

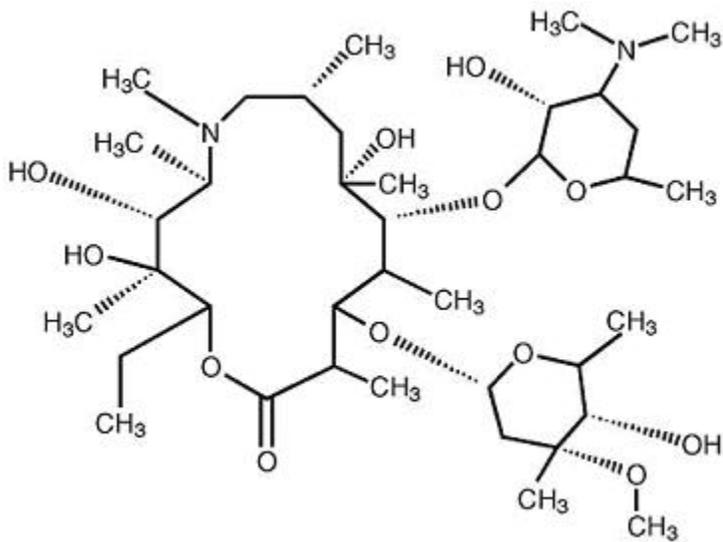
AZITHROMYCIN - azithromycin monohydrate tablet, film coated

Teva Pharmaceuticals USA Inc

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

DESCRIPTION

Azithromycin tablets USP contain the active ingredient azithromycin, USP, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin, USP has the chemical name (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- α -*L*-ribo-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)- β -*D*-xylo-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin, USP is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Azithromycin, USP has the following structural formula:



$C_{38}H_{72}N_2O_{12}$ M.W. 748.98

Azithromycin, USP, as the monohydrate, is a white to off-white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12} \cdot H_2O$ and a molecular weight of 767.

Azithromycin tablets USP contain azithromycin monohydrate equivalent to 600 mg azithromycin, USP. The tablets are supplied as white to off-white, unscored, film-coated modified-capsule-shaped tablets. They also contain the following inactive ingredients: butylated hydroxytoluene, calcium phosphate dibasic anhydrous, colloidal silicon dioxide, hypromellose (2910, 15cP) lactose monohydrate, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum.

The pharmacokinetic parameters of azithromycin in plasma after dosing as per labeled recommendations in healthy young adults and asymptomatic HIV-seropositive adults (age 18 to 40 years old) are portrayed in the following chart:

MEAN (CV%) PK PARAMETER

| DOSE/DOSAGE FORM (Serum, Except as Indicated) | Subjects | Day No. | C_{max} (mcg/ mL) | T_{max} (hr) | C_{24} (mcg/ mL) | AUC (mcg•hr/mL) | $T_{1/2}$ (hr) | Urinary Excretion (% of Dose) |
|---|----------|---------|------------------------|----------------|-----------------------|--------------------|----------------|-------------------------------------|
| 500 mg/250 mg Capsule | 12 | Day 1 | 0.41 | 2.5 | 0.05 | 2.6* | - | 4.5 |
| and 250 mg on Days 2 to 5 | 12 | Day 5 | 0.24 | 3.2 | 0.05 | 2.1* | - | 6.5 |
| 1200 mg/600 mg Tablets | 12 | Day 1 | 0.66 | 2.5 | 0.074 | 6.8† | 40 | - |
| %CV | | | (62%) | (79%) | (49%) | (64%) | (33%) | |
| 600 mg Tablet/Day | 7 | 1 | 0.33 | 2 | 0.039 | 2.4* | | |
| %CV | | | (25%) | (50%) | (36%) | (19%) | | |

| | | | | | | | | |
|-----------------------------------|---|----|-------|-------|-------|-------|------|---|
| | 7 | 22 | 0.55 | 2.1 | 0.14 | 5.8* | 84.5 | - |
| %CV | | | (18%) | (52%) | (26%) | (25%) | | - |
| 600 mg Tablet/Day (Leukocytes) | 7 | 22 | 252 | 10.9 | 146 | 4763* | 82.8 | - |
| %CV | | | (49%) | (28%) | (33%) | (42%) | - | - |

*AUC_{0 to 24}

†0 to last.

In these studies (500 mg Day 1, 250 mg Days 2 to 5), there was no significant difference in the disposition of azithromycin between male and female subjects. Plasma concentrations of azithromycin following single 500 mg oral and I.V. doses declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. With a regimen of 500 mg on Day 1 and 250 mg/day on Days 2 to 5, 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 asymptomatic HIV-seropositive adult subjects receiving 600 mg azithromycin tablets once daily for 22 days, steady state azithromycin serum levels were achieved by Day 15 of dosing.

When azithromycin capsules were administered with food, the rate of absorption (C_{max}) of azithromycin was reduced by 52% and the extent of absorption (AUC) by 43%.

