

## PRODUCT MONOGRAPH

Pr **AZITHROMYCIN**

Azithromycin Monohydrate

Tablets 250 mg and 600 mg

Antibiotic

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# AZITHROMYCIN

Azithromycin Monohydrate

## PART I: HEALTH PROFESSIONAL INFORMATION

### SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form / Strength     | Clinically Relevant Nonmedicinal Ingredients  |
|-------------------------|----------------------------|---|
| Oral                    | tablet /<br>250 mg, 600 mg | N/A<br><br><i>For a complete listing see Dosage Forms, Composition and Packaging section.</i> |

### INDICATIONS AND CLINICAL USE

AZITHROMYCIN (azithromycin monohydrate) is indicated for treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the following diseases and specific conditions. As recommended dosages, duration of therapy, and applicable patient populations vary among these infections, see DOSAGE AND ADMINISTRATION for specific dosing recommendations.

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

#### **ADULTS:**

##### **Treatment**

##### **Pharyngitis and tonsillitis:**

Pharyngitis and tonsillitis caused by *Streptococcus pyogenes* (group A  $\beta$ -hemolytic streptococci) occurring in individuals who cannot use first line therapy.

NOTE: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. AZITHROMYCIN is often effective in the eradication of susceptible strains of streptococci from the oropharynx. However, data establishing the efficacy of AZITHROMYCIN in the subsequent prevention of rheumatic fever are not available at present.

**Acute bacterial exacerbations of chronic obstructive pulmonary disease:**

Acute bacterial exacerbations of chronic obstructive pulmonary diseases caused by *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

**Community-acquired pneumonia:**

Community-acquired pneumonia caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* in patients for whom oral therapy is appropriate.

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

**Uncomplicated skin and skin structure infections:**

Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus*, *Streptococcus pyogenes* or *Streptococcus agalactiae*.

**Genitourinary tract infections:**

Urethritis and cervicitis due to *Neisseria gonorrhoeae* or *Chlamydia trachomatis*. Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established. Patients should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

**Prevention of Disseminated *Mycobacterium Avium* Complex (MAC) Disease:**

AZITHROMYCIN, taken at a dose of 1200 mg weekly, alone or in combination with rifabutin at its approved dose, is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in persons with advanced HIV infections (see DETAILED PHARMACOLOGY, Clinical Trials).

Because some strains are resistant to azithromycin, when applicable, appropriate culture and susceptibility tests should be initiated before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with AZITHROMYCIN may be initiated before results of these tests are known; once the results become available, antibiotic treatment should be

adjusted accordingly.

**Geriatrics:**

(See **WARNINGS AND PRECAUTIONS - Special Populations**).

**CONTRAINDICATIONS**

AZITHROMYCIN (Azithromycin Monohydrate) is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, other macrolide antibacterial agents, or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the Product Monograph.

**WARNINGS AND PRECAUTIONS**

**General**

Serious allergic reactions, including angioedema, anaphylaxis and dermatological reactions including Steven's Johnson syndrome and toxic epidermolysis 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* (Azithromycin Monohydrate). 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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents including Azithromycin and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis". After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile*.

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 in these patients is not recommended.

Rare cases of acute hepatic necrosis requiring liver transplant or causing death have been reported in patients following treatment with oral azithromycin.

Since liver is the major route of elimination for Azithromycin the use of AZITHROMYCIN (Azithromycin Monohydrate) should be undertaken with caution in patients with impaired hepatic function.

Due to limited data in subjects with GFR < 10 mL/min, caution should be exercised when prescribing oral azithromycin in these patients (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

Prolonged cardiac repolarisation and QT interval imparting a risk of developing cardiac arrhythmia and *torsades de pointes* can be seen in treatment with other macrolides. A similar effect has been reported with azithromycin and can not be completely ruled out. There is information that 'QT Related Adverse Events' may occur in some patients receiving azithromycin, although these adverse events have not been reported in clinical trials with azithromycin. There have been spontaneous reports from post-marketing experience of prolonged QT interval and *torsades de pointes* (see ADVERSE REACTIONS - Post marketing Experience). These include but are not limited to: one AIDS patient dosed at 750 mg to 1g daily experienced prolonged QT interval and *torsades de pointes*; a patient with previous history of arrhythmias who experienced *torsades 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.

### **Special Populations**

**Pregnant Women:** Animal studies have demonstrated that azithromycin crosses the placenta. Safety of Azithromycin for use in human pregnancy has not been established.

**Nursing Women:** There are no data on secretion in breast milk. Safety of Azithromycin for use in human lactation has not been established.

**Geriatrics (>65 years of age):** 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.

### **ADVERSE REACTIONS**

#### **Adverse Drug Reaction Overview**

The majority of side effects observed in controlled clinical trials involving patients treated with azithromycin were of a mild and transient nature. Approximately 0.7% of adult patients (n=3812) from the 5-day multiple dose clinical trials discontinued azithromycin therapy because

of drug related side effects. Discontinuation rates were slightly higher for PID patients receiving concomitant metronidazole therapy (4%).

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

Most of the side effects leading to discontinuation in patients on 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.*

### **Oral Regimen: Adults**

#### **Multiple-dose Regimens:**

In adult patients, the most common treatment-related side effects in patients receiving the 3 or 5 day oral multiple-dose regimens of azithromycin were related to the gastrointestinal system with diarrhea/loose stools (4-5%), abdominal pain (2-3%), vomiting (1%) and nausea (3-4%).

Treatment-related side effects that occurred with a frequency of 1% or less include:

|                          |  |
|--------------------------|--|
| <i>Cardiovascular:</i>   | hypertension   |
| <i>Gastrointestinal:</i> | dry mouth, esophagitis, gastroenteritis, rectal hemorrhage, cholestatic jaundice |
| <i>Genitourinary:</i>    | menorrhagia, urinary frequency, vaginitis  |
| <i>Special senses:</i>   | conjunctivitis   |
| <i>Nervous System:</i>   | dizziness  |
| <i>Allergic:</i>         | pruritis   |

**Single 1-gram Dose Regimen:**

In adult patients (n=904), side effects that occurred on the single one-gram dosing regimen of azithromycin with a frequency greater than 1% included diarrhea (6.1%), nausea (4.9%), abdominal pain (4.9%), vomiting (1.7%), vaginitis (1.3%), loose stools (1.2%), and dyspepsia (1.1%).

**Single 2-gram Dose Regimen:**

Overall, the most common side effects in patients receiving a single 2-gram dose of azithromycin were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of a 1% or greater included nausea (18.2%), diarrhea/loose stools (13.8%), vomiting (6.7%), abdominal pain (6.7%), vaginitis (2.2%), dyspepsia (1.1%), and dizziness (1.3%). The majority of these complaints were mild in nature.



**Prevention of *Mycobacterium Avium* Complex (MAC) Disease:**

Chronic therapy with azithromycin 1200 mg weekly regimen: The nature of side effects seen with the 1200 mg weekly dosing regimen for the prevention of *Mycobacterium avium* complex infection in severely immunocompromised HIV-infected patients were similar to those seen with short-term dosing regimens.

**Incidence<sup>1</sup> (%) of Treatment Related\* Adverse Events\*\* in HIV-Infected Patients Receiving Prophylaxis for Disseminated MAC**

|                                 | Study 155         |  | Study 174                                   |  |  |
|---------------------------------|-------------------|--|---|--|--|
|                                 | Placebo<br>(n=91) | Azithromycin<br>1200mg<br>weekly<br>(n=89) | Azithromycin<br>1200mg<br>weekly<br>(n=233) | Rifabutin<br>300mg<br>daily<br>(n=236) | Azithromycin<br>& Rifabutin<br>(n=224) |
| Mean Duration of Therapy (days) | 303.8             | 402.9                                      | 315   | 296.1                                  | 344.4                                  |
| Discontinuation of Therapy (%)  | 2.3               | 8.2  | 13.5  | 15.9                                   | 22.7                                   |
| <b>AUTONOMIC NERVOUS SYSTEM</b> |                   |  |   |  |  |
| Mouth Dry                       | 0                 | 0  | 0   | 3.0                                    | 2.7                                    |
| <b>CENTRAL NERVOUS SYSTEM</b>   |                   |  |   |  |  |
| Dizziness                       | 0                 | 1.1  | 3.9   | 1.7                                    | 0.4                                    |
| Headache                        | 0                 | 0  | 3.0   | 5.5                                    | 4.5                                    |
| <b>GASTROINTESTINAL</b>         |                   |  |   |  |  |
| Diarrhea                        | 15.4              | 52.8                                       | 50.2  | 19.1                                   | 50.9                                   |
| Loose Stools                    | 6.6               | 19.1                                       | 12.9  | 3.0                                    | 9.4                                    |
| Abdominal Pain                  | 6.6               | 27   | 32.2  | 12.3                                   | 31.7                                   |
| Dyspepsia                       | 1.1               | 9  | 4.7   | 1.7                                    | 1.8                                    |
| Flatulence                      | 4.4               | 9  | 10.7  | 5.1                                    | 5.8                                    |

