AZITHROMYCIN MONOHYDRATE- azithromycin monohydrate tablet
LUPIN LIMITED

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use azithromycin tablets USP safely and effectively. See full prescribing information for azithromycin tablets USP.

AZITHROMYCIN tablets USP, 600 mg, for oral use
Initial U.S. Approval: 1991

RECENT MAJOR CHANGES

INDICATIONS AND USAGE

Azithromycin tablets USP are a macrolide antibacterial indicated for mild to moderate infections caused by designated, susceptible bacteria:

- Mycobacterial Infections (1.2)

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.

DOSAGE AND ADMINISTRATION

- Mycobacterial Infections (2.2)

DOSAGE FORMS AND STRENGTHS

- Azithromycin tablets USP, 600 mg

CONTRAINDICATIONS

- Patients with known hypersensitivity to azithromycin, erythromycin, any macrolide, or ketolide antibiotic. (4.1)
- Patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin. (4.2)

WARNINGS AND PRECAUTIONS

- Serious (including fatal) allergic and skin reactions. Discontinue azithromycin and initiate appropriate therapy if reaction occurs. (5.1)
- Hepatotoxicity: Discontinue azithromycin immediately if signs and symptoms of hepatitis occur. (5.2)
- Prolongation of QT interval and cases of torsades de pointes have been reported. This risk which can be fatal should be considered in patients with certain cardiovascular disorders including known QT prolongation or history torsades de pointes, those with prorrhythmic conditions, and with other drugs that prolong the QT interval. (5.3)
- *Clostridium difficile* -associated diarrhea: Evaluate patients if diarrhea occurs. (5.4)
- Azithromycin exacerbate muscle weakness in persons with myasthenia gravis (5.5)

ADVERSE REACTIONS

The most common adverse reactions are diarrhea (5%), nausea (3%), abdominal pain (3%), or vomiting, (no percent given). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals, Inc. at 1-800-399-2561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Nelfinavir: Close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (7.1)
- Warfarin: Use with azithromycin may increase coagulation times; monitor prothrombin time. (7.2)

USE IN SPECIFIC POPULATIONS

- Pediatric Use: Safety and effectiveness in the treatment of patients under 6 months of age have not been established. (8.4)
- Geriatric Use: Elderly patients may be more susceptible to development of torsades de pointes arrhythmias (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Azithromycin tablets USP are a macrolide antibacterial drug indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below.

1.2 Mycobacterial Infections

Prophylaxis of Disseminated Mycobacterium avium complex (MAC) Disease

Azithromycin tablets USP, taken alone or in combination with rifabutin at its approved dose, is indicated for the prevention of disseminated MAC disease in persons with advanced HIV infection *[see DOSAGE AND ADMINISTRATION (2)]*.

Treatment of Disseminated MAC Disease

Azithromycin tablets USP, taken in combination with ethambutol, is indicated for the treatment of disseminated MAC infections in persons with advanced HIV infection *[see USE IN SPECIFIC POPULATIONS (8.4) AND CLINICAL STUDIES (14.1)].*

2 DOSAGE AND ADMINISTRATION

[see INDICATIONS AND USAGE (1)]

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

2.2 Mycobacterial Infections

Prevention of Disseminated MAC Infections

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

Treatment of Disseminated MAC Infections

Azithromycin 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 plus ethambutol at the discretion of the physician or health care provider.

3 DOSAGE FORMS AND STRENGTHS

Azithromycin Tablets USP, 600 mg are supplied as white, oval shaped film-coated tablets, engraved with "LU" on one side and "L13" on the other side containing azithromycin monohydrate USP equivalent to 600 mg of azithromycin USP. These are packaged in bottles of 30 tablets.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

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

4.2 Hepatic Dysfunction

Azithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson Syndrome and toxic epidermal necrolysis, have been reported rarely in patients on azithromycin therapy. *[see CONTRAINDICATIONS (4.1)]*.

Fatalities have been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure**.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is presently unknown.

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

5.2 Hepatotoxicity

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

5.3 QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- patients on drugs known to prolong the QT interval
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

5.4 Clostridium difficile-Associated Diarrhea (CDAD)

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 antibacterial 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.