The absolute bioavailability of two 600 mg tablets was 34% (CV = 56%). Administration of two 600 mg tablets with food increased C_{max} by 31% (CV = 43%) while the extent of absorption (AUC) was unchanged (mean ratio of AUCs = 1; CV = 55%).

The AUC of azithromycin in 250 mg capsules was unaffected by coadministration of an antacid containing aluminum and magnesium hydroxide with azithromycin; however, the C_{max} was reduced by 24%. Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin absorption.

When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin (500 mg Day 1, 250 mg Days 2 to 5) 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 high values in adults 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. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

AZITHROMYCIN CONCENTRATIONS FOLLOWING TWO 250 mg (500 mg) CAPSULES IN ADULTS

| TISSUE OR FLUID | TIME AFTER DOSE (h) | TISSUE OR FLUID CONCENTRATION (mcg/g or mcg/mL) * | CORRESPONDING PLASMA OR SERUM LEVEL (mcg/mL) | TISSUE (FLUID) PLASMA (SERUM) RATIO * |
|---------------------|---------------------|---|--|---------------------------------------|
| SKIN | 72 to 96 | 0.4 | 0.012 | 35 |
| LUNG | 72 to 96 | 4 | 0.012 | > 100 |
| SPUTUM [†] | 2 to 4 | 1 | 0.64 | 2 |
| SPUTUM [‡] | 10 to 12 | 2.9 | 0.1 | 30 |
| TONSIL [§] | 9 to 18 | 4.5 | 0.03 | > 100 |
| TONSIL [§] | 180 | 0.9 | 0.006 | > 100 |
| CERVIX [¶] | 19 | 2.8 | 0.04 | 70 |

*High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related. Azithromycin is concentrated in cell lysosomes which have a low intraorganelle pH, at which the drug's activity is reduced. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

†Sample was obtained 2 to 4 hours after the first dose.

‡Sample was obtained 10 to 12 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 was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 mcg/mL) in the presence of non-inflamed meninges.

Following oral administration of a single 1200 mg dose (two 600 mg tablets), the mean maximum concentration in peripheral leukocytes was 140 mcg/mL. Concentrations remained above 32 mcg/mL for approximately 60 hr. The mean half-lives for 6 males

and 6 females were 34 hr and 57 hr, respectively. Leukocyte to plasma C_{\max} ratios for males and females were 258 ($\pm 77\%$) and 175 ($\pm 60\%$), respectively, and the AUC ratios were 804 ($\pm 31\%$) and 541 ($\pm 28\%$), respectively. The clinical relevance of these findings is unknown.

Following oral administration of multiple daily doses of 600 mg (1 tablet/day) to asymptomatic HIV-seropositive adults, mean maximum concentration in peripheral leukocytes was 252 mcg/mL ($\pm 49\%$). Trough concentrations in peripheral leukocytes at steady-state averaged 146 mcg/mL ($\pm 33\%$). The mean leukocyte to serum C_{\max} ratio was 456 ($\pm 38\%$) and the mean leukocyte to serum AUC ratio was 816 ($\pm 31\%$). The clinical relevance of these findings is unknown.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL. Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

Renal Insufficiency

Azithromycin pharmacokinetics was investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1 g dose of azithromycin (4 x 250 mg capsules), the mean C_{\max} and AUC_{0 to 120} increased by 5.1% and 4.2%, respectively in subjects with GFR 10 to 80 mL/min compared to subjects with normal renal function (GFR > 80 mL/min). The mean C_{\max} and AUC_{0 to 120} increased 61% and 35%, respectively in subjects with end-stage renal disease (GFR < 10 mL/min) compared to subjects with normal renal function (GFR > 80 mL/min) (see **DOSAGE AND ADMINISTRATION**).

Hepatic Insufficiency

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

The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses adequate to reach therapeutic steady-state plasma levels is not known (see **PRECAUTIONS**).

Microbiology

Mechanism of Action

Azithromycin binds to the 23S rRNA of the bacterial 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was > 30 after one hour incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Activity of Azithromycin Against *Mycobacterium Avium* Complex (MAC)

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

The ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues (see **CLINICAL PHARMACOLOGY**).

Mechanism of Resistance

Complete cross-resistance between azithromycin and clarithromycin has been observed with MAC isolates. In most isolates, a single point mutation at a position that is homologous to the *Escherichia coli* positions 2058 or 2059 on the 23S rRNA gene is the mechanism producing this cross-resistance pattern.^{2,3}

Azithromycin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Mycobacterium Avium Complex (MAC)

Chlamydia trachomatis

Susceptibility Testing Methods

*Susceptibility Testing of *Mycobacterium Avium* Complex (MAC)*

Susceptibility testing may be done following the methodology of the Clinical and Laboratory Standards Institute (CLSI).¹

CLSI has established methods for testing the susceptibility of MAC clinical isolates and recommends utilizing clarithromycin to test for susceptibility to macrolides, including azithromycin.⁵

The clinical relevance of azithromycin *in vitro* susceptibility test results for other mycobacterial species, including *Mycobacterium tuberculosis*, has not been determined.

