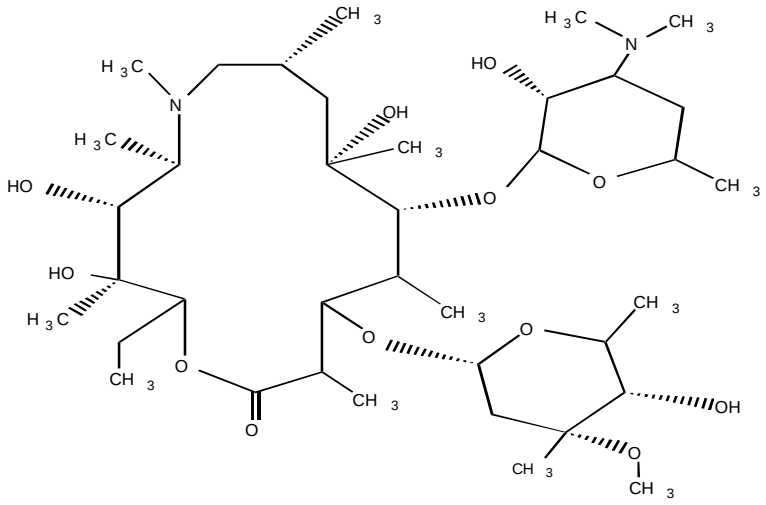
Serial #
REVISION DATE: 08-Dec-1999

ZITHROMAX®
(azithromycin capsules)
(azithromycin tablets)
and
(azithromycin for oral suspension)

DESCRIPTION

ZITHROMAX® (azithromycin capsules, 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® capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C Red #40). They also contain the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and sodium lauryl sulfate.

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 hydroxypropyl methyl cellulose, 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 capsules.

The pharmacokinetic parameters of azithromycin in plasma after dosing as per labeled recommendations in healthy young 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	2.37		
%CV			25%	(50%)	(36%)	(19%)		
	7	22	0.553	2.1	0.14	5.84	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%)	-	--
Source: Study 066-077								

[a]0-24 hr; [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.

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:

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), mean maximum concentration in peripheral leukocytes was 252 µg/mL (±49%). Concentrations remained above 146 µg/mL (±33%) for 24 hr at steady state. Leukocyte to serum C_{max} ratio was 456 and AUC ratio was 816.	Study #066-077

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.

There are no pharmacokinetic data available from studies in hepatically- or renally-impaired individuals.

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 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

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 isolated from AIDS patients. ~~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.~~	**Wording added to be consistent with Biaxin. See also Microbiology Section 7** **Struck out sentence moved below**

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, 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, 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 ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues.~~	**Sentence struck out.**

Azithromycin activity against 163 MAC isolates from AIDS patients was evaluated using Bactec™ 12B vials. Results showed an MIC of ≤32 µg/mL in >90% of isolates. Azithromycin was also shown to be active against phagocytized *M. avium* complex (MAC) in mouse and human macrophage cell cultures as well as in the beige mouse infection model.	**Microbiology Section 7, Table 3.1**

A cross resistance relationship between azithromycin and clarithromycin has been observed with some *Mycobacterium avium* complex (MAC) isolates. The various mechanisms of cross resistance between azithromycin and clarithromycin for *M. avium* complex organisms have not been fully characterized. The clinical significance of azithromycin and clarithromycin cross resistance is unknown.

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 ~~established~~ 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.	**Microbiology Section 7** **text consistent with Biaxin**

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.

Lower Respiratory Tract:
Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

Community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy.

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

Upper Respiratory Tract:
Streptococcal pharyngitis/tonsillitis–As an alternative to first line therapy of acute pharyngitis/tonsillitis due to *Streptococcus pyogenes* occurring in individuals who cannot use first line therapy.

NOTE: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Skin and Skin Structure
Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

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.

