examined following a 30 day reversibility period. It is concluded that, in spite of histological indications of phospholipidosis and high tissue concentrations of azithromycin, there was no biochemical evidence of phospholipid accumulation in affected organs (brain and liver).

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Oral Subacute/Neonatal DOGS					
Dog (Neonatal 3-5 days)	Oral (gavage)	103060	3/sex	5 weeks	Pups were removed from their mothers 2 hrs prior to dosing and then returned to their litters immediately thereafter. They were observed daily for developmental landmarks (eye opening, upper canine tooth eruption, ear opening and when pup "leaves the pack"). Body weights were obtained daily. Blood samples for clinical pathology profiles were drawn pretest and prior to dosing on Days 14 and Days 28 or 30. Blood samples for serum drug level determinations were obtained on Days 2, 22 or 24. Ophthalmological examinations were conducted at termination of the treatment period. All dogs were anesthetized and exsanguinated on Days 35 or 37 for necropsy. Selected organs were weighed. Tissues were taken for assays of drug concentrations and for histopathological evaluation.. With the exception of a possible lag in body weight gain of female pups, there were no treatment-related effects on developmental landmarks, hematology, clinical chemistry, ophthalmological findings nor upon organ weights. Mean blood concentrations of azithromycin, generally related to dose, especially at 10 and 30 mg/kg, were somewhat higher on Day 24 than on Day 2. Evidence of phospholipidosis, previously observed in other azithromycin animal studies, was detected microscopically as swollen vacuolated cells due to myelin figures, i.e., large lysosomes containing aggregates of undigested membranes. As in adult dogs, the dose related phospholipidosis was seen in selected tissues. The effects were minimal to mild at 10 mg/kg. Phospholipidosis was not observed in the brain or in liver. Other dose related lesions were swelling and vacuolation of cells of the tapetum lucidum of the eye due to tapetal rodlet swelling and dissolution, and degeneration and necrosis of epithelial cells lining the gallbladder. The latter occurred only in mid- and high dose animals. Twenty four (24) hrs after the last dose, tissue levels of drug were much higher than in serum with mean concentrations in the order of serum=brain <eye <kidney <liver=spleen.

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Oral Subacute/Neonatal DOGS					
Dog (Neonatal 3-5 days)	Oral (gavage)	103060	4/sex	11 days	Two/sex/group were necropsied at the end of the dosing period. The remaining animals were maintained for an additional 1 month dose free period prior to being necropsied. There were no treatment-related effects on developmental landmarks, body weight, hematology, clinical chemistry or organ weights. Evidence of phospholipidosis (PL) was observed microscopically at the end of the treatment period in the spleen of dogs given 30 or 60 mg/kg/day and at all dose levels in the neurons of the retina and sympathetic ganglion. The incidence and severity was generally dose-related. There was no evidence of PL in the liver or brain. At the end of the 1 month drug free period, the retina and sympathetic ganglion of animals given 10 mg/kg/day had no evidence of PL. PL was still evident, although at a reduced incidence and severity, at dose levels of 30 and 60 mg/kg/day. Following a 1-month drug-free period, tissue concentrations of azithromycin in the liver, kidney and spleen were approximately 1.5% of those observed at the end of dosing, indicating elimination of azithromycin from these organs. The extent of elimination from the retina could not be accurately quantitated in this study. However, the reversibility of the PL in the retina would suggest that elimination was occurring.
Dog (Neonatal 3-5 days) and 25 days	Oral (gavage)	1060	4/sex (3-5 days) 2/sex (25 days)	11 days and 30 Day Recovery Period	The purpose of this study was to further characterize the absorption and elimination of azithromycin from the choroid/retina of neonatal beagle dogs. At the end of the treatment period, 2/sex from the 3-5 day old dogs and all of the older dogs were necropsied. The remaining dogs were maintained for a 1-month dose-free period to further document the elimination of azithromycin from the retina. There were no treatment-related effects on developmental landmarks, body weight, hematology or clinical chemistry. Mean whole blood concentrations of azithromycin were dose related and increased between days 2 and 11. Liver and choroid/retina of all animals contained dose related concentrations of azithromycin. In general, these were higher in the dogs 3-5 days of age. Concentrations in the choroid/retina were less than those in the previous study (WEL 90-252) and were within historical predictions, while liver concentrations were similar to previous studies and within expectations. At the end of the one month treatment free period, the tissue concentrations of azithromycin had decreased and were within expected levels.