\* Includes those events considered possibly or probably related to study drug

\*\* > 2% adverse event rates for any group

<sup>1</sup> Reflects the occurrence of ≥ 1 event during the entire treatment period

**Incidence<sup>1</sup> (%) of Treatment Related\* Adverse Events\*\* in HIV-Infected Patients Receiving Prophylaxis for Disseminated MAC : Continued**

|  | Study 155         |  | Study 174                                   |  |  |
|--|-------------------|--|---|--|--|
|  | Placebo<br>(n=91) | Azithromycin<br>1200mg<br>weekly<br>(n=89) | Azithromycin<br>1200mg<br>weekly<br>(n=233) | Rifabutin<br>300mg<br>daily<br>(n=236) | Azithromycin<br>& Rifabutin<br>(n=224) |
| <b>GASTROINTESTINAL:<br/>CONTINUED</b> |                   |  |   |  |  |
| Nausea                                 | 11                | 32.6                                       | 27.0  | 16.5                                   | 28.1                                   |
| Vomiting                               | 1.1               | 6.7  | 9.0   | 3.8                                    | 5.8                                    |
| <b>GENERAL</b>                         |                   |  |   |  |  |
| Fever                                  | 1.1               | 0  | 2.1   | 4.2                                    | 4.9                                    |
| Fatigue                                | 0                 | 2.2  | 3.9   | 2.1                                    | 3.1                                    |
| Malaise                                | 0                 | 1.1  | 0.4   | 0                                      | 2.2                                    |
| <b>MUSCOSKELETAL</b>                   |                   |  |   |  |  |
| Arthralgia                             | 0                 | 0  | 3.0   | 4.2                                    | 7.1                                    |
| <b>PSYCHIATRIC</b>                     |                   |  |   |  |  |
| Anorexia                               | 1.1               | 0  | 2.1   | 4.2                                    | 4.9                                    |
| <b>SKIN &amp; APPENDAGES</b>           |                   |  |   |  |  |
| Pruritus                               | 3.3               | 0  | 3.9   | 3.4                                    | 7.6                                    |
| Rash                                   | 3.2               | 3.4  | 8.1   | 9.4                                    | 11.1                                   |
| Skin discolouration                    | 0                 | 0  | 0   | 2.1                                    | 2.2                                    |
| <b>SPECIAL SENSES</b>                  |                   |  |   |  |  |
| Tinnitus                               | 4.4               | 3.4  | 0.9   | 1.3                                    | 0.9                                    |
| Hearing Decreased                      | 2.2               | 1.1  | 0.9   | 0.4                                    | 0                                      |
| Taste Perversion                       | 0                 | 0  | 1.3   | 2.5                                    | 1.3                                    |

\* Includes those events considered possibly or probably related to study drug

\*\* > 2% adverse event rates for any group

<sup>1</sup> Reflects the occurrence of ≥ 1 event during the entire treatment period

Side effects related to the gastrointestinal tract were seen more frequently in patients receiving azithromycin than in those receiving placebo or rifabutin. In one of the studies, 86% of diarrheal episodes were mild to moderate in nature with discontinuation of therapy for this reason occurring in only 9/233 (3.8%) of patients.

### **Oral Regimen: Adults:**

The most common side effects (greater than 1%) in adult patients who received sequential IV/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%).

In adult women who received sequential 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:

|                          |  |
|--------------------------|--|
| <b>Allergic:</b>         | bronchospasm   |
| <b>Gastrointestinal:</b> | dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis |
| <b>Nervous System:</b>   | headache, somnolence   |
| <b>Special Senses:</b>   | taste perversion   |

### **Abnormal Hematologic and Clinical Chemistry Findings**

#### **Oral Therapy:**

##### **Adults:**

Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials in patients were reported as follows:

With an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, monocytes, albumin and blood glucose, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT), BUN, creatinine, blood glucose, platelet count, eosinophils and monocytes.

With an incidence of less than 1%: leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, LDH and phosphate.

The majority of subjects with elevated serum creatine also had abnormal values at baseline.

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

In multiple-dose clinical trials involving more than 4500 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities, one for treatment-related elevated transaminases and triglycerides and one because of a renal function abnormality.

**Prevention of *Mycobacterium Avium* complex (MAC) Disease:**

In these immunocompromised patients with advanced HIV infection, it was sometimes necessary to assess laboratory abnormalities developing on study with additional criteria if baseline values were outside the normal range.

**Prophylaxis Against Disseminated MAC Abnormal Laboratory Values**

| Criteria <sup>a</sup>               | Study 155           |  | Study 174                                     |  |  |
|-------------------------------------|---------------------|--|---|--|--|
|                                     | Placebo<br>(n = 88) | Azithromycin<br>1200mg<br>weekly<br>(n = 89) | Azithromycin<br>1200mg<br>weekly<br>(n = 208) | Rifabutin<br>300mg<br>daily<br>(n = 205) | Azithromycin<br>& Rifabutin<br>(n = 199) |
| Hemoglobin < 0.8 x LLN <sup>b</sup> | 31%                 | 30%  | 19%   | 26%                                      | 21%                                      |
| Platelet Count < 0.75 x LLN         | 19%                 | 16%  | 11%   | 10%                                      | 16%                                      |
| WBC Count < 0.75 x LLN              | 48%                 | 49%  | 60%   | 53%                                      | 60%                                      |
| Neutrophils < 0.5 x LLN             | 16%                 | 28%  | 23%   | 20%                                      | 29%                                      |
| < 500/mm <sup>3</sup>               | 6%                  | 13%  | 5%  | 6%                                       | 8%                                       |
| AST (SGOT) > 2.0 x ULN <sup>c</sup> | 28%                 | 39%  | 33%   | 18%                                      | 30%                                      |
| > 200 U/L                           | 10%                 | 8%   | 8%  | 3%                                       | 6%                                       |
| ALT (SGPT) > 2.0 x ULN              | 24%                 | 34%  | 31%   | 15%                                      | 27%                                      |
| > 250 U/L                           | 2%                  | 6%   | 8%  | 2%                                       | 6%                                       |

<sup>a</sup> secondary criteria also applied if baseline abnormal, as follows: Hemoglobin, 10% decrease; Platelet, 20% decrease; WBC count, 25% decrease; Neutrophils, 50% decrease; AST (SGOT), 50% increase; ALT (SGPT), 50% increase

<sup>b</sup> lower limit of normal

<sup>c</sup> upper limit of normal

In a phase I drug interaction study performed in normal volunteers, 1 of 6 subjects given the combination of azithromycin and rifabutin, 1 of 7 given rifabutin alone and 0 of 6 given azithromycin alone developed a clinically significant neutropenia (<500 cells/mm<sup>3</sup>).

### **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:

|                          |   |
|--------------------------|---|
| <i>Allergic:</i>         | Arthralgia, edema, anaphylaxis (with rare reports of fatalities), serum sickness, urticaria, vasculitis, angioedema, pruritus;  |
| <i>Cardiovascular:</i>   | Cardiac arrhythmias (including ventricular tachycardia), palpitations, hypotension. There have been rare reports of QT prolongation and <i>torsades de pointes</i> 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); |
| <i>Gastrointestinal:</i> | Anorexia, constipation, dehydration, vomiting/diarrhea rarely resulting in dehydration, pancreatitis, pseudomembranous colitis, rare reports of tongue discoloration;   |
| <i>General:</i>          | Asthenia, paresthesia, fatigue, muscle pain;  |
| <i>Genitourinary:</i>    | Interstitial nephritis, acute renal failure, nephrotic syndrome, vaginitis;   |
| <i>Hematopoietic:</i>    | Thrombocytopenia;   |
| <i>Liver/Biliary:</i>    | 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 rarely resulted in death;   |
| <i>Nervous System:</i>   | Aggressive reaction, anxiety, dizziness, hyperactivity, seizure, convulsions, nervousness, agitation and syncope  |
| <i>Skin/Appendages:</i>  | Serious skin reactions including erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis;   |
| <i>Special Senses:</i>   | Hearing disturbances including hearing loss, deafness and/or tinnitus, vertigo, reports of taste perversion, abnormal vision.   |

## **DRUG INTERACTIONS**

### **Drug-Drug Interactions**

#### **Antacids**

Aluminum and magnesium containing antacids (Maalox<sup>®</sup>) reduce the peak serum levels but not the extent of azithromycin absorption. AZITHROMYCIN (Azithromycin Monohydrate) and these drugs should not be taken simultaneously.

#### **Atorvastatin**

In healthy volunteers, co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter plasma concentrations of atorvastatin (based on HMG CoA-reductase inhibition assay).

#### **Carbamazepine**

In 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**

In healthy male volunteers, co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg a steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

#### **Cimetidine**

Administration of cimetidine (800 mg) two hours prior to Azithromycin had no effect on Azithromycin absorption.