Mycobacterial Infections	**Heading added to be consistent with Biaxin.**

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 Clinical Trials section.)	**"Prophylaxis" added to distinguish from new treatment indications below**

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.	**Study 189/189B and consistent with Biaxin**

Pulmonary Infections due to *Mycobacterium avium* Complex (MAC). ZITHROMAX®, taken in combination with other agents active against MAC, is indicated for the treatment of pulmonary infections due to MAC in non-HIV infected patients.	**From Wallace's publications**

CONTRAINDICATIONS

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

WARNINGS

Rare serious allergic reactions, including angioedema and anaphylaxis, have been reported rarely in patients on azithromycin therapy. (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.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia). Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to

severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients.

The following adverse events have not been reported in clinical trials with azithromycin, an azalide; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsade de pointes*, in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced torsade de pointes and subsequent myocardial infarction following a course of azithromycin therapy.	**Consistent with 250 mg tablet/oral suspension PI**

Information for Patients:
Patients should be cautioned to take ZITHROMAX® capsules at least one hour prior to a meal or at least two hours after a meal. Azithromycin capsules should not be taken with food.

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.

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 dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single 800 mg oral dose of fluconazole.	**Study 066-086**
Total exposure and half-life of 1200 mg azithromycin were unchanged and Cmax had a clinically insignificant decrease (18%) by coadministration with 800 mg fluconazole.	**Study 066-086**
A single dose of 1200 mg azithromycin had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir t.i.d. for 5 days).	**Study 066-085**
Coadministration of a single dose of 1200 mg azithromycin with steady-state nelfinavir (750 mg t.i.d). produced an approximately 16% decrease in mean AUC_{0-8} of nelfinavir and its M8 metabolite. Cmax was not affected.	**Study 066-094**
Coadministration of nelfinavir (750 mg t.i.d.) at steady state with a single dose of 1200 mg azithromycin increased the mean $AUC_{0-\infty}$ of azithromycin by 113% and mean Cmax by 136%.	**Study 066-094; Application**

Dose adjustment of azithromycin is not recommended. However, close monitoring for known side effects of azithromycin , when administered in conjunction with nelfinavir, is warranted.	**Summary, Section 3.H.1**
Following administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days to healthy subjects, coadministration of 1200 mg azithromycin on the 7th day had no significant effects on peak concentrations or total exposure or urinary excretion of either trimethoprim or sulfamethoxazole.	**Study 066-088**
Serum concentrations of azithromycin following administration of a single 1200 mg dose after administration of trimethoprim/sulfamethoxazole DS for 7 days were similar to those produced following a 1200 mg dose of azithromycin in other studies.	**Study 066-088**
Efavirenz, when administered at a dose of 400 mg for seven days produced a 22% increase in the Cmax of azithromycin administered as a 600 mg single dose. AUC was not affected.	**Efavirenz package insert**
Administration of a 600 mg single dose of azithromycin had no effect on the pharmacokinetics of efavirenz given at 400 mg doses for 7 days.	**Efavirenz package insert**

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.

Azithromycin (500 mg Day 1, 250 mg Days 2-5) did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

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.	**Direct proportions from 500 mg daily dose.**

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.

Prevention or Treatment of Disseminated *Mycobacterium avium* complex (MAC) Disease: Safety and efficacy of azithromycin for the prevention or treatment of MAC in 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. Two (2.8%) of these children prematurely discontinued treatment due to a side effect. A third child discontinued	**Added information from Studies 066-162, 066-167, 066-167S, 066-131, 066-354/354A, 066-185, NDA Sections 3.H.2 (Table 3.H.2.3 and 3.H.6**

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.	**(ISS)**

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.)

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 pulmonary disease due to 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 loss of hearing.(See DOSAGE AND ADMINISTRATION).	**ISS, Table H.2.3**

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 TRIALS.)