*Susceptibility Testing of *Chlamydia Trachomatis**

There is no standardized *in vitro* susceptibility test method for *C. trachomatis*.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Azithromycin Tablets USP and other antibacterial drugs, Azithromycin Tablets USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Azithromycin Tablets USP are indicated for the treatment of MAC infection and prophylaxis against MAC Infection (pneumonia: see **WARNINGS**) caused by susceptible isolates.

Treatment of Disseminated Mycobacterium Avium Complex (MAC) Disease

Azithromycin Tablets USP, taken in combination with ethambutol, are indicated for the treatment of disseminated MAC infections in persons with advanced HIV infection (see **DOSAGE AND ADMINISTRATION, CLINICAL STUDIES**).

Prophylaxis of Disseminated Mycobacterium Avium Complex (MAC) Disease

Azithromycin Tablets USP, taken alone or in combination with rifabutin at its approved dose, are indicated for the prevention of disseminated MAC disease in persons with advanced HIV infection (see **DOSAGE AND ADMINISTRATION, CLINICAL STUDIES**).

CONTRAINDICATIONS

Azithromycin tablets are contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic. Azithromycin tablets are contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

WARNINGS

Hypersensitivity

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported (see **CONTRAINDICATIONS**). Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure**. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

Clostridium Difficile-Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides, including azithromycin. Cases of torsade de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Although the absolute risk is unknown, it appears to be low with azithromycin likely due to the lack of appreciable drug interactions, and the observation that it is rarely reported as a postmarket adverse event. However, it would be prudent to avoid use in patients with known prolongation of the QT interval, patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

PRECAUTIONS

General

Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR < 10 mL/min, caution should be exercised when prescribing azithromycin in these patients (see **CLINICAL PHARMACOLOGY, Renal Insufficiency**).

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

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

Information for Patients

Azithromycin tablets may be taken with or without food. However, increased tolerability has been observed when tablets are taken with food.

Patients should also be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Patients should be counseled that antibacterial drugs including azithromycin tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When azithromycin tablets are prescribed to treat bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by azithromycin tablets or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions

Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of azithromycin (500 mg) absorption.

Administration of cimetidine (800 mg) two hours prior to azithromycin had no effect on azithromycin (500 mg) absorption.

A single oral dose of 1200 mg azithromycin (2 x 600 mg azithromycin tablets) did not alter the pharmacokinetics of a single 800 mg oral dose of fluconazole in healthy adult subjects.

Total exposure (AUC) and half-life of azithromycin following the single oral tablet dose of 1200 mg were unchanged and the reduction in C_{max} was not significant (mean decrease of 18%) by coadministration with 800 mg fluconazole.

A single oral dose of 1200 mg azithromycin (2 x 600 mg azithromycin tablets) had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir tid for 5 days) in healthy adult subjects.

Coadministration of a single oral dose of 1200 mg azithromycin (2 x 600 mg azithromycin tablets) with steady-state nelfinavir (750 mg tid) to healthy adult subjects produced a decrease of approximately 15% in mean $AUC_{0\text{ to }8}$ of nelfinavir and its M8 metabolite.

Mean C_{max} of nelfinavir and its M8 metabolite were not significantly affected. No dosage adjustment of nelfinavir is required when nelfinavir is coadministered with azithromycin.

Coadministration of nelfinavir (750 mg tid) at steady state with a single oral dose of 1200 mg azithromycin increased the mean $AUC_{0\text{ to }\infty}$ of azithromycin by approximately a factor of 2 times (range of up to 4 times) of that when azithromycin was given alone.

The mean C_{max} of azithromycin was also increased by approximately a factor of 2 times (range of up to 5 times) of that when azithromycin was given alone. Dose adjustment of azithromycin is not recommended. However, when administered in conjunction with nelfinavir, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted (see **ADVERSE REACTIONS**).

Following administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days to healthy adult subjects,

coadministration of 1200 mg azithromycin (2 x 600 mg azithromycin tablets) on the 7th day had no significant effects on peak concentrations (C_{max}), total exposure (AUC), and the urinary excretion of either trimethoprim or sulfamethoxazole.

Coadministration of trimethoprim/sulfamethoxazole DS for 7 days had no significant effect on the peak concentration (C_{max}) and total exposure (AUC) of azithromycin following administration of the single 1200 mg tablet dose to healthy adult subjects.

Administration of a 600 mg single oral dose of azithromycin had no effect on the pharmacokinetics of efavirenz given at 400 mg doses for 7 days to healthy adult subjects.

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 oral dose, while the AUC of azithromycin was not affected.

Azithromycin (500 mg Day 1, 250 mg Days 2 to 5) did not affect the plasma levels or pharmacokinetics of theophylline administered as a single intravenous dose. The effect of azithromycin on the plasma levels or pharmacokinetics of theophylline administered in multiple doses resulting in therapeutic steady-state levels of theophylline is not known. However, concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Therefore, until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.

