NDA 50-693/S-015
NDA 50-730/S-025

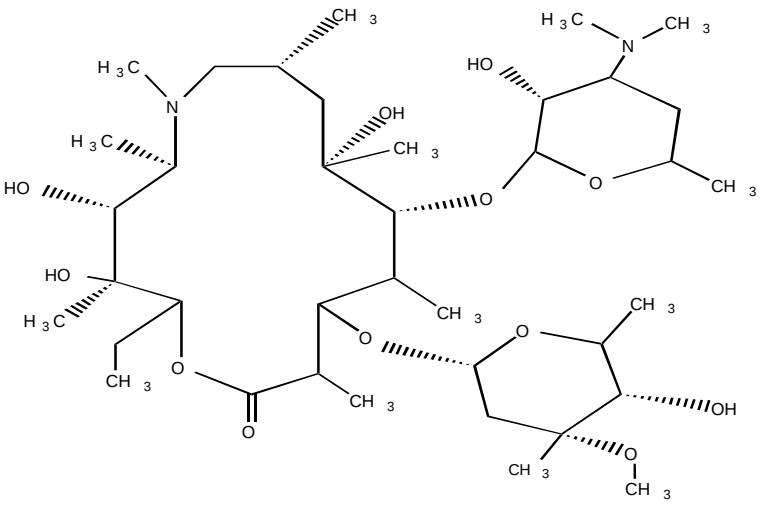
ZITHROMAX®

(azithromycin tablets)
and
(azithromycin for oral suspension)

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

DESCRIPTION

ZITHROMAX (azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, 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 dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12}\bullet 2H_2O$ and a molecular weight of 785.0.

ZITHROMAX tablets contain azithromycin dihydrate equivalent to 600 mg azithromycin. The tablets are supplied as white, modified oval-shaped, film-coated tablets. They also contain the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate and an aqueous film coat consisting of hypromellose, titanium dioxide, lactose and triacetin.

ZITHROMAX for oral suspension is supplied in a single dose packet containing azithromycin dihydrate equivalent to 1 g azithromycin. It also contains the following inactive ingredients: colloidal silicon dioxide, sodium phosphate tribasic, anhydrous; spray dried artificial banana flavor, spray dried artificial cherry flavor, and sucrose.

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 1 g single dose packet is bioequivalent to four 250 mg azithromycin capsules.

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

MEAN (CV%) PK PARAMETER

DOSE/DOSAGE FORM (serum, except as indicated)	Subjects	Day No.	C_{max} (µg/mL)	T_{max} (hr)	C_{24} (µg/mL)	AUC (µg•hr/mL)	$T_{½}$ (hr)	Urinary Excretion (% of dose)
500 mg/250 mg capsule	12	Day 1	0.41	2.5	0.05	2.6[a]	–	4.5
and 250 mg on Days 2-5	12	Day 5	0.24	3.2	0.05	2.1[a]	–	6.5
1200 mg/600 mg tablets	12	Day 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	0.039	2.4[a]		
%CV			25%	(50%)	(36%)	(19%)		
	7	22	0.55	2.1	0.14	5.8[a]	84.5	-
%CV			(18%)	(52%)	(26%)	(25%)		-
600 mg tablet/day (leukocytes)	7	22	252	10.9	146	4763[a]	82.8	-
%CV			(49%)	(28%)	(33%)	(42%)	-	-

[a] AUC_{0-24}; [b] 0-last.

In these studies (500 mg Day 1, 250 mg Days 2-5), 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 2-5, 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 ZITHROMAX 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%.

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=1.00; CV=55%).

The AUC of azithromycin in 250 mg capsules was unaffected by coadministration of an antacid containing aluminum and magnesium hydroxide with ZITHROMAX (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 2-5) 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:

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

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (µg/g or µg/mL)[1]	CORRESPONDING PLASMA OR SERUM LEVEL (µg/mL)	TISSUE (FLUID) PLASMA (SERUM) RATIO[1]
SKIN	72-96	0.4	0.012	35
LUNG	72-96	4.0	0.012	>100
SPUTUM*	2-4	1.0	0.64	2
SPUTUM**	10-12	2.9	0.1	30
TONSIL***	9-18	4.5	0.03	>100
TONSIL***	180	0.9	0.006	>100
CERVIX****	19	2.8	0.04	70

[1] 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 2-4 hours after the first dose

** Sample was obtained 10-12 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 µg/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 µg/mL. Concentrations remained above 32 µg/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 (±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-seropositive adults, mean maximum concentration in peripheral leukocytes was 252 µg/mL (±49%). Trough concentrations in peripheral leukocytes at steady-state averaged 146 µg/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.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 2 µg/mL. 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 1.0 g dose of azithromycin (4 × 250 mg capsules), the mean C_{max} and $AUC_{0\text{-}120}$ 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 $AUC_{0\text{-}120}$ 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.)

Mechanism of Action: Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

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.

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 the INDICATIONS AND USAGE section.