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. As has been experienced with macrolide antimicrobials, reversible hearing impairment was observed in 5% of patients in the pivotal clinical trial for the treatment of disseminated MAC in patients with AIDS. Other treatment related side effects occuring 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.	**ISS 066-189, Tables 6.3.2, 4.1.2**

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.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis and rare reports of tongue discoloration.
General: Asthenia, paresthesia and anaphylaxis (rarely fatal).
Genitourinary: Interstitial nephritis and acute renal failure, moniliasis, vaginitis.
Hematopoietic: Thrombocytopenia.
Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death.
Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, and agitation.
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, rare reports of taste perversion.

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 TRIALS 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 five-fold elevation in alkaline phosphatase (3/35, 9%). Causality of these laboratory abnormalities due to the use of study drug has not been established.	Study 066-189, tables 3.1 and 7.3

DOSAGE AND ADMINISTRATION
(See INDICATIONS AND USAGE.)

ZITHROMAX® capsules should be given at least 1 hour before or 2 hours after a meal. ZITHROMAX® capsules should not be mixed with or taken with food.

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

Prevention of Disseminated MAC Infections	**Heading added**

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 infection or pulmonary infections due to *Mycobacterium avium* complex.	**Format comparable to Biaxin.**
Disseminated MAC Infections ZITHROMAX® should be taken at a daily dose of 600 mg, in combination with other antimycobacterial drugs that have shown *in vitro* activity against MAC, including ethambutol at the recommended dose.	**Study 066-189**
Pulmonary MAC Infections For the treatment of pulmonary infections due to MAC, Zithromax should be taken at daily doses of 600 mg in combination with other antimycobacterial drugs that have shown *in vitro* activity against MAC. (See PRECAUTIONS: Geriatric Use.)	**Information from Wallace's papers.**
For patients in whom oral administration is not feasible, Zithromax I.V. may be administered at a dose of 250 mg to afford exposure comparable to 600 mg oral. (See CLINICAL PHARMACOLOGY; Please also refer to the Zithromax I.V. package insert)	**NDA 50-730, Study 066-062**

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 four 250 mg capsules or as one single dose packet (1 g).

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.**

HOW SUPPLIED

ZITHROMAX® capsules (imprinted with "Pfizer 305") are supplied in red opaque hard-gelatin capsules containing azithromycin dihydrate equivalent to 250 mg of azithromycin. These are packaged in bottles and blister cards of 6 capsules (Z-PAKS™) as follows:

Bottles of 50	NDC 0069-3050-50
Boxes of 3 (Z-PAKS™ of 6)	NDC 0069-3050-34
Unit Dose package of 50	NDC 0069-3050-86

Store capsules below 30°C (86°F).

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 OF DISEASE DUE TO DISSEMINATED *MYCOBACTERIUM AVIUM* COMPLEX (MAC) (See INDICATIONS AND USAGE):

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* 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. (*Methodology per Inderlied CB, et al. Determination of *In Vitro* Susceptibility of *Mycobacterium avium* Complex Isolates to Antimicrobial Agents by Various Methods. Antimicrob. Agents Chemother 1987; 31: 1697-1702.)

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

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.

REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically–Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests–Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

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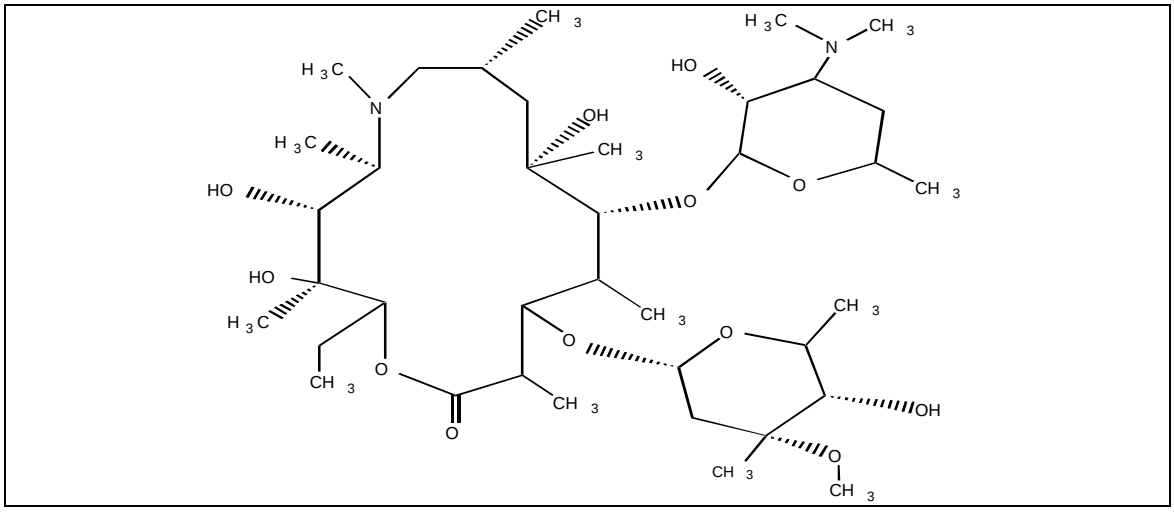
Ser No. _____