Although, in a study of 22 healthy men, a 5 day course of azithromycin did not affect the prothrombin time from a subsequently administered dose of warfarin, spontaneous postmarketing reports suggest that concomitant administration of azithromycin

may potentiate the effects of oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Dose adjustments are not indicated when azithromycin and zidovudine are coadministered. When zidovudine (100 mg q3h x 5) was coadministered with daily azithromycin (600 mg, n = 5 or 1200 mg, n = 7), mean C_{max} , AUC and Cl_r increased by 26% (CV 54%), 10% (CV 26%) and 38% (CV 114%), respectively. The mean AUC of phosphorylated zidovudine increased by 75% (CV 95%), while zidovudine glucuronide C_{max} and AUC increased by less than 10%. In another study, addition of 1 gram azithromycin per week to a regimen of 10 mg/kg daily zidovudine resulted in 25% (CV 70%) and 13% (CV 37%) increases in zidovudine C_{max} and AUC, respectively. Zidovudine glucuronide mean C_{max} and AUC increased by 16% (CV 61%) and 8% (CV 32%), respectively.

Doses of 1200 mg/day azithromycin for 14 days in 6 subjects increased C_{max} of concurrently administered didanosine (200 mg q12h) by 44% (54% CV) and AUC by 14% (23% CV). However, none of these changes were significantly different from those produced in a parallel placebo control group of subjects.

Preliminary data suggest that coadministration of azithromycin and rifabutin did not markedly affect the mean serum concentrations of either drug. Administration of 250 mg azithromycin daily for 10 days (500 mg on the first day) produced mean concentrations of azithromycin 1 day after the last dose of 53 ng/mL when coadministered with 300 mg daily rifabutin and 49 mg/mL when coadministered with placebo. Mean concentrations 5 days after the last dose were 23 ng/mL and 21 ng/mL in the two groups of subjects. Administration of 300 mg rifabutin for 10 days produced mean concentrations of rifabutin one half day after the last dose of 60 mg/mL when coadministered with daily 250 mg azithromycin and 71 ng/mL when coadministered with placebo. Mean concentrations 5 days after the last dose were 8.1 ng/mL and 9.2 ng/mL in the two groups of subjects.

The following drug interactions have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin—elevated digoxin levels.

Ergotamine or dihydroergotamine—acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia.

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

Drugs metabolized by the cytochrome P⁴⁵⁰ system—elevations of serum carbamazepine, cyclosporine, hexobarbital, and phenytoin levels.

Laboratory Test Interactions

There are no reported laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (i.e., 200 mg/kg/day). These doses, based on a mg/m² basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg.

With regard to the MAC treatment dose of 600 mg daily, on a mg/m²/day basis, the doses in rats and mice are approximately 3.3 and 1.7 times the human dose, respectively.

With regard to the MAC prophylaxis dose of 1200 mg weekly, on a mg/m²/day basis, the doses in rats and mice are approximately 2 and 1 times the human dose, respectively.

No evidence of impaired fertility or harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when azithromycin is administered to a nursing woman.

Pediatric Use

In controlled clinical studies, azithromycin has been administered to pediatric patients ranging in age from 6 months to 12 years. For information regarding the use of azithromycin for oral suspension in the treatment of pediatric patients, please refer to the **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections of the prescribing information for azithromycin for oral suspension 100 mg/5 mL and 200 mg/5 mL bottles.

Safety in HIV-Infected Pediatric Patients

Safety and efficacy of azithromycin for the prevention or treatment of MAC in HIV-infected children have not been established. Safety data are available for 72 children 5 months to 18 years of age (mean 7 years) who received azithromycin for treatment of opportunistic infections. The mean duration of therapy was 242 days (range 3 to 2004 days) at doses of < 1 to 52 mg/kg/day (mean 12 mg/kg/day). Adverse events were similar to those observed in the adult population, most of which involved the gastrointestinal tract. Treatment related reversible hearing impairment in children was observed in 4 subjects (5.6%). Two (2.8%) children prematurely discontinued treatment due to side effects: one due to back pain and one due to abdominal pain, hot and cold flushes, dizziness, headache, and numbness. A third child discontinued due to a laboratory abnormality (eosinophilia). The protocols upon which these data are based specified a daily dose of 10 to 20 mg/kg/day (oral and/or I.V.) of azithromycin.

Geriatric Use

Pharmacokinetic parameters in older volunteers (65 to 85 years old) were similar to those in younger volunteers (18 to 40 years old) for the 5 day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen (see **CLINICAL PHARMACOLOGY**).

In multiple-dose clinical trials of oral azithromycin, 9% of patients were at least 65 years of age (458/4949) and 3% of patients (144/4949) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Elderly patients may be more susceptible to development of torsade de pointes arrhythmia than younger patients (see **WARNINGS**). Azithromycin 600 mg tablets contain 0.13 mg of sodium per tablet.