5.5 Exacerbation of Myasthenia Gravis

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

5.7 Development of Drug-Resistant Bacteria

Prescribing azithromycin 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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, most of the reported adverse reactions 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 adverse reactions. Serious adverse reactions included angioedema and cholestatic jaundice. Most of the adverse reactions leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain *[see CLINICAL STUDIES (14.2)]*.

Multiple-dose regimen

Overall, the most common adverse reactions 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 adverse reactions occurred in patients on the multiple-dose regimen of azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Cardiovascular:

Palpitations and 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 adverse reactions 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 (14)]*.

Chronic therapy with 600 mg daily regimen combined with ethambutol

The nature of adverse reactions 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 adverse reactions 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 adverse reactions considered related to study drug occurred in 8 of 88 (9.1%) of subjects.

Single 1 gram dose regimen

Overall, the most common adverse reactions in patients receiving a single-dose regimen of 1 gram of azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Adverse reactions that occurred in patients on the single 1 gram dosing regimen of azithromycin with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of azithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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

Allergic:

Arthralgia, edema, urticaria, and angioedema.

Cardiovascular:

Arrhythmias, including ventricular tachycardia, and hypotension. There have been reports of QT prolongation and *torsades de pointes*.

Gastrointestinal:

Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and tongue discoloration.

General:

Asthenia, paresthesia, fatigue, malaise, and anaphylaxis

Genitourinary:

Interstitial nephritis, acute renal failure, and vaginitis.

Hematopoietic:

Thrombocytopenia.

Liver/Biliary:

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure, *[see WARNINGS AND PRECAUTIONS (5.2)]*.

Nervous System:

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

Psychiatric:

Aggressive reaction and anxiety.

Skin/Appendages:

Pruritus, and serious skin reactions including erythema multiforme, Stevens -Johnson syndrome, and toxic epidermal necrolysis.

Special Senses:

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

6.3 Laboratory Abnormalities

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

- 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 1 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^3).

Laboratory abnormalities seen in clinical trials for the prevention of disseminated *Mycobacterium avium* disease in severely immunocompromised HIV-infected patients *[see CLINICAL STUDIES (14)]*

Chronic therapy (median duration: 87.5 days, range: 1 to 229 days) that resulted in laboratory abnormalities in >5% of 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.

7 DRUG INTERACTIONS

7.1 Nelfinavir

Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. *[see ADVERSE REACTIONS (6)]*.

7.2 Warfarin

Spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

7.3 Potential Drug-Drug Interaction with Macrolides

Interactions with the following drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin or phenytoin are used with azithromycin careful monitoring of patients is advised.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B:

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 daily doses in rats and mice, based on body surface area, are estimated to be 3.2 and 1.6 times, respectively, an adult daily dose of 600 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Azithromycin has been reported to be excreted in breast milk in small amounts. Caution should be exercised when azithromycin is administered to a nursing woman.

8.4 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, *[see INDICATIONS AND USAGE (1)* and *DOSAGE AND ADMINISTRATION (2)]* of the prescribing information for azithromycin for oral suspension 100 mg/5 mL and 200 mg/5 mL bottles.

HIV-Infected Pediatric Patients

The 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 reactions 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 adverse reactions: 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 IV) of azithromycin.

8.5 Geriatric Use

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 torsades de pointes arrhythmias than younger patients. [see *WARNINGS AND PRECAUTIONS (5.3)]*.

Azithromycin 600 mg tablets contain 1.5 mg of sodium per tablet.

Geriatric Patients with Opportunistic Infections, Including (MAC) Disease

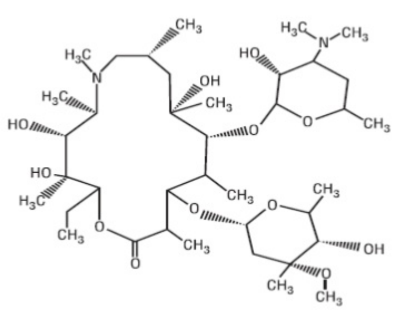
Safety data are available for 30 patients (65 to 94 years old) treated with azithromycin at doses >300 mg/day for a mean of 207 days. These patients were treated for a variety of opportunistic infections, including MAC. The adverse reactions were generally similar to that seen in younger patients, except for a higher incidence of adverse reactions relating to the gastrointestinal system and to reversible impairment of hearing *[see DOSAGE AND ADMINISTRATION (2)]*.