Revised December 1999

ZITHROMAX®
(azithromycin for injection)
For IV infusion only

DESCRIPTION

ZITHROMAX® (azithromycin for injection) contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for intravenous injection. 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-hepta-methyl-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 749.00. Azithromycin has the following structural formula:



Azithromycin, as the dihydrate, is a white crystalline powder with a molecular formula of $C_{38}H_{72}N_2O_{12} \cdot 2H_2O$ and a molecular weight of 785.0.

ZITHROMAX® (azithromycin for injection) consists of azithromycin dihydrate and the following inactive ingredients: citric acid and sodium hydroxide. ZITHROMAX® (azithromycin for injection) is supplied in lyophilized form in a 10-mL vial equivalent to 500 mg of azithromycin for

intravenous administration. Reconstitution, according to label directions, results in approximately 5 mL of ZITHROMAX® for intravenous injection with each mL containing azithromycin dihydrate equivalent to 100 mg of azithromycin.

CLINICAL PHARMACOLOGY

In patients hospitalized with community-acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean Cmax ± S.D. achieved was 3.63 ± 1.60 μg/mL, while the 24-hour trough level was 0.20 ± 0.15 μg/mL, and the AUC_{24} was 9.60 ± 4.80 μg·h/mL.

The mean Cmax, 24-hour trough and AUC_{24} values were 1.14 ± 0.14 μg/mL, 0.18 ± 0.02 μg/mL, and 8.03 ±0.86 μg· h/mL, respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/mL. Similar pharmacokinetic values were obtained in patients hospitalized with community-acquired pneumonia that received the same 3-hour dosage regimen for 2-5 days.

Plasma concentrations (μg/mL ± S.D.) after the last daily intravenous infusion of 500 mg azithromycin

Infusion Concentration, Duration	Time after starting the infusion (hr)								
	0.5	1	2	3	4	6	8	12	24
2 mg/mL, 1 hr[a]	2.98 ±1.12	3.63 ±1.73	0.60 ±0.31	0.40 ±0.23	0.33 ±0.16	0.26 ±0.14	0.27 ±0.15	0.20 ±0.12	0.20 ±0.15
1 mg/mL, 3 hr[b]	0.91 ±0.13	1.02 ±0.11	1.14 ±0.13	1.13 ±0.16	0.32 ±0.05	0.28 ±0.04	0.27 ±0.03	0.22 ±0.02	0.18 ±0.02

a = 500 mg (2 mg/mL) for 2-5 days in Community-acquired pneumonia patients.

b = 500 mg (1 mg/mL) for 5 days in healthy subjects.

The average CL_t and V_d values were 10.18 mL/min/kg and 33.3 L/kg, respectively, in 18 normal volunteers receiving 1000 to 4000-mg doses given as 1 mg/mL over 2 hours.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg intravenous azithromycin showed only an 8% increase in C_{max} but a 61% increase in AUC_{24} reflecting a threefold rise in C_{24} trough levels.