Geriatric Patients With Opportunistic Infections, Including *Mycobacterium Avium* Complex (MAC) Disease

Safety data are available for 30 patients (65 to 94 years old) treated with azithromycin at doses > 300 mg/day for a mean of 207 days. These patients were treated for a variety of opportunistic infections, including MAC. The side effect profile was generally similar to that seen in younger patients, except for a higher incidence of side effects relating to the gastrointestinal system and to reversible impairment of hearing (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple-dose clinical trials discontinued azithromycin therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Rarely but potentially serious side effects were angioedema and cholestatic jaundice.

Clinical

Multiple-Dose Regimen

Overall, the most common side effects in adult patients receiving a multiple-dose regimen of azithromycin were related to the gastrointestinal system with diarrhea/loose stools (5%), nausea (3%), and abdominal pain (3%) being the most frequently reported.

No other side effects occurred in patients on the multiple-dose regimen of azithromycin with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain.

Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.

Genitourinary: Monilia, vaginitis, and nephritis.

Nervous System: Dizziness, headache, vertigo, and somnolence.

General: Fatigue.

Allergic: Rash, photosensitivity, and angioedema.

Chronic Therapy With 1200 mg Weekly Regimen

The nature of side effects seen with the 1200 mg weekly dosing regimen for the prevention of *Mycobacterium avium* infection in severely immunocompromised HIV-infected patients were similar to those seen with short term dosing regimens (see **CLINICAL STUDIES**).

Chronic Therapy With 600 mg Daily Regimen Combined With Ethambutol

The nature of side effects seen with the 600 mg daily dosing regimen for the treatment of *Mycobacterium avium* complex infection in severely immunocompromised HIV-infected patients were similar to those seen with short term dosing regimens. Five percent of patients experienced reversible hearing impairment in the pivotal clinical trial for the treatment of disseminated MAC in patients with AIDS. Hearing impairment has been reported with macrolide antibiotics, especially at higher doses. Other treatment related side effects occurring in > 5% of subjects and seen at any time during a median of 87.5 days of therapy include: abdominal pain (14%), nausea (14%), vomiting (13%), diarrhea (12%), flatulence (5%), headache (5%) and abnormal vision (5%). Discontinuations from treatment due to laboratory abnormalities or side effects considered related to study drug occurred in 8/88 (9.1%) of subjects.

Postmarketing Experience

Adverse events reported with azithromycin during the postmarketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria, angioedema.

Cardiovascular: Arrhythmias including ventricular tachycardia, hypotension. There have been rare reports of QT prolongation and *torsade de pointes*.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and rare reports of tongue discoloration.

General: Asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal).

Genitourinary: Interstitial nephritis and acute renal failure, vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: Adverse reactions related to hepatic dysfunction have been reported in postmarketing experience with azithromycin (see **WARNINGS, Hepatotoxicity**).

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.

Psychiatric: Aggressive reaction and anxiety.

Skin/Appendages: Pruritus, rarely serious skin reactions including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

Special Senses: Hearing disturbances including hearing loss, deafness, and/or tinnitus, reports of taste/smell perversion and/or loss.

Laboratory Abnormalities

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

With an incidence of 1 to 2%, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT, and AST (SGOT).

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

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

In multiple-dose clinical trials involving more than 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

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/mm³).

Laboratory abnormalities seen in clinical trials for the prevention of disseminated *Mycobacterium avium* disease in severely immunocompromised HIV-infected patients are presented in the **CLINICAL STUDIES** section.

Chronic therapy (median duration: 87.5 days, range: 1 to 229 days) that resulted in laboratory abnormalities in > 5% subjects with normal baseline values in the pivotal trial for treatment of disseminated MAC in severely immunocompromised HIV infected patients treated with azithromycin 600 mg daily in combination with ethambutol include: a reduction in absolute neutrophils to < 50% of the lower limit of normal (10/52, 19%) and an increase to five times the upper limit of normal in alkaline phosphatase (3/35, 9%). These findings in subjects with normal baseline values are similar when compared to all subjects for analyses of neutrophil reductions (22/75 [29%]) and elevated alkaline phosphatase (16/80 [20%]). Causality of these laboratory abnormalities due to the use of study drug has not been established.

DOSAGE AND ADMINISTRATION

(See **INDICATIONS AND USAGE**.)

Not for pediatric use.

Pediatric Use

For pediatric patients, please refer to the **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections of the prescribing information for azithromycin for oral suspension 100 mg/5 mL and 200 mg/5 mL bottles.

Azithromycin tablets may be taken without regard to food. However, increased tolerability has been observed when tablets are taken with food.

Prevention of Disseminated MAC Infections

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

Treatment of Disseminated MAC Infections

Azithromycin tablets should be taken at a daily dose of 600 mg, in combination with ethambutol at the recommended daily dose of 15 mg/kg. Other antimycobacterial drugs that have shown *in vitro* activity against MAC may be added to the regimen of azithromycin tablets plus ethambutol at the discretion of the physician or health care provider.