10 OVERDOSAGE

Adverse reactions 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.

11 DESCRIPTION

Azithromycin tablets USP contains the active ingredient azithromycin, a macrolide antibacterial drug, for oral administration. Azithromycin has the chemical name (*2R,3S,4R,5R,8R,10R,11R,12S,13S,14R*)-13-[(2,6-dideoxy-3-*C*-methyl -3-*O*-methyl-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 is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.0. Azithromycin has the following structural formula:



Azithromycin, as the monohydrate, is a white to almost white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}$•H_2O and a molecular weight of 767.0.

Azithromycin tablets USP contain azithromycin monohydrate equivalent to 600 mg azithromycin. They also contain the following inactive ingredients: croscarmellose sodium, dibasic calcium phosphate, hydroxypropyl methyl cellulose, lactose monohydrate, magnesium stearate, sodium lauryl sulfate, titanium dioxide and triacetin.

Organic Impurities Test Pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Azithromycin is a macrolide antibacterial drug *[see MICROBIOLOGY (12.4)]*.

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 of incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

12.2 Pharmacodynamics

Based on animal models of infection, the antibacterial activity of azithromycin appears to correlate with the ratio of area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for certain pathogens (*S. pneumoniae* and *S. aureus*). The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with azithromycin.

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with oral azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose-and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

12.3 Pharmacokinetics

The pharmacokinetic parameters of azithromycin in plasma after dosing as per labeled recommendations in healthy young adults and asymptomatic HIV-positive 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)	$T_{½}$ (hr)	Urinary Excretion (% of dose)
500 mg/250 mg capsule	12	1	0.41	2.5	0.05	2.6*	–	4.5
and 250 mg on Days 2 to 5	12	5	0.24	3.2	0.05	2.1*	–	6.5
1200 mg/600 mg tablets	12	1	0.66	2.5	0.074	6.8[b]	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_{0-24}; [b]0-last.

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-positive adult subjects receiving 600 mg azithromycin tablets once daily for 22 days, steady state azithromycin serum levels were achieved by Day 15 of dosing.

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.

Absorption

The 1 gram single-dose packet is bioequivalent to four 250 mg azithromycin capsule

When the oral suspension of azithromycin was administered with food, the C_{max} increased by 46% and the AUC by 14%.

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%).

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL.

The antibacterial activity of azithromycin is pH related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Azithromycin has been shown to penetrate into tissues in humans, including skin, lung, tonsil, and cervix. 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 importance of these tissue concentration data is unknown.

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 hours. The mean half-lives for 6 males and 6 females were 34 hours and 57 hours, respectively. Leukocyte-to-plasma C_{max} ratios for males and females were 258 (±77%) and 175 (±60%), respectively, and the AUC ratios were 804 (±31%) and 541 (±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-positive adults, mean maximum concentration in peripheral leukocytes was 252 mcg/mL (±49%). Trough concentrations in peripheral leukocytes at steady-state averaged 146 mcg/mL (±33%). The mean leukocyte-to-serum C_{max} ratio was 456 (±38%) and the mean leukocyte to serum AUC ratio was 816 (±31%). The clinical relevance of these findings is unknown.

Metabolism

In vitro and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. 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.

Specific Populations

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_{0-120} 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_{0-120} 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).

Hepatic Insufficiency:

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

Gender:

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended on the basis of gender.

Geriatric Patients:

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 Geriatric Use (8.5)].*

Pediatric Patients:

For information regarding the pharmacokinetics of azithromycin for oral suspension in pediatric patients, see the prescribing information for azithromycin for oral suspension 100 mg/5 mL and 200 mg/5 mL bottles.

Drug-drug Interactions:

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 1 and the effects of other drugs on the pharmacokinetics of azithromycin are shown in Table 2.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 1. No dosage adjustment of drugs listed in Table 1 is recommended when co-administered with azithromycin.