Following single oral doses of 500 mg azithromycin to 12 healthy volunteers, C_{max}, trough level, and AUC_{24} were reported to be 0.41 μg/mL, 0.05 μg/mL, and 2.6 μg·h/mL, respectively. These oral values are approximately 38%, 83%, and 52% of the values observed following a single 500-mg I.V. 3-hour infusion (C_{max}: 1.08 μg/mL, trough: 0.06 μg/mL, and AUC^{24}: 5.0 μg·h/mL).

Thus, plasma concentrations are higher following the intravenous regimen throughout the 24-hour interval. The pharmacokinetic parameters on day 5 of azithromycin 250-mg capsules following a 500-mg oral loading dose to healthy young adults (age 18-40 years old) were as follows: C_{max}: 0.24 µg/mL, AUC_{24}: 2.1 µg·h/mL. Tissue levels have not been obtained following intravenous infusions of azithromycin. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios following oral administration of azithromycin are shown in the following table:

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

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (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.

Tissue levels were determined following a single oral dose of 500 mg azithromycin in 7 gynecological patients. Approximately 17 hours after dosing, azithromycin concentrations were 2.7 µg/g in ovarian tissue, 3.5 µg/g in uterine tissue, and 3.3 µg/g in salpinx. Tissue levels have not been obtained following intravenous infusion of azithromycin.

In a multiple-dose study in 12 normal volunteers utilizing a 500-mg (1 mg/mL) one-hour intravenous-dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the 1st dose and 14% after the 5th dose. These values

are greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin. Biliary excretion is a major route of elimination for unchanged drug, following oral administration.

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.

Microbiology: 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.

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 of the package insert for ZITHROMAX® (azithromycin for injection).

Aerobic gram-positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae

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
Neisseria gonorrhoeae

"Other" microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma hominis
Mycoplasma pneumoniae

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

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

of the package insert for ZITHROMAX® (azithromycin tablets) and ZITHROMAX® (azithromycin for oral suspension).

Aerobic gram-positive microorganisms
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Haemophilus ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

"Other" microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

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

Azithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 0.5 µg/mL or less against most (≥90%) strains of streptococci listed below and MIC's of 2.0 µg/mL or less against most (≥90%) strains of other listed 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 clinical trials.

Aerobic gram-positive microorganisms
Streptococci (Groups C, F, G)
Viridans group streptococci

Aerobic gram-negative microorganisms
Bordetella pertussis

Anaerobic microorganisms
Peptostreptococcus species
Prevotella bivia

"Other" microorganisms
Ureaplasma urealyticum

Susceptibility Tests

Azithromycin can be solubilized for *in vitro* susceptibility testing using dilution techniques by dissolving in a minimum amount of 95% ethanol and diluting to the working stock concentration with broth.

Dilution Techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus* species, *Neisseria gonorrhoeae*, and streptococci:

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

For testing *Haemophilus* species:[a]

MIC (µg/mL)	Interpretation
≤ 4	Susceptible (S)

[a] This interpretive standard is applicable only to broth microdilution susceptibility testing with *Haemophilus* species using *Haemophilus* Test Medium (HTM)[1].

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing streptococci including *S. pneumoniae:*[b]

MIC (µg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1	Intermediate (I)
≥ 2	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

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

A report of "Susceptible" indicates that the pathogen is likely to respond to monotherapy with azithromycin. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that achievable drug concentrations are unlikely to be inhibitory; other therapy should be selected.

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

Microorganism	MIC (µg/mL)
Haemophilus influenzae ATCC 49247[a]	1.0-4.0
Staphylococcus aureus ATCC 29213	0.5-2.0
Streptococcus pneumoniae ATCC 49619[b]	0.06-0.25

[a] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)[1].

[b] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.[1]

Diffusion Techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-µg azithromycin to test the susceptibility of microorganisms to 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:

For testing aerobic microorganisms (including streptococci)[a] except *Haemophilus* species and *Neisseria gonorrhoeae:*

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

[a] These zone diameter standards for streptococci apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2[2].