Renal Insufficiency

No dosage adjustment is recommended for subjects with renal impairment (GFR \leq 80 mL/min). The mean AUC_{0 to 120} was similar in subjects with GFR 10 to 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 **CLINICAL PHARMACOLOGY, Renal Insufficiency**).

Hepatic Insufficiency

The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established. No dosage adjustment recommendations can be made in patients with impaired hepatic function (see **CLINICAL PHARMACOLOGY, Hepatic Impairment**).

HOW SUPPLIED

Azithromycin Tablets USP are available as follows:

600 mg: White to off-white, unscored, film-coated, modified-capsule-shaped tablet containing azithromycin monohydrate equivalent to 600 mg azithromycin, USP. Debossed with “93” on one side and “7147” on the other side of the tablet. These are packaged in bottles of 30 tablets.

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

CLINICAL STUDIES IN PATIENTS WITH ADVANCED HIV INFECTION FOR THE PREVENTION AND TREATMENT OF DISEASE DUE TO DISSEMINATED MYCOBACTERIUM AVIUM COMPLEX (MAC)

(See **INDICATIONS AND USAGE**.)

Prevention of Disseminated MAC Disease

Two randomized, double blind clinical trials were performed in patients with CD4 counts $<$ 100 cells/ μ L. The first study (155) compared azithromycin (1200 mg once weekly) to placebo and enrolled 182 patients with a mean CD4 count of 35 cells/ μ L. The second study (174) randomized 723 patients to either azithromycin (1200 mg once weekly), rifabutin (300 mg daily) or the combination of both. The mean CD4 count was 51 cells/ μ L. The primary endpoint in these studies was disseminated MAC disease. Other endpoints included the incidence of clinically significant MAC disease and discontinuations from therapy for drug-related side effects.

MAC Bacteremia

In trial 155, 85 patients randomized to receive azithromycin and 89 patients randomized to receive placebo met study entrance criteria. Cumulative incidences at 6, 12 and 18 months of the possible outcomes are in the following table:

| Cumulative Incidence Rate, %: Placebo (n = 89) | | | | |
|---|--------------------|------|--------------------|-------------------|
| Month | MAC Free and Alive | MAC | Adverse Experience | Lost to Follow-up |
| 6 | 69.7 | 13.5 | 6.7 | 10.1 |
| 12 | 47.2 | 19.1 | 15.7 | 18 |
| 18 | 37.1 | 22.5 | 18 | 22.5 |
| Cumulative Incidence Rate, %: Azithromycin (n = 85) | | | | |
| Month | MAC Free and Alive | MAC | Adverse Experience | Lost to Follow-up |

| | | | | |
|----|------|------|------|------|
| 6 | 84.7 | 3.5 | 9.4 | 2.4 |
| 12 | 63.5 | 8.2 | 16.5 | 11.8 |
| 18 | 44.7 | 11.8 | 25.9 | 17.6 |

The difference in the one year cumulative incidence rates of disseminated MAC disease (placebo–azithromycin) is 10.9%. This difference is statistically significant ($p = 0.037$) with a 95% confidence interval for this difference of (0.8%, 20.9%). The comparable number of patients experiencing adverse events and the fewer number of patients lost to follow-up on azithromycin should be taken into account when interpreting the significance of this difference.

In trial 174, 223 patients randomized to receive rifabutin, 223 patients randomized to receive azithromycin, and 218 patients randomized to receive both rifabutin and azithromycin met study entrance criteria. Cumulative incidences at 6, 12 and 18 months of the possible outcomes are recorded in the following table:

| Cumulative Incidence Rate, %: Rifabutin (n = 223) | | | | |
|--|--------------------|------|--------------------|-------------------|
| Month | MAC Free and Alive | MAC | Adverse Experience | Lost to Follow-up |
| 6 | 83.4 | 7.2 | 8.1 | 1.3 |
| 12 | 60.1 | 15.2 | 16.1 | 8.5 |
| 18 | 40.8 | 21.5 | 24.2 | 13.5 |
| Cumulative Incidence Rate, %: Azithromycin (n = 223) | | | | |
| Month | MAC Free and Alive | MAC | Adverse Experience | Lost to Follow-up |
| 6 | 85.2 | 3.6 | 5.8 | 5.4 |
| 12 | 65.5 | 7.6 | 16.1 | 10.8 |
| 18 | 45.3 | 12.1 | 23.8 | 18.8 |
| Cumulative Incidence Rate, %: Azithromycin/Rifabutin Combination (n = 218) | | | | |
| Month | MAC Free and Alive | MAC | Adverse Experience | Lost to Follow-up |
| 6 | 89.4 | 1.8 | 5.5 | 3.2 |
| 12 | 71.6 | 2.8 | 15.1 | 10.6 |
| 18 | 49.1 | 6.4 | 29.4 | 15.1 |

Comparing the cumulative one year incidence rates, azithromycin monotherapy is at least as effective as rifabutin monotherapy. The difference (rifabutin–azithromycin) in the one year rates (7.6%) is statistically significant ($p = 0.022$) with an adjusted 95% confidence interval (0.9%, 14.3%). Additionally, azithromycin/rifabutin combination therapy is more effective than rifabutin alone. The difference (rifabutin–azithromycin/rifabutin) in the cumulative one year incidence rates (12.5%) is statistically significant ($p < 0.001$) with an adjusted 95% confidence interval of (6.6%, 18.4%). The comparable number of patients experiencing adverse events and the fewer number of patients lost to follow-up on rifabutin should be taken into account when interpreting the significance of this difference.