#### **Coumarin-Type Oral Anticoagulants**

In clinical trials, azithromycin did not affect the prothrombin time response to a single dose of warfarin.

During the post-marketing period, there have been reports of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants.

Although a causal relationship has not been established, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

### **Cyclosporine**

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of

cyclosporine, the resulting cyclosporine  $C_{max}$  and  $AUC_{0-5}$  were found to be significantly elevated. Consequently, 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**

Daily doses of 1200 azithromycin had no effect on the pharmacokinetics of didanosine.

### **Efavirenz**

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 had no effect on the pharmacokinetics of efavirenz given at 400 mg doses for seven days.

### **Fluconazole**

A single dose of 1200 mg azithromycin 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.

### **Indinavir**

A single dose of 1200 mg azithromycin had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir t.i.d. for 5 days).

### **Midazolam**

In healthy volunteers (N=12), co-administration of azithromycin 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**

Coadministration of a single dose of 1200 mg azithromycin with steady-state nelfinavir (750 mg t.i.d.) 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 t.i.d.) at steady-state with a single dose of 1200 mg azithromycin increased the mean  $AUC_{0-\infty}$  of azithromycin by 113 % and mean  $C_{max}$  by 136 %.

Dose adjustment of azithromycin is not recommended. However, close monitoring for known side effects of azithromycin, when administered in conjunction with nelfinavir, is warranted.

### **Rifabutin**

Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

### **Sildenafil**

In normal healthy male volunteers, there was no evidence of a statistically significant effect of azithromycin (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**

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**

Following administration of trimethoprim / sulfamethoxazole DS (160 mg / 800 mg) for 7 days to healthy subjects, coadministration of 1200 mg azithromycin on Day 7 had not significant effects on peak concentrations or total exposure or urinary excretion of either trimethoprim or sulfamethoxazole.

Serum concentrations of azithromycin following administration of a single 1200 mg dose after administration of trimethoprim / sulfamethoxazole DS for 7 days were similar to those produced following a 1200 mg dose of azithromycin in other studies.

### **Zidovudine**

Single 1 g doses and multiple 1200 mg or 600 mg doses azithromycin did not affect the plasma pharmacokinetics or urinary excretion of zidovudine or its glucoronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine in peripheral blood mononuclear cells.

### **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 postmarketing 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:

**Digoxin:** Elevation of digoxin levels.

**Disopyramide:** Increase in pharmacological effects.

**Ergotamine or dihydroergotamine:** Acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

**Triazolam:** Decreases in the clearance of triazolam and increases in the pharmacologic effect of triazolam.

**Drugs metabolized by the cytochrome P450 system:** Elevations of serum hexobarbital, cisapride, and phenytoin levels.

**Antihistamines:** Prolongation of QT intervals, palpitations or cardiac arrhythmias with concomitant administration of astemizole or terfenadine.

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.

**Drug-Food Interactions**

Interactions with food have not been established.

**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**

### **Hepatic Impairment:**

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. Nonetheless, since the liver is the principal route of elimination for azithromycin, the use of AZITHROMYCIN (Azithromycin Monohydrate) should be undertaken with caution in patients with impaired hepatic function.

### **Renal Impairment:**

No dosage adjustment of AZITHROMYCIN is recommended for subjects with mild to moderate (GFR 10-80 mL/min) renal impairment. The mean  $AUC_{0-120}$  was similar in subjects with GFR 10-80 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR < 10 mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment. (See ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

### **Administration**

#### **ADULTS**

##### **Dosing in relation to FOOD:**

AZITHROMYCIN Tablets can be taken with or without food.

#### **UPPER AND LOWER RESPIRATORY INFECTIONS / SKIN AND SKIN STRUCTURE INFECTIONS:**

The recommended dose of AZITHROMYCIN for individuals 16 years of age or older in the treatment of mild to moderate acute bacterial exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia of mild severity, uncomplicated skin and skin structure infections, and for pharyngitis/tonsillitis (as second-line therapy) due to the indicated organisms is: 500 mg as a single dose on the first day followed by 250 mg once daily on days 2 through 5 for a total dose of 1.5 grams.

## **GENITOURINARY INFECTIONS:**

The recommended dose of AZITHROMYCIN for the treatment of genital ulcer disease due to *Haemophilus ducreyi* (chancroid) and non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 gram (1000 mg) oral dose of AZITHROMYCIN . This dose can be administered as four 250 mg tablets.

The recommended dose of AZITHROMYCIN for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* is: a single 2 gram (2000 mg) dose of AZITHROMYCIN. This dose can be administered as eight 250 mg tablets.

## **FOR PREVENTION OF DISSEMINATED *MYCOBACTERIUM AVIUM* COMPLEX (MAC) DISEASE:**

The recommended dose of AZITHROMYCIN for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease is 1200 mg (two 600 mg tablets) taken once weekly. This dose of AZITHROMYCIN may be continued with the approved dosage regimen of rifabutin.

## **OVERDOSAGE**

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. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

AZITHROMYCIN (Azithromycin Monohydrate), a macrolide antibiotic of the azalide subclass, exerts its antibacterial action by binding to the 50s ribosomal subunits of susceptible bacteria and suppressing protein synthesis.

### **Pharmacokinetics:**

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%.

Food does not affect the absorption of Azithromycin in the tablet dosage form. Azithromycin Monohydrate tablets can be taken with or without food.

Plasma concentrations of azithromycin decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. The prolonged half-life is likely due to extensive uptake and subsequent release of drug from tissues. Over the dose range of 250 to 1000 mg orally, the serum concentrations are related to dose. The long tissue half-life and large volume of distribution result from intracytoplasmic uptake and storage in lysosomal phospholipid complexes.

In adults, the following pharmacokinetic data have been reported:

| <b>DOSE/DOSAGE FORM</b> | <b>SUBJECTS</b> | <b>C<sub>max</sub><br/>(<math>\mu</math>g/mL)</b> | <b>T<sub>max</sub><br/>(hr)</b> | <b>AUC<br/>(<math>\mu</math>g.hr/mL)</b> | <b>T<sub>1/2</sub><br/>(hr)</b> |
|-------------------------|-----------------|---|---------------------------------|--|---------------------------------|
| 500mg/250mg tablet      | 12; fasted      | 0.34  | 2.1                             | 2.49 <sup>a</sup>                        | -                               |
| 500mg/250mg tablet      | 12; fed         | 0.41  | 2.3                             | 2.40 <sup>a</sup>                        | -                               |
| 1200mg/600mg tablet     | 12; fasted      | 0.66  | 2.5                             | 6.8 <sup>b</sup>                         | 40                              |

<sup>a</sup> 0- 48 hr, <sup>b</sup>0-last

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.

### **Special Populations and Conditions**

**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.

**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. Nonetheless, since the liver is the principal route of elimination for azithromycin, the use of oral AZITHROMYCIN preparations should be undertaken with caution in patients with impaired hepatic function.

**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) (see DOSAGE AND ADMINISTRATION).

## STORAGE AND STABILITY

Store AZITHROMYCIN (Azithromycin Monohydrate) film-coated tablets at controlled room temperature (15-30°C).

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

250 mg: Each pink, film-coated, capsular-shaped AZITHROMYCIN (Azithromycin Monohydrate) tablet, embossed “Σ” on the upper face, and “AT 250 ” on the lower face, contains azithromycin monohydrate equivalent to 250 mg of azithromycin.

600 mg: Each White to off-white, film-coated, oval, biconvex AZITHROMYCIN (Azithromycin Monohydrate) tablet, with “Σ” on the upper face, and “AT | 600 ” on the lower face, contains Azithromycin Monohydrate equivalent to 600 mg of azithromycin.

### **Composition:**

AZITHROMYCIN tablets are available in 2 strengths, namely 250mg and 600 mg. Each tablet contains azithromycin monohydrate as the active (medicinal) ingredient.

The following inactive ingredients are common to all tablet strengths: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, sodium lauryl sulphate, magnesium stearate, Titanium dioxide, Talc, Lecithin (Soya), and Xanthum gum.

The 250 mg tablets also contain: Ponceau 4R Aluminum Lake, Carmoisine (Azorubine) Aluminum Lake, and Quinoline Yellow Lake.

### **Packaging:**

250 mg: Blister strips of 6 tablets and HDPE bottles of 30s and 100s.