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the C_{max} and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 2 *[see DRUG INTERACTIONS (7.3)].*

Table 1: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin

Co-administered Drug	**Dose of Co-administered Drug**	**Dose of Azithromycin**	**n**	**Ratio (with/without azithromycin) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1**	
				Mean C_{max}	**Mean AUC**
Atorvastatin	10 mg/day for 8 days	500 mg/day orally on days 6 to 8	12	0.83 (0.63 to 1.08)	1.01 (0.81 to 1.25)
Carbamazepine	200 mg/day for 2 days, then 200 mg twice a day for 18 days	500 mg/day orally for days 16 to 18	7	0.97 (0.88 to 1.06)	0.96 (0.88 to 1.06)
Cetirizine	20 mg/day for 11 days	500 mg orally on day 7, then 250 mg/day on days 8 to 11	14	1.03 (0.93 to 1.14)	1.02 (0.92 to 1.13)
Didanosine	200 mg orally twice a day for 21 days	1,200 mg/day orally on days 8 to 21	6	1.44 (0.85 to 2.43)	1.14 (0.83 to 1.57)
Efavirenz	400 mg/day for 7 days	600 mg orally on day 7	14	1.04*	0.95*
Fluconazole	200 mg orally single dose	1,200 mg orally single dose	18	1.04 (0.98 to 1.11)	1.01 (0.97 to 1.05)
Indinavir	800 mg three times a day for 5 days	1,200 mg orally on day 5	18	0.96 (0.86 to 1.08)	0.90 (0.81 to 1)
Midazolam	15 mg orally on day 3	500 mg/day orally for 3 days	12	1.27 (0.89 to 1.81)	1.26 (1.01 to 1.56)
Nelfinavir	750 mg three times a day for 11 days	1,200 mg orally on day 9	14	0.90 (0.81 to 1.01)	0.85 (0.78 to 0.93)
Sildenafil	100 mg on days 1 and 4	500 mg/day orally for 3 days	12	1.16 (0.86 to 1.57)	0.92 (0.75 to 1.12)
Theophylline	4 mg/kg IV on days 1, 11, 25	500 mg orally on day 7, 250 mg/day on days 8 to 11	10	1.19 (1.02 to 1.4)	1.02 (0.86 to 1.22)
Theophylline	300 mg orally BID ×15 days	500 mg orally on day 6, then 250 mg/day on days 7 to 10	8	1.09 (0.92 to 1.29)	1.08 (0.89 to 1.31)
Triazolam	0.125 mg on day 2	500 mg orally on day 1, then 250 mg/day on day 2	12	1.06*	1.02*
Trimethoprim/ Sulfamethoxazole	160 mg/800 mg/day orally for 7 days	1,200 mg orally on day 7	12	0.85 (0.75 to 0.97)/ 0.90 (0.78 to 1.03)	0.87 (0.80 to 0.95)/ 0.96 (0.88 to 1.03)
Zidovudine	500 mg/day orally for 21 days	600 mg/day orally for 14 days	5	1.12 (0.42 to 3.02)	0.94 (0.52 to 1.7)
Zidovudine	500 mg/day orally for 21 days	1,200 mg/day orally for 14 days	4	1.31 (0.43 to 3.97)	1.3 (0.69 to 2.43)

* -90% Confidence interval not reported

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

Co-administered Drug	**Dose of Co-administered Drug**	**Dose of Azithromycin**	**n**	**Ratio (with/without co-administered drug) of Azithromycin Pharmacokinetic Parameters (90% CI); No Effect = 1**	
				Mean C_{max}	**Mean AUC**
Efavirenz	400 mg/day for 7 days	600 mg orally on day 7	14	1.22 (1.04 to 1.42)	0.92*

Fluconazole	200 mg orally single dose	1,200 mg orally single dose	18	0.82 (0.66 to 1.02)	1.07 (0.94 to 1.22)
Nelfinavir	750 mg three times a day for 11 days	1,200 mg orally on day 9	14	2.36 (1.77 to 3.15)	2.12 (1.80 to 2.50)

* -90% Confidence interval not reported

12.4 Microbiology

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in *[see INDICATIONS AND USAGE (1)].*

Aerobic Gram-Positive Microorganisms

Staphylococcus aureus

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

NOTE: Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of *Enterococcus faecalis* and methicillin-resistant *staphylococci* are resistant to azithromycin.