In Study 174, sensitivity testing⁴ was performed on all available MAC isolates from subjects randomized to either azithromycin, rifabutin or the combination. The distribution of MIC values for azithromycin from susceptibility testing of the breakthrough isolates was similar between study arms. As the efficacy of azithromycin in the treatment of disseminated MAC has not been established, the clinical relevance of these *in vitro* MICs as an indicator of susceptibility or resistance is not known.

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 Study 155, discontinuations for drug-related toxicity occurred in 8.2% of subjects treated with azithromycin and 2.3% of those given placebo ($p = 0.121$). In Study 174, 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%; $p = 0.209$).

Safety

As these patients with advanced HIV disease were taking multiple concomitant medications and experienced a variety of intercurrent illnesses, it was often difficult to attribute adverse events to study medication. Overall, the nature of side effects seen on the weekly

dosage regimen of azithromycin over a period of approximately one year in patients with advanced HIV disease was similar to that previously reported for shorter course therapies.

INCIDENCE OF ONE OR MORE TREATMENT RELATED* ADVERSE EVENTS† IN HIV INFECTED PATIENTS RECEIVING PROPHYLAXIS FOR DISSEMINATED MAC OVER APPROXIMATELY 1 YEAR

| | Study 155 | | Study 174 | | |
|---------------------------------|---------------------|--|---|--|--|
| | Placebo (N = 91) | Azithromycin 1200 mg Weekly (N = 89) | Azithromycin 1200 mg Weekly (N = 233) | Rifabutin 300 mg Daily (N = 236) | Azithromycin + Rifabutin (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 |
| Autonomic Nervous System | | | | | |
| Mouth Dry | 0 | 0 | 0 | 3 | 2.7 |
| Central Nervous System | | | | | |
| Dizziness | 0 | 1.1 | 3.9 | 1.7 | 0.4 |
| Headache | 0 | 0 | 3 | 5.5 | 4.5 |
| Gastrointestinal | | | | | |
| Diarrhea | 15.4 | 52.8 | 50.2 | 19.1 | 50.9 |
| Loose Stools | 6.6 | 19.1 | 12.9 | 3 | 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 |
| Nausea | 11 | 32.6 | 27 | 16.5 | 28.1 |
| Vomiting | 1.1 | 6.7 | 9 | 3.8 | 5.8 |
| General | | | | | |
| 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 |
| Musculoskeletal | | | | | |
| Arthralgia | 0 | 0 | 3 | 4.2 | 7.1 |
| Psychiatric | | | | | |
| Anorexia | 1.1 | 0 | 2.1 | 2.1 | 3.1 |
| Skin & Appendages | | | | | |
| Pruritus | 3.3 | 0 | 3.9 | 3.4 | 7.6 |
| Rash | 3.2 | 3.4 | 8.1 | 9.4 | 11.1 |
| Skin discoloration | 0 | 0 | 0 | 2.1 | 2.2 |
| Special Senses | | | | | |
| Tinnitus | 4.4 | 3.4 | 0.9 | 1.3 | 0.9 |
| Hearing Decreased | 2.2 | 1.1 | 0.9 | 0.4 | 0 |
| Uveitis | 0 | 0 | 0.4 | 1.3 | 1.8 |
| 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 (except uveitis)

Side effects related to the gastrointestinal tract were seen more frequently in patients receiving azithromycin than in those receiving placebo or rifabutin. In Study 174, 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.

Changes in Laboratory Values

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

Prophylaxis Against Disseminated MAC Abnormal Laboratory Values*

| | | Placebo | | Azithromycin 1200 mg Weekly | | Rifabutin 300 mg Daily | | Azithromycin & Rifabutin | |
|----------------|---|---------|----|--------------------------------|----|---------------------------|----|-----------------------------|----|
| Hemoglobin | < 8 g/dl | 1/51 | 2% | 4/170 | 2% | 4/114 | 4% | 8/107 | 8% |
| Platelet Count | < 50 x 10 ³ /mm ³ | 1/71 | 1% | 4/260 | 2% | 2/182 | 1% | 6/181 | 3% |
| WBC Count | < 1 x 10 ³ /mm ³ | 0/8 | 0% | 2/70 | 3% | 2/47 | 4% | 0/43 | 0% |
| Neutrophils | < 500/mm ³ | 0/26 | 0% | 4/106 | 4% | 3/82 | 4% | 2/78 | 3% |
| SGOT | > 5 x ULN [†] | 1/41 | 2% | 8/158 | 5% | 3/121 | 3% | 6/114 | 5% |
| SGPT | > 5 x ULN | 0/49 | 0% | 8/166 | 5% | 3/130 | 2% | 5/117 | 4% |
| Alk Phos | > 5 x ULN | 1/80 | 1% | 4/247 | 2% | 2/172 | 1% | 3/164 | 2% |