600 mg: Blister strips of 6 tablets and HDPE bottles of 30s and 100s.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper Name: Azithromycin Monohydrate

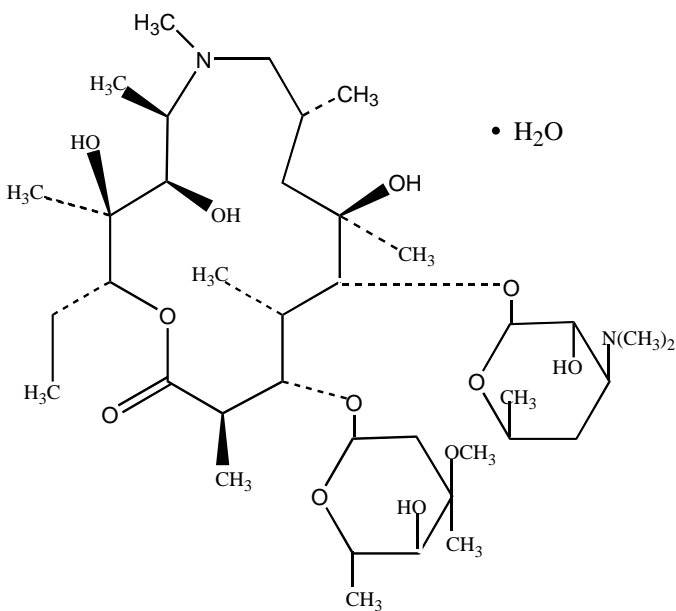
Chemical Name: 9-deoxo-9 $\alpha$ -aza-9 $\alpha$ -methyl-9 $\alpha$ -homoerythromycin A monohydrate

Molecular Formula: C<sub>38</sub>H<sub>72</sub>N<sub>2</sub>O<sub>12</sub>·1H<sub>2</sub>O

Molecular Mass: 767.0 (monohydrate)

749.0 (anhydrous)

Structural formula:



*Azithromycin monohydrate*

Physicochemical properties: Azithromycin Monohydrate is a white to off-white crystalline powder. It's aqueous solubility at 22.4°C is 0.088 mg/mL.

pKa: 7.7



## CLINICAL TRIALS

### Comparative Bioavailability Studies

A randomized, single-dose, cross-over comparative bioavailability study of AZITHROMYCIN (Azithromycin Monohydrate) tablets 600 mg and Zithromax™ 600 mg tablets (Pfizer Canada Inc.) has been performed in healthy male volunteers in the fasting state.

#### Table of the Comparative Bioavailability Data Azithromycin (1 x 600 mg)

From measured data

Geometric Mean

Arithmetic Mean (CV%)

| Parameter                        | Test<br>Azithromycin<br>Tablets | Reference<br>Zithromax™ ‡ | % Ratio of<br>Geometric<br>Means | 90%<br>Confidence<br>Interval |
|----------------------------------|---------------------------------|---------------------------|----------------------------------|-------------------------------|
| AUC <sub>0-72</sub><br>(ng.h/mL) | 4678.18<br>4864.30 (29.1)       | 4718.12<br>4896.19 (28.8) | 99.15                            | 92.39-106.41                  |
| AUC <sub>i</sub><br>(ng.h/mL)    | 5619.64<br>5828.84 (28.0)       | 5578.50<br>5787.63 (28.7) | 100.74                           | 93.63-108.39                  |
| C <sub>max</sub><br>(ng/mL)      | 470.70<br>494.89 (32.1)         | 480.11<br>512.26 (39.5)   | 98.04                            | 87.15-110.29                  |
| T <sub>max</sub> *<br>(h)        | 36.4                            | 43.5                      | --                               |                               |
| T <sub>1/2</sub> *<br>(h)        | 22.2                            | 22.3                      | --                               |                               |

‡ Zithromax™ is manufactured by Pfizer Canada Inc. and was purchased in Canada.

\* expressed as arithmetic mean (CV%) only.

# Indicate % Confidence Interval (i.e., 90% or 95%) in the column heading and list for the AUC<sub>T</sub>, AUC<sub>i</sub> and C<sub>MAX</sub> (if required).



## **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 ( $p=0.005$ ). 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 from 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  $\mu\text{g/mL}$  and is attained 2-3 hours after dosing with areas under the curve of 2.6  $\mu\text{g}\cdot\text{hr/mL}$  ( $AUC_{0-24}$ ) and 3.7  $\mu\text{g}\cdot\text{hr/mL}$  ( $AUC_{0-48}$ ) and trough levels of 0.05  $\mu\text{g/mL}$ . These oral values are approximately 38%, 83%, and 52% of the values observed following a single 500 mg I.V. 3-hour infusion:  $C_{max}$  1.08  $\mu\text{g/mL}$ , trough level 0.06  $\mu\text{g/mL}$ , and  $AUC_{24}$  5.0  $\mu\text{g}\cdot\text{hr/mL}$ . Thus, plasma concentrations are higher following the intravenous regimen throughout the 24-hour interval.

Also refer to tabulated pharmacokinetic data reported in adults under ACTIONS AND CLINICAL PHARMACOLOGY, 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\***

|  | <b>Day 1</b> | <b>Day 5</b> |
|--|--------------|--------------|
| $C_{max}$ ( $\mu\text{g/mL}$ )                 | 0.41         | 0.24         |
| $T_{max}$ (h)                                  | 2.5          | 3.2          |
| $AUC_{0-24}$ ( $\mu\text{g}\cdot\text{h/mL}$ ) | 2.6          | 2.1          |
| $C_{min}$ ( $\mu\text{g/mL}$ )                 | 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 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, $\mu\text{g/mL}$ )                            | 0.310         | 0.446 | 0.383 | 0.290         | 0.182 |
| Serum $\text{AUC}_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr/mL}$ ) | 15.2          |       |       | 14.5          |       |
| $K_{el}$ ( $\text{hr}^{-1}$ )                                    | 0.0101        |       |       | 0.0105        |       |
| Serum $T_{1/2}$  | 68.6 hr       |       |       | 66.0 hr       |       |

Mean  $\text{AUC}_{0-\infty}$  for both regimens were similar, with a ratio of  $\text{AUC}_{0-\infty}$  (3-day) /  $\text{AUC}_{0-\infty}$  (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 ( $\text{AUC}_{0-288}$ ) in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following either the 5-day or 3-day regimen was more than 1000-fold and 800-fold greater than in serum, respectively. Administration of the same total dose with either the 5-day or 3-day regimen may be expected to provide comparable concentrations of azithromycin with MN and PMN leukocytes.

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

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

|                                   | C <sub>max</sub><br>(µg/mL) | trough level<br>(µg/mL) | AUC <sub>0-24</sub><br>(µg.h/mL) |
|-----------------------------------|-----------------------------|-------------------------|----------------------------------|
| 500 mg single oral dose           | 0.41                        | 0.05                    | 2.5                              |
| 500 mg I.V. infusion over 3 hours | 1.08                        | 0.06                    | 5                                |

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

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

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

| <b>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</b> |   |                                      |                           |                            |
|--|---|--------------------------------------|---------------------------|----------------------------|
| <b>Tissue or Fluid</b>   | <b>Sample Time after Final Dose (hrs)</b> | <b>Tissue or Fluid µg/g or µg/mL</b> | <b>Plasma/Serum µg/mL</b> | <b>Concentration Ratio</b> |
| 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                                      | 4.5                                  | 0.03                      | 150                        |
|  | 180                                       | 0.93                                 | 0.006                     | 155                        |
| Cervix***  | 19  | 2.8                                  | 0.04                      | 70                         |

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

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

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

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

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

Following a five-day dosing regimen, human bile contains concentrations of azithromycin much greater (approximately 200 g/mL) than those in serum (<0.1 g/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 600mg 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<sub>max</sub> by 31% while the extent of absorption (AUC) was unchanged.

## MICROBIOLOGY

The *in vitro* susceptibility of clinical isolates to azithromycin is presented in Table 1 (gram-positive bacteria), Table 2 (fastidious gram-negative organisms), Table 3 (aerobic gram-negative species), Table 4 (anaerobic organisms), Table 5 (*mycoplasmataceae* and intracellular pathogens) and Table 6 (*Streptococcus pneumoniae*). For susceptibility testing both agar and broth dilution methods were used. In the agar dilution method, each inoculum spot contained approximately  $2 \times 10^4$  cells/strain. In the broth dilution method, final inoculum size was  $\geq 1 \times 10^6$  colony-forming units per mL. *Chlamydia* organisms were tested in McCoy monolayers. *Beta*-lactamase production has not been shown to produce an effect on the activity of azithromycin.