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 EXPLORATORY TOXICOLOGY					
Rat	Oral (gavage)	10 0 40 200 chloroquine: 25	5/sex 10/sex 10/sex	5 days	Animals (5/sex/group) from the 40 and 200 mg/kg azithromycin and chloroquine groups were removed from treatment for 23 days to study the effect of reversibility. No elevations in tissue phospholipid levels or hepatic necrosis were seen at any dose. Myelin figures were seen in liver, bile ducts and retinal pigmented epithelium. One chloroquine animal had a few myelin figures in retinal ganglion cells.
Rat	Oral (gavage)	0 200	10/sex	42 days	Phospholipid levels were significantly elevated above control in liver, kidney, spleen and lymphocytes ($p<.05$).

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Dog	Oral (gavage)	0 azithromycin: 10 40 200 chloroquine: 15	1/sex 2/sex 1/sex	5 days	The livers of the 200 mg/kg azithromycin animals showed the highest drug concentration (>4000 mcg/g) of any tissues in the series of experiments. This was accompanied by a 38% elevation in hepatic phospholipids, multifocal hepatic necrosis and marked accumulation of myelin figures in both hepatocytes and bile duct epithelium. Myelin figures were also seen in the liver at 40 mg/kg azithromycin (drug concentration = 817 mcg/g) and with chloroquine but not with 10 mg/kg azithromycin. Azithromycin caused the formation of myelin figures in retinal ganglion cells from equivocal at 10 mg/kg to moderate at 200 mg/kg. The effect was less severe than chloroquine, 15 mg/kg, which caused a marked degree of myelin figure formation in retinal ganglion cells.
Dog	Oral (gavage)	0 azithromycin: 30 erythromycin: 400	1/sex 2/sex 2/sex	5 days	Reversal periods of 22 and 36 days were included for those animals treated with azithromycin (1/sex/period). Tissue phospholipids were elevated in the livers of erythromycin animals only. Myelin figures or enlarged lysosomes were seen to a minimal extent in the retinal ganglion cells, liver and choroid plexus of azithromycin animals and in the liver of erythromycin dogs. The drug concentrations were markedly reduced at the end of the reversal periods and no myelin figures remained in the liver or choroid plexus.
Dog	Oral (gavage)	erythromycin: 400	2/sex	5 days	Dogs were necropsied immediately after the last dose. A few myelin figures were seen in the retinal ganglion cells of one animal.
Dogs Atapetal Tapetal	Oral	azithromycin: 0 100 0 100	 3 (2M,1F) 3 (2F, 1M) 3 (2M, 1F) 3 (2F, 1M)	35-36 days	Ophthalmoscopic examinations revealed no changes in the atapetal dogs while tapetal decolouration, dulling of normal reflectivity and loss of colour difference at the tapetal junctional zone was observed in the tapetal dogs. Light and/or electron microscopic examination of the retinas of both tapetal and atapetal dogs revealed signs of phospholipidosis in ganglion cells, the inner nuclear layer and inner and outer plexiform layers. Other changes observed in both tapetal and atapetal dogs are comparable to those observed in previous studies at the same dose.
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 LEVEL	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 postnatal 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)	30 70 0 140	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 mcg/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 mcg/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 to 360 mcg/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 mcg/mL in the presence and 7.5 mcg/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.

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

PrAZITHROMYCIN FOR INJECTION, USP
Powder for Injection 500 mg azithromycin per vial

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 monohydrate.
Non-medicinal ingredients: 392 mg (for ADD Vantage) or 384.6 mg (for Flip Top) of anhydrous citric acid and sodium hydroxide for pH adjustment.

Azithromycin for Injection, USP comes in the following dosage forms:
Azithromycin for injection (as azithromycin monohydrate), 500 mg/vial or 100 mg/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 has been reported to be 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);
- 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 will always be prepared and given to you by a doctor or a healthcare professional.

Azithromycin for Injection, USP 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 healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Flip Top Vial:
Reconstituted Solution: Stable for 24 hours stored at controlled room temperature (20 to 25°C).
Diluted solution: Stable for 24 hours between 20 and 25°C, or for 7 days if stored under refrigeration (5°C). For single-use only. Discard any unused portion after use.

ADD-Vantage Vial:
Reconstituted Solution: Stable for 24 hours at controlled room temperature (20 to 25°C), or 7 days if stored under refrigeration (5°C).

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 Government of Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp) or by calling 1-800-463-6001.

This leaflet was prepared by Hospira Healthcare Corporation.

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