*excludes subjects outside of the relevant normal range at baseline

[†]= Upper Limit of Normal

Treatment of Disseminated MAC Disease

One randomized, double blind clinical trial (Study 189) was performed in patients with disseminated MAC. In this trial, 246 HIV infected patients with disseminated MAC received either azithromycin 250 mg qd (N = 65), azithromycin 600 mg qd (N = 91) or clarithromycin 500 mg bid (N = 90), each administered with ethambutol 15 mg/kg qd, for 24 weeks. Patients were cultured and clinically assessed every 3 weeks through week 12 and monthly thereafter through week 24. After week 24, patients were switched to any open label therapy at the discretion of the investigator and followed every 3 months through the last follow up visit of the trial. Patients were followed from the baseline visit for a period of up to 3.7 years (median: 9 months). MAC isolates recovered during study treatment or post-treatment were obtained whenever possible.

The primary endpoint was sterilization by week 24. Sterilization was based on data from the central laboratory, and was defined as two consecutive observed negative blood cultures for MAC, independent of missing culture data between the two negative observations. Analyses were performed on all randomized patients who had a positive baseline culture for MAC.

The azithromycin 250 mg arm was discontinued after an interim analysis at 12 weeks showed a significantly lower clearance of bacteremia compared to clarithromycin 500 mg bid.

Efficacy results for the azithromycin 600 mg qd and clarithromycin 500 mg bid treatment regimens are described in the following table:

Response to Therapy of Patients Taking Ethambutol and Either Azithromycin 600 mg qd or Clarithromycin 500 mg bid

| | Azithromycin 600 mg qd | Clarithromycin 500 mg bid | *95.1% CI on difference |
|--|------------------------|---------------------------|-------------------------|
| Patients With Positive Culture at Baseline | 68 | 57 | |
| Week 24 | | | |
| Two Consecutive Negative Blood Cultures [†] | 31/68 (46%) | 32/57 (56%) | [-28, 7] |
| Mortality | 16/68 (24%) | 15/57 (26%) | [-18, 13] |

*[95% confidence interval] on difference in rates (azithromycin-clarithromycin)

[†]Primary endpoint

The primary endpoint, rate of sterilization of blood cultures (two consecutive negative cultures) at 24 weeks, was lower in the azithromycin 600 mg qd group than in the clarithromycin 500 mg bid group.

Sterilization by Baseline Colony Count

Within both treatment groups, the sterilization rates at week 24 decreased as the range of MAC cfu/mL increased.

| | Azithromycin 600 mg (N = 68) | Clarithromycin 500 mg bid (N = 57) |
|--|---|---|
| Groups Stratified by MAC Colony Counts at Baseline | No. (%) Subjects in Stratified Group Sterile at Week 24 | No. (%) Subjects in Stratified Group Sterile at Week 24 |
| ≤ 10 cfu/mL | 10/15 (66.7%) | 12/17 (70.6%) |
| 11 to 100 cfu/mL | 13/28 (46.4%) | 13/19 (68.4%) |
| 101 to 1,000 cfu/mL | 7/19 (36.8%) | 5/13 (38.5%) |

| | | |
|------------------------|-----------|-------------|
| 1,001 to 10,000 cfu/mL | 1/5 (20%) | 1/5 (20%) |
| > 10,000 cfu/mL | 0/1 (0%) | 1/3 (33.3%) |

Susceptibility Pattern of MAC Isolates

Susceptibility testing was performed on MAC isolates recovered at baseline, at the time of breakthrough on therapy or during post-therapy follow-up. The T100 radiometric broth method was employed to determine azithromycin and clarithromycin MIC values. Azithromycin MIC values ranged from < 4 to > 256 mcg/mL and clarithromycin MICs ranged from < 1 to > 32 mcg/mL. The individual MAC susceptibility results demonstrated that azithromycin MIC values could be 4 to 32 fold higher than clarithromycin MIC values.

During study treatment and post-treatment follow up for up to 3.7 years (median: 9 months) in study 189, a total of 6/68 (9%) and 6/57 (11%) of the patients randomized to azithromycin 600 mg daily and clarithromycin 500 mg bid, respectively, developed MAC blood culture isolates that had a sharp increase in MIC values. All twelve MAC isolates had azithromycin MIC's \geq 256 mcg/mL and clarithromycin MIC's > 32 mcg/mL. These high MIC values suggest development of drug resistance. However, at this time, specific breakpoints for separating susceptible and resistant MAC isolates have not been established for either macrolide.

ANIMAL TOXICOLOGY

Phospholipidosis (intracellular phospholipid binding) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs administered doses which, based on pharmacokinetics, are as low as 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. The significance of these findings for humans is unknown.

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