**TABLE 1**

***In vitro* activity of azithromycin against clinical isolates of gram-positive bacteria**

| Microorganism                                  | # of Strains | MIC (mg/L) |      |            |
|--|--------------|------------|------|------------|
|  |              | Range      | 50%  | 90%        |
| <i>Staphylococcus aureus</i>                   | 100          | NA         | 0.78 | 1.56       |
| <i>S. aureus</i> , erythromycin-resistant      | 16           | NA         | >50  | NA         |
| <i>S. aureus</i> , methicillin-resistant       | 21           | 0.25-16    | >16  | NA         |
| <i>Staphylococcus epidermidis</i>              | 17           | NA         | 0.78 | 0.78       |
| <i>S. epidermidis</i> , erythromycin-resistant | 12           | NA         | >50  | NA         |
| <i>Streptococcus pyogenes</i>                  | 17           | NA         | 0.1  | 0.1        |
| <i>S. pyogenes</i> , erythromycin-resistant    | 7            | NA         | >50  | NA         |
| <i>Streptococcus pneumoniae</i>                | 50           | 0.015-0.12 | 0.06 | 0.06       |
| <i>S. pneumoniae</i> , erythromycin-resistant  | 10           | NA         | >4.0 | NA         |
| <i>Streptococcus agalactiae</i>                | 54           | NA         | 0.05 | 0.10       |
| <i>Streptococcus viridans</i> group            | 78           | NA         | 0.03 | 2 (100%)   |
| <i>Streptococcus milleri</i> group             | 19           | NA         | 0.03 | 0.06(100%) |
| <i>Corynebacterium</i> species                 | 12           | 0.008->128 | 16   | 128        |
| <i>Enterococcus faecalis</i>                   | 64           | NA         | 1.56 | >50        |
| <i>Enterococcus faecium</i>                    | 14           | 0.5->64    | 4    | >64        |



NA= not available

**TABLE 2**  
**Susceptibility of fastidious gram-negative organisms to azithromycin**

| Microorganism                     | # of Strains | MIC (mg/L)    |       |       |
|-----------------------------------|--------------|---------------|-------|-------|
|                                   |              | Range         | 50%   | 90%   |
| <i>Haemophilus influenzae</i>     | 70           | NA            | 0.4   | 0.8   |
| <i>Haemophilus parainfluenzae</i> | 4            | NA            | NA    | 1.0   |
| <i>Haemophilus ducreyi</i>        | 100          | ≤0.0005-0.004 | 0.002 | 0.004 |
| <i>Moraxella catarrhalis</i>      | 17           | NA            | 0.015 | 0.03  |
| <i>Neisseria gonorrhoeae</i>      | 30           | NA            | 0.12  | 0.25  |
| Penicillinase-producing           | 13           | NA            | 0.062 | 0.125 |
| <i>Neisseria meningitidis</i>     | 10           | 0.025-0.12    | 0.06  | 0.12  |
| <i>Campylobacter spp.</i>         | 10           | NA            | 0.25  | 0.5   |
| <i>Campylobacter jejuni</i>       | 12           | 0.03-0.12     | 0.6   | 0.12  |
| <i>Helicobacter pylori</i>        | 97           | ≤0.008-0.25   | 0.12  | 0.25  |
| <i>Gardnerella vaginalis</i>      | 48           | ≤0.03-0.125   | NA    | ≤0.03 |
| <i>Bordetella pertussis</i>       | 34           | NA            | NA    | 0.015 |
| <i>Bordetella parapertussis</i>   | 20           | NA            | NA    | 0.125 |
| <i>Pasteurella multocida</i>      | 16           | NA            | 0.20  | 0.39  |
| <i>Pasteurella haemolytica</i>    | 14           | NA            | 0.20  | 0.20  |

NA = not available

**TABLE 3**  
**Susceptibility of Enterobacteriaceae and other aerobic gram-negative species to azithromycin**

| Microorganism                              | # of Strains | MIC (mg/L) |     |      |
|--|--------------|------------|-----|------|
|  |              | Range      | 50% | 90%  |
| <i>Escherichia coli</i>                    | 280          | NA         | 4   | 8    |
| <i>Escherichia coli</i><br>Enterotoxigenic | 10           | NA         | NA  | 4    |
| <i>Escherichia coli</i><br>Enteroinvasive  | 10           | NA         | NA  | 4    |
| <i>Salmonella typhi</i>                    | 20           | NA         | NA  | 4    |
| <i>Salmonella enteritidis</i>              | 16           | NA         | 2   | 4    |
| <i>Shigella sonnei</i>                     | 15           | NA         | 1   | 2    |
| <i>Shigella flexneri</i>                   | 20           | NA         | NA  | 2    |
| <i>Shigella dysenteriae</i>                | 20           | NA         | NA  | 2    |
| <i>Vibrio cholerae</i>                     | 10           | NA         | NA  | 0.12 |
| <i>Vibrio parahaemolyticus</i>             | 10           | NA         | NA  | 0.25 |
| <i>Aeromonas hydrophila</i>                | 10           | NA         | NA  | 4    |
| <i>Plesiomonas shigelloides</i>            | 10           | NA         | NA  | 1    |
| <i>Yersinia enterocolitica</i>             | 32           | NA         | 0.8 | 3.1  |
| <i>Klebsiella pneumoniae</i>               | 16           | NA         | 8   | 16   |
| <i>Klebsiella oxytoca</i>                  | 11           | NA         | 8   | 16   |
| <i>Enterobacter aerogenes</i>              | 23           | NA         | 4   | 8    |
| <i>Enterobacter cloacae</i>                | 31           | NA         | 8   | 16   |
| <i>Serratia marcescens</i>                 | 18           | NA         | 64  | >64  |
| <i>Proteus mirabilis</i>                   | 14           | NA         | >64 | NA   |

NA = not available

**TABLE 3 : Continued****Susceptibility of Enterobacteriaceae and other aerobic gram-negative species to azithromycin**

| Microorganism                      | # of Strains | MIC (mg/L) |      |     |
|------------------------------------|--------------|------------|------|-----|
|                                    |              | Range      | 50%  | 90% |
| <i>Proteus vulgaris</i>            | 12           | NA         | >64  | NA  |
| <i>Citrobacter freundii</i>        | 19           | NA         | 8    | 16  |
| <i>Citrobacter diversus</i>        | 10           | 8-16       | 8    | 16  |
| <i>Morganella morganii</i>         | 10           | 128->128   | >128 | NA  |
| <i>Providencia stuartii</i>        | 10           | 64->64     | >64  | NA  |
| <i>Acinetobacter calcoaceticus</i> | 13           | NA         | 0.25 | 4.0 |
| <i>Pseudomonas aeruginosa</i>      | 10           | 32->64     | >64  | NA  |

NA = not available

**TABLE 4**  
***In vitro* activity of azithromycin against anaerobic organisms**

| Microorganism                               | # of Strains | MIC (mg/L) |           |             |
|---|--------------|------------|-----------|-------------|
|   |              | Range      | 50%       | 90%         |
| <i>Actinomyces spp.</i>                     | 23           | NA         | 0.12 mode | 0.5 (100%)  |
| <i>Bacteroides bivius</i>                   | 15           | 0.125-4    | 1.0       | 2.0         |
| <i>Bacteroides fragilis</i>                 | 58           | NA         | 3.12      | 6.25        |
| <i>Bacteroides oralis</i>                   | 9            | 0.125-16   | 1.0       | 8.0         |
| <i>Bacteroides spp.</i>                     | 21           | 0.06-8.0   | 0.5       | 8.0 (100%)  |
| <i>Clostridium perfringens</i>              | 13           | NA         | 0.78      | 0.78        |
| <i>Clostridium difficile</i>                | 20           | NA         | 3.12      | 6.25        |
| <i>Fusobacterium spp.</i>                   | 19           | NA         | 1.0 mode  | 2.0 (100%)  |
| <i>Mobiluncus spp.</i>                      | 20           | ≤0.03-0.06 | 0.03      | 0.06        |
| <i>Peptococcus spp.</i>                     | 12           | NA         | 1.56      | 3.12        |
| <i>Peptostreptococcus spp.</i>              | 19           | NA         | 0.5 mode  | 8.0 (100%)  |
| <i>Poryphromonas spp.</i>                   | 16           | NA         | 0.5 mode  | 0.5 (100%)  |
| <i>Prevotella spp.</i>                      | 31           | NA         | 0.25 mode | 1.0 (100%)  |
| <i>Propionibacterium acnes</i>              | 21           | 0.06-13    | 0.06      | 0.13 (100%) |
| <i>Actinobacillus actinomycetemcomitans</i> | 79           | 0.25-2.0   | 1.0       | 2.0         |

NA = not available

**TABLE 5****Activity of azithromycin against Mycoplasmataceae and intracellular pathogens**

| Microorganism                 | # of Strains | MIC (mg/L) |             |                 |
|-------------------------------|--------------|------------|-------------|-----------------|
|                               |              | Range      | 50%         | 90%             |
| <i>Listeria monocytogenes</i> | 14           | 1-2        | 1.0         | 2.0             |
| <i>Legionella pneumophila</i> | 14           | 0.12-2     | 0.5         | 2.0             |
| <i>Legionella spp.</i>        | 21           | NA         | 0.5         | 2.0             |
| <i>Chlamydia trachomatis</i>  | 10<br>89     | 0.064-0.25 | 0.064<br>NA | 0.25            |
| <i>Chlamydia pneumoniae</i>   | 34           | ≤0.015-1.0 | 0.25        | 0.5             |
| <i>Mycoplasma pneumoniae</i>  | 18           | ≤0.01      | NA          | ≤0.01<br>(100%) |
| <i>Mycoplasma hominis</i>     | 64           | 1-8        | 4.0         | 4.0             |
| <i>Ureaplasma urealyticum</i> | 30           | 0.125-0.5  | 0.25        | 0.5             |