Aerobic Gram-Negative Microorganisms

Haemophilus influenzae

Moraxella catarrhalis

Other Microorganisms

Chlamydia trachomatis

Beta-lactamase production should have no effect on azithromycin activity.

Azithromycin has been shown to be active *in vitro* and in the prevention and treatment of disease caused by the following microorganisms:

Mycobacteria

Mycobacterium avium complex (MAC) consisting of:

Mycobacterium avium

Mycobacterium intracellulare

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

Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 mcg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic Gram-Positive Microorganisms

Streptococci (Groups C, F, G)

Viridans group streptococci

Aerobic Gram-Negative Microorganisms

Bordetella pertussis

Campylobacter jejuni

Haemophilus ducreyi

Legionella pneumophila

Anaerobic Microorganisms

Bacteroides bivius

Clostridium perfringens

Peptostreptococcus species

Other Microorganisms

Borrelia burgdorferi

Mycoplasma pneumoniae

Treponema pallidum

Ureaplasma urealyticum

Susceptibility Testing of Bacteria Excluding Mycobacteria

The *in vitro* potency of azithromycin is markedly affected by the pH of the microbiological growth medium during incubation. Incubation in a 10% CO_2 atmosphere will result in lowering of media pH (7.2 to 6.6) within 18 hours and in an apparent reduction of the *in vitro* potency of azithromycin. Thus, the initial pH of the growth medium should be 7.2 to 7.4, and the CO_2 content of the incubation atmosphere should be as low as practical.

Azithromycin can be solubilized for *in vitro* susceptibility testing by dissolving in a minimum amount of 95% ethanol and diluting to working concentration with water.

Dilution Techniques

Quantitative methods are used to determine minimal inhibitory concentrations that provide reproducible estimates of the susceptibility of bacteria to antibacterial compounds. One such standardized procedure uses a standardized dilution method[1](broth, agar or microdilution) or equivalent with azithromycin powder. The MIC values should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

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 microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that usually achievable drug concentrations are unlikely to be inhibitory and that other therapy should be selected.

Measurement of MIC or minimum bacterial concentration (MBC) and achieved antibacterial compound concentrations may be appropriate to guide therapy in some infections. *[see CLINICAL PHARMACOLOGY (12)]* section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antibacterial drug product.)

Standardized susceptibility test procedures require the use of laboratory control microorganisms. Standard azithromycin powder should provide the following MIC values:

Microorganism	MIC (mcg/mL)
Escherichia coli ATCC 25922	2 to 8
Enterococcus faecalis ATCC 29212	1 to 4
Staphylococcus aureus ATCC 29213	0.25 to 1

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antibacterial compounds. One such standardized procedure[2] that has been recommended for use with disks to test the susceptibility of microorganisms to azithromycin uses the 15 mcg azithromycin disk. Interpretation involves the correlation of the diameter obtained in the disk test with the MIC for azithromycin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 mcg azithromycin disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 18	Susceptible (S)
14 to 17	Intermediate (I)
≤ 13	Resistant (R)

Interpretation should be as stated above for results using dilution techniques.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms. The 15 mcg azithromycin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Staphylococcus aureus ATCC 25923	21 to 26

In Vitro Activity of Azithromycin Against Mycobacteria

Azithromycin has demonstrated *in vitro* activity against MAC organisms. While gene probe techniques may be used to distinguish between *M. avium* and *M. intracellulare*, many studies only reported results on MAC isolates. Azithromycin has also been shown to be active against phagocytized MAC organisms in mouse and human macrophage cell cultures as well as in the beige mouse infection model.

Various *in vitro* methodologies employing broth or solid media at different pHs, with and without oleic acid-albumin-dextrose-catalase (OADC), have been used to determine azithromycin MIC values for MAC strains. In general, azithromycin MIC values decreased 4 to 8 fold as the pH of Middlebrook 7H11 agar media increased from 6.6 to 7.4. At pH 7.4, azithromycin MIC values determined with Mueller-Hinton agar were 4 fold higher than that observed with Middlebrook 7H12 media at the same pH. Utilization of oleic OADC in these assays has been shown to further alter MIC values. The relationship between azithromycin and clarithromycin MIC values has not been established. In general, azithromycin MIC values were observed to be 2 to 32 fold higher than clarithromycin independent of the susceptibility method employed.