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 2.0 µg/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

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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 7.2-7.4, 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 antimicrobial 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 (µg/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 MBC and achieved antimicrobial compound concentrations may be appropriate to guide therapy in some infections. (See CLINICAL PHARMACOLOGY section for further information on drug concentrations achieved in infected body sites and other pharmacokinetic properties of this antimicrobial drug product.)

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

Microorganism	MIC (µg/mL)
Escherichia coli ATCC 25922	2.0-8.0
Enterococcus faecalis ATCC 29212	1.0-4.0
Staphylococcus aureus ATCC 29213	0.25-1.0

Diffusion Techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] that has been recommended for use with disks to test the susceptibility of microorganisms to azithromycin uses the 15-µg azithromycin disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimal inhibitory concentration (MIC) for azithromycin.

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

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

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-µg azithromycin disk should provide the following zone diameters in these laboratory test quality control strains:

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

***In Vitro* Activity of Azithromycin Against Mycobacteria.**
Azithromycin has demonstrated *in vitro* activity against *Mycobacterium avium* complex (MAC) organisms. While gene probe techniques may be used to distinguish between *M. avium* and *M. intracellulare*, many studies only reported results on *M. avium* complex (MAC) isolates. Azithromycin has also been shown to be active against phagocytized *M. avium* complex (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 *Mycobacterium avium* complex 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 acid-albumin-dextrose-catalase (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)

Drug Resistance:
Complete cross-resistance between azithromycin and clarithromycin has been observed with *Mycobacterium avium* complex (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] *Mycobacterium avium* complex (MAC) isolates exhibiting cross-resistance show an increase in azithromycin MICs to ≥128 µg/mL with clarithromycin MICs increasing to ≥32 µg/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 *M. avium* complex strains produce the 23S rRNA mutation.

Susceptibility testing for *Mycobacterium avium* complex (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 minimal inhibitory concentration (MIC) values against *Mycobacterium avium* complex (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.

INDICATIONS AND USAGE

ZITHROMAX (azithromycin) is indicated for the treatment of patients with mild to moderate infections (pneumonia: see WARNINGS) caused by susceptible strains of the designated microorganisms in the specific conditions listed below.

Sexually Transmitted Diseases
Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis*.

ZITHROMAX, at the recommended dose, should not be relied upon to treat gonorrhea or syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis may mask or delay the symptoms of incubating gonorrhea or syphilis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with ZITHROMAX may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zithromax (azithromycin) and other antibacterial drugs, Zithromax (azithromycin) 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.

Mycobacterial Infections

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Prophylaxis of Disseminated *Mycobacterium avium* complex (MAC) Disease
ZITHROMAX, taken alone or in combination with rifabutin at its approved dose, is indicated for the prevention of disseminated *Mycobacterium avium* complex (MAC) disease in persons with advanced HIV infection. (See DOSAGE AND ADMINISTRATION, CLINICAL STUDIES)

Treatment of Disseminated *Mycobacterium avium* complex (MAC) Disease
ZITHROMAX, taken in combination with ethambutol, is indicated for the treatment of disseminated MAC infections in persons with advanced HIV infection. (See DOSAGE AND ADMINISTRATION, CLINICAL STUDIES)

CONTRAINDICATIONS

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

WARNINGS

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.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ZITHROMAX, 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.

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**).

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization.

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

Prescribing Zithromax (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.

Information for Patients:
ZITHROMAX tablets may be taken with or without food. However, increased tolerability has been observed when tablets are taken with food.

ZITHROMAX for oral suspension in single 1 g packets can be taken with or without food after constitution.

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 Zithromax (azithromycin) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Zithromax (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 Zithromax (azithromycin) 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 ZITHROMAX® 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 Cmax 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 ZITHROMAX® 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 ZITHROMAX® tablets) with steady-state nelfinavir (750 mg tid) to healthy adult subjects produced a decrease of approximately 15% in mean AUC_{0-8} of nelfinavir and its M8 metabolite. Mean Cmax 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 $AUC_{0-\infty}$ of azithromycin by approximately a factor of 2-times (range of up to 4 times) of that when azithromycin was given alone. The mean Cmax 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 ZITHROMAX® tablets) on the 7^{th} 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 2-5) 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 post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Dose adjustments are not indicated when azithromycin and zidovudine are coadministered. When zidovudine (100 mg q3h x5) was coadministered with daily azithromycin (600 mg, n=5 or 1200 mg, n=7), mean C_{max}, AUC and Clr 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 8.0% (CV 32%), respectively.

Doses of 1200 mg/day azithromycin for 14 days in 6 subjects increased C_{max} of concurrently administered didanosine (200 mg *q*.12h) 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 P^{450} 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/m^2 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/m^2/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/m^2/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 ZITHROMAX (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 ZITHROMAX (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 3-2004 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 10-20 mg/kg/day (oral and/or I.V.) of azithromycin.

Geriatric Use: Pharmacokinetic parameters in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 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.

ZITHROMAX 600 mg tablets contain 2.1 mg of sodium per tablet. ZITHROMAX for oral suspension 1 gram single-dose packets contain 37.0 mg of sodium per packet.