NA = not available

**TABLE 6**  
**Published azithromycin susceptibility results for *Streptococcus pneumoniae***

| Numbers Tested  | MIC <sub>50</sub> | MIC <sub>90</sub> | Method Employed   |
|-----------------|-------------------|-------------------|---|
| 10              | ≤0.025            | 0.05              | BHI <sup>a</sup> agar + 5% bovine serum, incubation in 3% CO <sub>2</sub> |
| 28              | 0.12              | 0.25              | MHA + 5% sheep blood  |
| 20              | 0.06              | 0.12              | MHA + 5% sheep blood  |
| 13              | 0.6               | 0.12              | MHA + 5% sheep blood  |
| 10              | ≤0.06             | ≤0.06             | MHA ± 1% haemoglobin and Iso vitalex                                      |
| 10 <sup>b</sup> | >4                | >4                |   |
| 27              | 0.06              | 0.12              | Iso-sensitest broth + 2% horse serum                                      |
| 50              | 0.06              | 0.06              | Oxoid DS agar + 4% lysed horse blood                                      |
| 18              | 0.5               | 2.0               | CSMBH + 3% lysed horse blood  |
| 25              | 0.12              | 0.12              | CSMBH + 3% lysed horse blood  |

<sup>a</sup> Abbreviations: BHI, Brain Heart Infusion; MHA, Mueller Hinton Agar; SMHB, supplemented Mueller Hinton Broth.

<sup>b</sup> Erythromycin resistant strains

These data suggest that there is cross-resistance between erythromycin and azithromycin.

**Diffusion Techniques:** Measurement of zone-inhibition diameters by the agar diffusion method of Kirby and Bauer is the recommended means of susceptibility testing. A standard 15 µg disc is used. Results of laboratory testing should be interpreted using the following criteria (NCCLS Performance Standards for Antimicrobial Susceptibility Testing, Volume 18, No. 1, January 1998):

| <b>Organisms Other than <i>Haemophilus spp.</i>,<br/><i>Neisseria gonorrhoeae</i>, and <i>Streptococci</i></b> |                       |
|--|-----------------------|
| <b>Zone Diameter<br/>(mm)</b>  | <b>Interpretation</b> |
| ≥18  | (S) Susceptible       |
| 14-17  | (I) Intermediate      |
| ≤13  | (R) Resistant         |

| <b><i>Haemophilus spp.</i>*</b> |                       |
|---------------------------------|-----------------------|
| <b>Zone Diameter<br/>(mm)</b>   | <b>Interpretation</b> |
| ≥12                             | (S) Susceptible       |
| -                               | (I) Intermediate      |
| -                               | (R) Resistant         |

\* These zone diameter standards apply only to tests with *Haemophilus spp.* using *Haemophilus* Test Medium (HTM).

| <b><i>Streptococci</i> Including <i>Streptococcus pneumoniae</i>*</b> |                       |
|---|-----------------------|
| <b>Zone Diameter (mm)</b>   | <b>Interpretation</b> |
| ≥18   | (S) Susceptible       |
| 14-17   | (I) Intermediate      |
| ≤13   | (R) Resistant         |

\* These zone diameters for *streptococci* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO<sub>2</sub>.

No interpretative criteria have been established for testing *Neisseria gonorrhoeae*. This species is not usually tested.

A report of “Susceptible” indicates that the pathogen is likely to respond to monotherapy with azithromycin. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the organism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretations. A report of “Resistant” indicates that achievable drug concentrations are unlikely to be inhibitory and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 15 µg azithromycin disk should give the following diameter (NCCLS Performance Standards for Antimicrobial Susceptibility Testing, Volume 18, No. 1, January 1998):

| <b>Organism</b>                 | <b>Zone Diameter (mm)</b> |
|---------------------------------|---------------------------|
| <i>S. aureus</i> ATCC 25923     | 21-26                     |
| <i>H. influenzae</i> ATCC 49247 | 13-21                     |
| <i>S. pneumoniae</i> ATCC 49619 | 19-25                     |



**Dilution Techniques:** Broth and agar dilution methods, such as those recommended by the NCCLS, may be used to determine the minimum inhibitory concentrations (MIC) of azithromycin, using the following criteria (NCCLS Performance Standards for Antimicrobial Susceptibility Testing, Volume 18, No.1, January 1998):

| <b>Organisms Other Than <i>Haemophilus spp.</i>,<br/><i>Neisseria gonorrhoeae</i>, and <i>Streptococci</i></b> |                       |
|--|-----------------------|
| <b>MIC (mg/L)</b>  | <b>Interpretation</b> |
| ≤2   | (S) Susceptible       |
| 4  | (I) Intermediate      |
| ≥8   | (R) Resistant         |

| <b><i>Haemophilus spp.</i>*</b> |                       |
|---------------------------------|-----------------------|
| <b>MIC (mg/L)</b>               | <b>Interpretation</b> |
| ≤4                              | (S) Susceptible       |
| -                               | (I) Intermediate      |
| -                               | (R) Resistant         |

\* These interpretative standards are applicable only to broth microdilution susceptibility tests with *Haemophilus spp.* using *Haemophilus* Test Medium.

| <b><i>Streptococci</i> Including <i>Streptococcus pneumoniae</i></b> |                       |
|--|-----------------------|
| <b>MIC (mg/L)</b>  | <b>Interpretation</b> |
| ≤0.5   | (S) Susceptible       |
| 1  | (I) Intermediate      |
| ≥2   | (R) Resistant         |

The *in vitro* potency of azithromycin is markedly affected by the pH of the microbiological growth medium during incubation. Incubation in a CO<sub>2</sub> atmosphere will result in lowering of media pH (7.2 to 6.6, 18h in 10% CO<sub>2</sub>) and a reduction in potency of azithromycin. Thus, the initial pH of the growth medium should be physiological (7.2-7.4) and the CO<sub>2</sub> content of the incubation atmosphere should be as low as is practical. Azithromycin can be solubilized for *in vitro* testing by dissolving in a minimum amount of 95% ethanol and diluting to working concentration with water.

As with standard diffusion methods, dilution methods require the use of laboratory control organisms. Standard azithromycin powder should provide the following MIC values (NCCLS Performance Standards for Antimicrobial Susceptibility Testing, Volume 18, No. 1, January 1998):

| <b>Organism</b>                 | <b>MIC (mg/L)</b> |
|---------------------------------|-------------------|
| <i>H. influenzae</i> ATCC 49247 | 1-4               |
| <i>S. pneumoniae</i> ATCC 49619 | 0.06-0.25         |
| <i>S. aureus</i> ATCC 29213     | 0.5-2.0           |

## TOXICOLOGY

### Acute Toxicity: Mice and Rats

| <b>Oral and Intraperitoneal Toxicity Studies in Mice and Rats</b> |                |            |   |
|---|----------------|------------|---|
| <b>Route</b>  | <b>Species</b> | <b>Sex</b> | <b>LD<sub>50</sub><br/>(mg of free base/kg)</b> |
| 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<br><600                                    |
| I/P   | Mice           | F          | N/A*  |
| I/P   | Rats           | M          | >500<br><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.

## Subacute and Chronic Toxicity

| SPECIES                      | ROUTE            | DOSE<br>mg/kg/day     | ANIMALS<br>PER DOSE<br>LEVEL | DURATION                      | FINDINGS  |
|------------------------------|------------------|-----------------------|------------------------------|-------------------------------|---|
| <b>ORAL in Adult Animals</b> |                  |                       |                              |                               |   |
| Rat<br>(Adult)               | Oral<br>(gavage) | 0<br>50<br>100<br>200 | 10/sex                       | 36 days<br>+<br>reversibility | <p>Cecal enlargement was dose-related. Elevated serum hepatic enzyme (SGPT, SGPT, 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.</p> <p>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.</p> <p>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.</p> <p>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.</p> |

|                |                  |   |  |   |  |
|----------------|------------------|---|--|---|--|
| Dog<br>(Adult) | Oral<br>(gavage) | 0<br>25<br>50<br>100  | 3/sex                                    | 36 days   | <p>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.</p> <p>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.</p> |
| Rat<br>(Adult) | Oral<br>(gavage) | 40<br>(10days on<br>10days off)<br><br>0 continu.<br>10 ”<br>20 ” | 15/sex<br><br>25/sex                     | 190-193 days<br><br>+<br><br>reversibility                    | <p>Sporadic mild elevations in SGOT and SGPT occurred in all dose groups during and after the treatment period. There was no evidence of phospholipidosis.</p>   |
| Dog<br>(Adult) | Oral<br>(gavage) | 40<br>(10days on<br>10days off)<br><br>0<br>10<br>20              | 4/sex<br><br>4/sex<br>+ 2/sex<br>+ 2/sex | 190 days<br><br>+<br><br>reversibility<br>1 month<br>2 months | <p>Sporadic elevations in SGPT levels occurred at 20 and 40 mg/kg only.</p> <p>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.</p>  |