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

Drug 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.[3,4] MAC isolates exhibiting cross-resistance show an increase in azithromycin MICs to ≥128 mcg/mL with clarithromycin MICs increasing to ≥32 mcg/mL. These MIC values were determined employing the radiometric broth dilution susceptibility testing method with Middlebrook 7H12 medium. The clinical significance of azithromycin and clarithromycin cross-resistance is not fully understood at this time but preclinical data suggest that reduced activity to both agents will occur after MAC strains produce the 23S rRNA mutation.

Susceptibility Testing for MAC

The disk diffusion techniques and dilution methods for susceptibility testing against gram-positive and gram-negative bacteria should not be used for determining azithromycin MIC values against mycobacteria. *In vitro* susceptibility testing methods and diagnostic products currently available for determining MIC values against MAC organisms have not been standardized or validated.

Azithromycin MIC values will vary depending on the susceptibility testing method employed, composition and pH of media, and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *M. avium* or *M. intracellulare* are susceptible or resistant to azithromycin have not been established.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found in rats given daily doses up to 10 mg/kg (approximately 0.2 times an adult daily dose of 600 mg based on body surface area).

13.2 Animal Toxicology

Phospholipidosis (intracellular phospholipid accumulation) 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/or pancreas) in dogs and rats treated with azithromycin at doses which, expressed on the basis of body surface area, are similar to or less than the highest recommended adult human dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (50 mg/kg/day dose) at the observed maximal plasma concentration of 1.3 mcg/mL (1.6 times the observed C_{max} of 0.821 mcg/mL at the adult dose of 2 g.) Similarly, it has been shown in the dog (10 mg/kg/day dose) at the observed maximal serum concentration of 1 mcg/mL (1.2 times the observed C_{max} of 0.821 mcg/mL at the adult dose of 2 g).

Phospholipidosis was also observed in neonatal rats dosed for 18 days at 30 mg/kg/day, which is less than the pediatric dose of 60 mg/kg based on body surface area. It was not observed in neonatal rats treated for 10 days at 40 mg/kg/day with mean maximal serum concentrations of 1.86 mcg/ml, approximately 1.5 times the C_{max} of 1.27 mcg/ml at the pediatric dose. Phospholipidosis has been observed in neonatal dogs (10 mg/kg/day) at maximum mean whole blood concentrations of 3.54 mcg/ml, approximately 3 times the pediatric dose C_{max}.

The significance of the finding for animals and for humans is unknown.

14 CLINICAL STUDIES

14.1 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 (1)]

Prevention of Disseminated MAC Disease

Two randomized, double-blind clinical trials were performed in patients with CD4 counts <100 cells/µL. The first trial (Study 155) compared azithromycin (1200 mg once weekly) to placebo and enrolled 182 patients with a mean CD4 count of 35 cells/mcgL. The second trial (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/mcgL. The primary endpoint in these trials 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 Study 155, 85 patients randomized to receive azithromycin and 89 patients randomized to receive placebo met the 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 Study 174, 223 patients randomized to receive rifabutin, 223 patients randomized to receive azithromycin, and 218 patients randomized to receive both rifabutin and azithromycin met the 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 testing[5] 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 trial 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 reactions to study medication. Overall, the nature of adverse reactions seen on the weekly dosage regimen of azithromycin over a period of approximately one year in patients with advanced HIV disease were similar to that previously reported for shorter course therapies.

INCIDENCE OF ONE OR MORE TREATMENT-RELATED[a]ADVERSE REACTIONS[b]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

[a]Includes those reactions considered possibly or probably related to study drug

[b]>2% adverse reaction rates for any group (except uveitis)

Adverse reactions 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 trial with additional criteria if baseline values were outside the relevant normal range.