Geriatric Patients with Opportunistic Infections, Including *Mycobacterium avium* complex (MAC) Disease: Safety data are available for 30 patients (65-94 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 ZITHROMAX (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 ZITHROMAX 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 ZITHROMAX 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.

Single 1-gram dose regimen: Overall, the most common side effects in patients receiving a single-dose regimen of 1 gram of ZITHROMAX were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

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

Post-Marketing Experience:
Adverse events reported with azithromycin during the post-marketing 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 *torsades 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: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death.
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 1-2%, 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/mm^3).

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: 1-229 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.

NDA 50-693/S-015
NDA 50-730/S-025

DOSAGE AND ADMINISTRATION
(See INDICATIONS AND USAGE.)

ZITHROMAX for oral suspension (single dose 1 g packet) can be taken with or without food after constitution. Not for pediatric use. For pediatric suspension, please refer to the INDICATIONS AND USAGE and DOSAGE AND ADMINISTRATION sections of the prescribing information for ZITHROMAX (azithromycin for oral suspension) 100 mg/5 mL and 200 mg/5 mL bottles.

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

The recommended dose of ZITHROMAX for the treatment of non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 gram (1000 mg) dose of ZITHROMAX. This dose can be administered as as one single dose packet (1 g).

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

Treatment of Disseminated MAC Infections
ZITHROMAX® 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.

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DIRECTIONS FOR ADMINISTRATION OF ZITHROMAX for oral suspension in the single dose packet (1 g): The entire contents of the packet should be mixed thoroughly with two ounces (approximately 60 mL) of water. Drink the entire contents immediately; add an additional two ounces of water, mix, and drink to assure complete consumption of dosage. **The single dose packet should not be used to administer doses other than 1000 mg of azithromycin. This packet not for pediatric use.**

Renal Insufficiency:No dosage adjustment is recommended for subjects with renal impairment (GFR≤80mL/min). The mean AUC_{0-120} was similar in subjects with GFR 10-80 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR<10mL/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

ZITHROMAX 600 mg tablets (engraved on front with “PFIZER” and on back with “308”) are supplied as white, modified oval-shaped, film-coated tablets containing azithromycin dihydrate equivalent to 600 mg azithromycin. These are packaged in bottles of 30 tablets. ZITHROMAX tablets are supplied as follows:

Bottles of 30	NDC 0069-3080-30

Tablets should be stored at or below 30°C (86°F).

ZITHROMAX for oral suspension is supplied in single dose packets containing azithromycin dihydrate equivalent to 1 gram of azithromycin as follows:

Boxes of 10 Single Dose Packets (1 g)	NDC 0069-3051-07
Boxes of 3 Single Dose Packets (1 g)	NDC 0069-3051-75

Store single dose packets between 5° and 30°C (41° and 86°F).

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

NDA 50-693/S-015
NDA 50-730/S-025

Two randomized, double blind clinical trials were performed in patients with CD4 counts <100 cells/µL. The first study (155) compared azithromycin (1200 mg once weekly) to placebo and enrolled 182 patients with a mean CD4 count of 35 cells/µL. 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/µL. 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	18.0
18	37.1	22.5	18.0	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 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 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	3.0	2.7
Central Nervous System					
Dizziness	0	1.1	3.9	1.7	0.4
Headache	0	0	3.0	5.5	4.5
Gastrointestinal					
Diarrhea	15.4	52.8	50.2	19.1	50.9
Loose Stools	6.6	19.1	12.9	3.0	9.4
Abdominal Pain	6.6	27	32.2	12.3	31.7
Dyspepsia	1.1	9	4.7	1.7	1.8
Flatulence	4.4	9	10.7	5.1	5.8
Nausea	11	32.6	27.0	16.5	28.1
Vomiting	1.1	6.7	9.0	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	3.0	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	$<50 \times 10^3/mm^3$	1/71 1%	4/260 2%	2/182 1%	6/181 3%
WBC Count	$<1 \times 10^3/mm^3$	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	$>5 \times$ ULN[a]	1/41 2%	8/158 5%	3/121 3%	6/114 5%
SGPT	$>5 \times$ ULN	0/49 0%	8/166 5%	3/130 2%	5/117 4%
Alk Phos	$>5 \times$ ULN	1/80 1%	4/247 2%	2/172 1%	3/164 2%

[a]=Upper Limit of Normal
*excludes subjects outside of the relevant normal range at baseline

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

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%)
11-100 cfu/mL	13/28 (46.4%)	13/19 (68.4%)
101-1,000 cfu/mL	7/19 (36.8%)	5/13 (38.5%)
1,001-10,000 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 µg/mL and clarithromycin MICs ranged from <1 to >32 µg/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 ≥256 µg/mL and clarithromycin MIC's >32 µg/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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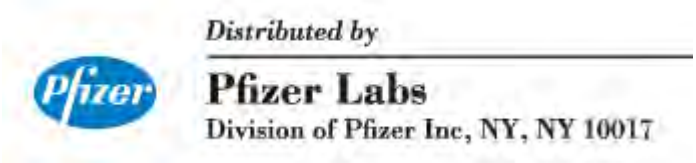

LAB-0022-9.0
Revised June 2010