|             |               |                    |       |  |   |
|-------------|---------------|--------------------|-------|--|---|
| Dog (Adult) | Oral (gavage) | 0<br>30<br><br>100 | 6/sex | 6 months<br><br>2 months<br><br>+<br><br>reversibility | <p>Selected animals were sacrificed at end of treatment; sacrifices (1/sex/dose level) were also performed 1 mn (100 mg/kg), 2 mns (30 mg/kg) and 4 mns (100 mg/kg) post-treatment. Necropsies of remaining animals were performed 7 mns (30 mg/kg) and 11 mns (100 mg/kg) post treatment.</p> <p>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.</p> <p>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.</p> <p>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.</p> |
|-------------|---------------|--------------------|-------|--|---|

|  |               |                         |                          |  |   |
|--|---------------|-------------------------|--------------------------|--|---|
|  |               |                         |                          |  | 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.   |
| Dog (Adult)  | Oral (gavage) | 0<br>30<br>100          | 6/sex                    | 6 months<br><br>+<br>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.  |
| <b>ORAL in Neonatal Animals</b><br>Oral Subacute/Neonatal RATS |               |                         |                          |  |   |
| Rat (Neonatal 4 days)  | Oral (gavage) | 0<br>10<br>20<br><br>40 | 10/sex<br><br><br>10/sex | 18 days (day 4 to day 21 postpartum)<br><br>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 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) | 0<br>40<br>60<br>80     | 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.<br><br>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 phospholipidosis, 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<br>(Neonatal<br>4 days) | Oral<br>(gavage) | 0<br>100<br>120<br>140 | 10/sex                               | 18 days<br>(day 4 to<br>day 21<br>postpartum)  | <p>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.</p> <p>There were no clinical signs of toxicity.</p> <p>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.</p>   |
| Rat<br>(Neonatal<br>4 days) | Oral<br>(gavage) | 0<br>30<br>70<br>140   | 20/sex<br>10/sex<br>10/sex<br>20/sex | <p>18 days<br/>(day 4 to<br/>day 21<br/>postpartum)</p> <p>and</p> <p>30 Day<br/>Reversibility<br/>Period for<br/>10/sex in<br/>groups<br/>treated by 0<br/>and 140<br/>mg/kg.</p> | <p>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.</p> <p>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.</p> <p>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 the serum. The concentration of azithromycin in the serum, liver and brain had declined substantially when next measured in 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.</p> |

|  |  |  |  |  |   |
|--|--|--|--|--|---|
|  |  |  |  |  | <p>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.</p> <p>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).</p> |
|--|--|--|--|--|---|

| SPECIES                            | ROUTE            | DOSE<br>mg/kg/day   | ANIMALS<br>PER DOSE<br>LEVEL | DURATION | FINDINGS  |
|------------------------------------|------------------|---------------------|------------------------------|----------|---|
| <b>Oral Subacute/Neonatal DOGS</b> |                  |                     |                              |          |   |
| Dogs<br>(Neonatal<br>3-5 days)     | Oral<br>(gavage) | 0<br>10<br>30<br>60 | 3/sex                        | 5 weeks  | <p>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 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.</p> <p>With the exception of a possible lag in body weight gain of female pups, there were no treatment-related effects on development 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, ie., 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 &lt;eye &lt;kidney &lt;liver=spleen.</p> |

|  |                  |                     |   |  |  |
|--|------------------|---------------------|---|--|--|
| Dogs<br>(Neonatal<br>3-5 days)                   | Oral<br>(gavage) | 0<br>10<br>30<br>60 | 4/sex   | 11 days  | <p>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.</p> <p>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.</p> <p>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.</p> |
| Dogs<br>(Neonatal<br>3-5 days)<br>and<br>25 days | Oral<br>(gavage) | 0<br>10<br>60       | 4/sex<br>(3-5 days)<br><br>2/sex<br>(25 days) | 11 days<br>and<br>30 Day<br>Recovery<br>Period | <p>The purpose of this study was to further characterize the absorption and elimination of azithromycin from the choroid/retina of neonatal beagle dogs. At end of the treatment period, 2/sex from the 3-5 day old dogs and all of the older dogs were necropsied. Remaining dogs were maintained for a 1 month dose free period to document the elimination of azithromycin from the retina.</p> <p>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.</p>  |

| <b>INTRAVENOUS in Adult Animals</b>   |                  |  |                               |                            |  |
|---------------------------------------|------------------|--|-------------------------------|----------------------------|--|
| Rat<br>(Adult)                        | IV               | 10<br>20<br><br>20 (every<br>other day)    | 10/sex                        | 14 days                    | No untoward effects.   |
| Dog<br>(Adult)                        | IV               | 10<br>20<br><br>10 (every<br>other day)    | 3/sex                         | 14 days                    | No untoward effects with 3 exceptions in the former two groups.<br><br>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<br>(Adult)                        | IV               | 5<br>10<br>20                              | 10/sex                        | 1 month<br>(36-39<br>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<br>(Adult)                        | IV               | 5<br>10<br>20                              | 3/sex                         | 1 month<br>(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. |
| <b>SPECIAL EXPLORATORY TOXICOLOGY</b> |                  |  |                               |                            |  |
| Rat                                   | Oral<br>(gavage) | 10<br>0<br>40<br>200<br>chloroquine:<br>25 | 5/sex<br>10/sex<br><br>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<br>(gavage) | 0<br>200                                   | 10/sex                        | 42 days                    | Phospholipid levels were significantly elevated above control in liver, kidney, spleen and lymphocytes ( $p < .05$ ).  |

|                             |                  |   |  |                                       |   |
|-----------------------------|------------------|---|--|---------------------------------------|---|
| Dog                         | Oral<br>(gavage) | 0<br>azithromycin:<br>10<br>40<br>200<br><br>chloroquine:<br>15 | 1/sex<br>2/sex<br><br><br>1/sex                              | 5 days                                | The livers of the 200 mg/kg azithromycin animals showed highest drug concentration (> 4000 µg/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 µg/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<br>(gavage) | 0<br>azithromycin:<br>30<br>erythromycin<br>:<br>400            | 1/sex<br>2/sex<br><br><br>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<br>(gavage) | erythromycin<br>:<br>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<br>Atapetal<br>Tapetal | Oral             | azithromycin:<br><br>0<br>100<br><br>0<br>100                   | <br><br>3 (2M,1F)<br>3 (2F,1M)<br><br>3 (2M,1F)<br>3 (2F,1M) | 35-36 days                            | Ophthalmoscopic examinations revealed no changes in the atapetal dogs while tapetal decoloration, dulling of normal reflectivity and loss of color 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.<br><br>Other changes observed in both tapetal and atapetal dogs are comparable to those observed in previous studies at the same dose.  |
| <b>SPECIAL TOXICOLOGY</b>   |                  |   |  |                                       |   |
| Rabbit                      | IM               | 0<br>200<br>400<br>(single dose)                                | 3/sex  | 3 days and<br>7 days<br>(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<br>10<br>(single<br>dose) | 3/sex | 1 and 2<br>days<br>(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**

| <b>SPECIES</b>                                | <b>ROUTE</b>     | <b>DOSE<br/>mg/kg/day</b> | <b>ANIMALS<br/>PER<br/>DOSE<br/>LEVEL</b>            | <b>DURATION</b>                                 | <b>FINDINGS</b>  |
|---|------------------|---------------------------|--|---|--|
| <b>FERTILITY AND REPRODUCTIVE PERFORMANCE</b> |                  |                           |  |   |  |
| Rat   | Oral<br>(gavage) | 0<br>10<br>20             | 15 M/dose<br>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<br>(gavage) | 30                        | 15M/dose<br>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.   |
| <b>FERTILITY EFFECT ON MALES OR FEMALES</b>   |                  |                           |  |   |  |
| Rat   | Oral             | 0<br>30                   | 40M/dose<br>80F/dose<br>(Fertile<br>animals<br>only) | 64 days<br>(males)<br><br>See text<br>(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.<br>Group 1: Drug treated males mated with drug treated females.<br>Group 2: Drug treated males mated with control females.<br>Group 3: Control males mated with drug treated females.<br>Group 4: Control males mated with control females.<br>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**

| <b>SPECIES</b>        | <b>ROUTE</b>     | <b>DOSE<br/>mg/kg/day</b> | <b>ANIMALS<br/>PER<br/>DOSE<br/>LEVEL</b> | <b>DURATION</b>           | <b>FINDINGS</b>  |
|-----------------------|------------------|---------------------------|---|---------------------------|--|
| Mice                  | Oral<br>(gavage) | 0<br>10<br>20<br>40       | 20  | days 6-13<br>of gestation | Azithromycin was not toxic to the dams or their fetuses nor was there evidence of teratogenicity.  |
| Mice                  | Oral<br>(gavage) | 0<br>50<br>100<br>200     | 20  | days 6-13<br>of gestation | Azithromycin was not toxic to the dams or their fetuses nor was there evidence of teratogenicity.  |
| Rat                   | Oral<br>(gavage) | 0<br>10<br>20<br>40       | 20  | days 6-15<br>of gestation | Azithromycin was not toxic to the dams or their fetuses nor was there evidence of teratogenicity.  |
| Rat                   | Oral<br>(gavage) | 0<br>50<br>100<br>200     | 20  | days 6-15<br>of gestation | Azithromycin was not toxic to the dams 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.              |
| <b>PERI/POSTNATAL</b> |                  |                           |   |                           |  |
| Rat                   | Oral<br>(gavage) | 0<br>10<br>20<br>40       | 15  | See text                  | Azithromycin administered from day 15 p.i. through end of gestation and for the whole period of lactation was not toxic to the dams. The pre- and post-natal developments of pups were not affected.   |
| Rat                   | Oral<br>(gavage) | 0<br>50<br>100<br>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 their litter size and not to drug administration. No drug-related external or visceral anomalies were observed. |