PROPHYLAXIS AGAINST DISSEMINATED MAC ABNORMAL LABORATORY VALUES[a]

		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 × 10^3/mm^3	1/71 1%	4/260 2%	2/182 1%	6/181 3%
WBC Count	<1 × 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 × ULN*	1/41 2%	8/158 5%	3/121 3%	6/114 5%
SGPT	>5 × ULN	0/49 0%	8/166 5%	3/130 2%	5/117 4%
Alk Phos	>5 × ULN	1/80 1%	4/247 2%	2/172 1%	3/164 2%

[a]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 daily (N=65), azithromycin 600 mg daily (N=91), or clarithromycin 500 mg twice a day (N=90), each administered with ethambutol 15 mg/kg daily, for 24 weeks. Blood cultures and clinical assessments were performed 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 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 twice a day. Efficacy results for the azithromycin 600 mg daily and clarithromycin 500 mg twice a day treatment regimens are described in the following table:

RESPONSE TO THERAPY OF PATIENTS TAKING ETHAMBUTOL AND EITHER AZITHROMYCIN 600 MG DAILY OR CLARITHROMYCIN 500 MG TWICE A DAY			
	Azithromycin 600 mg daily	**Clarithromycin 500 mg twice a day**	***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 daily group than in the clarithromycin 500 mg twice a day 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 twice a day(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 (20.0%)	1/5 (20%)
>10,000 cfu/mL	0/1 (0.0%)	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 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 twice a day respectively, developed MAC blood culture isolates that had a sharp increase in MIC values. All twelve MAC isolates had azithromycin MICs ≥256 mcg/mL and clarithromycin MICs >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.

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16 HOW SUPPLIED/STORAGE AND HANDLING

Azithromycin Tablets USP, 600 mg are supplied as white, oval shaped film-coated tablets, engraved with "LU" on one side and "L13" on the other side containing azithromycin monohydrate USP equivalent to 600 mg of azithromycin USP.

These are packaged in bottles of 30 tablets as follows:

Bottles of 30 Tablets: NDC 68180-162-06

Tablets should be stored at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

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, should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When azithromycin is 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 or other antibacterial drugs in the future.

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

Manufactured for:

Lupin Pharmaceuticals, Inc.

Baltimore, Maryland 21202

United States

Manufactured by:

Lupin Limited

Goa - 403722

India

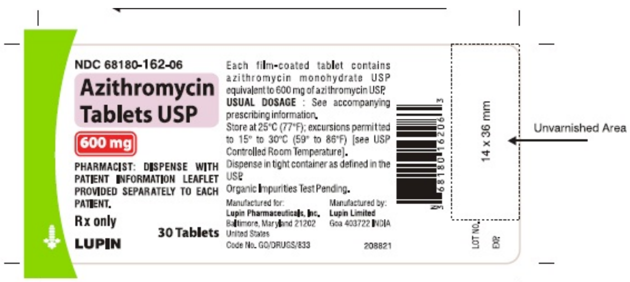
May 2015 ID #214409

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL

Azithromycin Tablets USP, 600 mg

30 Tablets- Container Label

NDC 68180-162-06



AZITHROMYCIN MONOHYDRATE
azithromycin monohydrate tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:57297-162
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
AZITHROMYCIN MONOHYDRATE (UNII: JTE4MNN1MD) (AZITHROMYCIN ANHYDROUS - UNII:J2KLZ20U1M)	AZITHROMYCIN ANHYDROUS	600 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CALCIUM PHOSPHATE, DIBASIC, ANHYDROUS (UNII: L11K75P92J)	
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
HYPROMELLOSE 2910 (15 MPA.S) (UNII: 36SFW2JZ0W)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
SODIUM LAURYL SULFATE (UNII: 368GB5141J)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
TRIACETIN (UNII: XHX3C3X673)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	OVAL	**Size**	19mm
Flavor		**Imprint Code**	LU;L13
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:57297-162-06	30 in 1 CONTAINER; Type 0: Not a Combination Product		

Marketing Information			
Marketing Category	**Application Number or Monograph Citation**	**Marketing Start Date**	**Marketing End Date**
ANDA	ANDA065400	07/22/2015	

Labeler - LUPIN LIMITED (675923163)

Registrant - LUPIN LIMITED (675923163)

Establishment			
Name	**Address**	**ID/FEI**	**Business Operations**
LUPIN LIMITED		677600414	manufacture(57297-162) , pack(57297-162)