## Neonatal Studies

| SPECIES | ROUTE            | DOSE<br>mg/kg/day      | ANIMALS<br>PER DOSE<br>LEVEL | DURATION  | FINDINGS   |
|---------|------------------|------------------------|------------------------------|---|--|
| Rat     | Oral             | 0<br>10<br>20<br>40    | 10/sex                       | 18 days<br>(4-21 days<br>postpartum<br>10 days<br>(4-13 days<br>postpartum) | There was no evidence of toxicity and no observation of phospholipidosis.  |
| Rat     | Oral<br>(gavage) | 0<br>40<br>60<br>80    | 5/sex                        | 18 days<br>(4-21 days<br>postpartum)  | Azithromycin induced dose-related microscopic evidence of phospholipidosis only in the bile duct epithelium of both males and females.   |
| Rat     | Oral<br>(gavage) | 0<br>100<br>120<br>140 | 5/sex                        | 18 days<br>(4-21 days<br>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. |

|     |                  |                          |                          |  |  |
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| Rat | Oral<br>(gavage) | 30<br>70<br><br>0<br>140 | 10/sex<br><br><br>20/sex | 18 days<br>(4-21 days<br>postpartum)<br><br>+<br><br>reversibility | <p>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 (&lt; 0.01 µg/mL) and the concentration of azithromycin in the liver, brain, and serum was substantially lower than that found one day after the last dose. In spite of the high azithromycin concentrations detected in both the liver and brain at 24 hours after the last dose, the phospholipid levels in these tissues from rats given azithromycin were generally no greater than those of the vehicle-treated controls at both the end of the dosing period and after the one-month reversibility period.</p> <p>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.</p> <p>No light microscopic evidence of phospholipidosis remained in high dose animals examined after a 30-day reversibility period.</p> |
|-----|------------------|--------------------------|--------------------------|--|--|

## **Carcinogenicity**

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

## **Genetic Toxicology**

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

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

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

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

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

## **Antigenicity Studies**

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

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**PART III: CONSUMER INFORMATION**

**AZITHROMYCIN**  
(Azithromycin Monohydrate)

This leaflet is part III of a three-part "Product Monograph" published when AZITHROMYCIN was approved for sale in Canada and is designed specifically for Consumers.

This leaflet is a summary and will not tell you everything about AZITHROMYCIN. Contact your doctor or pharmacist if you have any questions about the drug.

**ABOUT THIS MEDICATION**

**What the medication is used for:**

AZITHROMYCIN is an antibiotic medicine taken once a day to treat the following types of infections in adults: bronchitis, certain types of skin infections, strep throat (pharyngitis, tonsillitis), and pneumonia.

**Can Antibiotics Cure A Cold or Flu?**

No. Antibiotics work only on infections caused by bacteria. They do not kill viruses.

No antibiotic, including AZITHROMYCIN, can treat viral infections such as the common cold and the flu.

**What it does:**

AZITHROMYCIN helps to stop the growth of the bacteria that cause infection. It gets into infected tissue where it is released slowly over time. The medicine fights the infection for several days after the last dose is taken.

**When it should not be used:**

AZITHROMYCIN (Azithromycin Monohydrate) is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, other antibacterial agents, or to any ingredient in the formulation or component of the container.

This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

**What the medicinal ingredient is:**

azithromycin monohydrate.

**What the important nonmedicinal ingredients are:**

The following inactive ingredients are common to all tablet strengths:  
dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, sodium lauryl sulphate, magnesium stearate, Titanium dioxide, Talc, Lecithin (Soya), and Xanthum gum.

The 250 mg tablets also contain: Ponceau 4R Aluminum Lake,

Carmoisine (Azorubine) Aluminum Lake, and Quinoline Yellow Lake.

**What dosage forms it comes in:**

AZITHROMYCIN is available in 2 strengths, mainly: tablets 250 mg and 600 mg

**WARNINGS AND PRECAUTIONS**

Only your doctor can decide if AZITHROMYCIN is right for you. Before you start AZITHROMYCIN, be sure to tell the doctor if you:

- are taking any prescription medicines, including theophylline or warfarin
- are taking any over the counter medicines you can buy without a prescription, including natural/herbal remedies or antacids
- are pregnant, think you are pregnant, or are breast feeding
- have ever had any liver or kidney problems
- have any other medical problems
- have ever had an allergic reaction to any medicines, including antibiotics such as erythromycin
- have ever had an allergic reaction to azithromycin or any of the ingredients of AZITHROMYCIN (see **ABOUT THIS MEDICATION**)

**INTERACTIONS WITH THIS MEDICATION**

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

**PROPER USE OF THIS MEDICATION**

AZITHROMYCIN can be taken with or without food.

**Usual dose:**

**250 mg AZITHROMYCIN** for 5 days

Day 1: Take 2 tablets once

Days 2-5: Take 1 tablet daily

**600 mg AZITHROMYCIN**

The recommended dose of AZITHROMYCIN for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease is 1200 mg (two 600 mg tablets) taken once weekly.

You should begin to feel better within the first few days, but be sure to take AZITHROMYCIN for the full number of days your doctor prescribed. If you stop taking AZITHROMYCIN too soon, your infection could come back. The next infection may be worse and be more difficult to treat. If you are not able to take all the medicine, tell your doctor.

**Overdose:**

In case of accidental overdose, call your doctor right away or go to the nearest emergency room.

**Missed Dose:**

If a dose of this medication is missed, it should be taken as soon as possible. This will help to keep a constant amount of medication in the blood. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double doses.

### SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, AZITHROMYCIN may cause some side effects that are usually mild to moderate and go away after the medicine is stopped. The most common ones are:

- nausea
- diarrhea
- stomach pain
- vomiting

As with other antibiotics, if you develop diarrhea that becomes severe and watery or does not go away, stop taking the medicine and call your doctor. This could be a sign of a serious medical problem.

Allergic reactions to AZITHROMYCIN are rare, but these reactions can be very serious if not treated right away by a doctor.

If you think you might be having an allergic reaction to AZITHROMYCIN, stop taking the medicine and call your doctor right away. If you cannot reach your doctor, go to the nearest hospital emergency room. Symptoms of a severe allergic reaction may include trouble breathing; swelling of the face, mouth, and neck; severe skin rash or blisters.

AZITHROMYCIN may cause other less common side effects besides those listed here. If you have any unexpected side effects while taking AZITHROMYCIN, contact your doctor, nurse or pharmacist.

### SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

| Symptom / effect |   | Talk with your doctor or pharmacist |              | Stop taking drug and call your doctor or pharmacist |
|------------------|---|-------------------------------------|--------------|---|
|                  |   | Only if severe                      | In all cases |   |
| Common           | -diarrhea<br>-nausea<br>-stomach pain<br>-vomiting                | ✓                                   |              |   |
| Uncommon         | -symptoms of severe allergic reaction<br>-unexpected side effects |                                     | ✓            | ✓   |

*This is not a complete list of side effects. For any unexpected effects while taking AZITHROMYCIN, contact your doctor or pharmacist.*

### HOW TO STORE IT

Keep AZITHROMYCIN and all medicines out of the reach of children.

Store AZITHROMYCIN at controlled room temperature (between 15-30 °C).

### REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Health Canada by:

toll-free telephone: 866-234-2345

toll-free fax: 866-678-6789

By email: [cadtmp@hc-sc.gc.ca](mailto:cadtmp@hc-sc.gc.ca)

By regular mail:

National AR Centre

Marketed Health Products Safety and Effectiveness

Information Division

Marketed Health Products Directorate

Tunney's Pasture, AL 0701C

Ottawa ON K1A 0K9

***NOTE: Before contacting Health Canada, you should contact your physician or pharmacist.***

## **MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, 4513347 Canada Inc., at: 306.270.2975.

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