For testing *Haemophilus* species:[b]

Zone Diameter (mm)	Interpretation
≥ 12	Susceptible (S)

[b] This zone diameter standard is applicable only to tests with *Haemophilus* species using *Haemophilus* Test Medium (HTM)[2].

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

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

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for azithromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-µg azithromycin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49247[a]	13-21

Staphylococcus aureus ATCC 25923	21-26
Streptococcus pneumoniae ATCC 49619[b]	19-25

[a] These quality control limits are applicable only to tests conducted with *H. influenzae* ATCC 49247 using *Haemophilus* Test Medium (HTM)[2].

[b] These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2[2].

INDICATIONS AND USAGE

ZITHROMAX® (azithromycin for injection) is indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see **DOSAGE AND ADMINISTRATION** for dosing recommendations.

Community-acquired pneumonia due to *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Staphylococcus aureus*, or *Streptococcus pneumoniae* in patients who require initial intravenous therapy.

Pelvic inflammatory disease due to *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Mycoplasma hominis* in patients who require initial intravenous therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with ZITHROMAX®.

ZITHROMAX® (azithromycin for injection) should be followed by ZITHROMAX® by the oral route as required. (See **DOSAGE AND ADMINISTRATION**.)

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative microorganism 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.

CONTRAINDICATIONS

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; therefore, caution should be exercised when prescribing azithromycin in these patients.

ZITHROMAX® (azithromycin for injection) should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. (See **DOSAGE AND ADMINISTRATION**.)

Local I.V. site reactions have been reported with the intravenous administration of azithromycin. The incidence and severity of these reactions were the same when 500 mg azithromycin were given over 1 hour (2 mg/mL as 250 mL infusion) or over 3 hours (1 mg/mL as 500 mL infusion). (See **ADVERSE REACTIONS**.) All volunteers who received infusate concentrations above 2.0 mg/mL experienced local I.V. site reactions and, therefore, higher concentrations should be avoided.

The following adverse events have not been reported in clinical trials with azithromycin; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia, and *torsades de pointes*, in individuals with prolonged QT intervals. There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsades de pointes* and subsequent myocardial infarction following a course of oral azithromycin therapy.

Information for Patients:

Patients should be cautioned not to take aluminum- and magnesium-containing antacids and azithromycin by the oral route simultaneously.

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

Drug Interactions: Aluminum- and magnesium-containing antacids reduce the peak serum levels (rate) but not the AUC (extent) of orally administered azithromycin.

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

Azithromycin given by the oral route 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.

Azithromycin given by the oral route did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

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 - Increased pharmacologic effect of triazolam by decreasing the clearance of triazolam.

Drugs metabolized by the cytochrome P^{450} system - elevations of serum carbamazepine, terfenadine, 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. No evidence of impaired fertility due to azithromycin was found.

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 by the oral route). 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 by the oral route. 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.

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: Safety and effectiveness of azithromycin for injection in children or adolescents under 16 years have not been established. In controlled clinical studies, azithromycin has been administered to pediatric patients (age 6 months to 16 years) by the oral route. For information

regarding the use of ZITHROMAX® (azithromycin for oral suspension) in the treatment of pediatric patients, 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.

Geriatric Use: Pharmacokinetic studies with intravenous azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65-85 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen.

ADVERSE REACTIONS

In clinical trials of intravenous azithromycin for community-acquired pneumonia, in which 2-5 I.V. doses were given, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. The majority of patients in these trials had one or more comorbid diseases and were receiving concomitant medications. Approximately 1.2% of the patients discontinued intravenous ZITHROMAX® therapy, and a total of 2.4% discontinued azithromycin therapy by either the intravenous or oral route because of clinical or laboratory side effects.

In clinical trials conducted in patients with pelvic inflammatory disease, in which 1-2 I.V. doses were given, 2% of women who received monotherapy with azithromycin and 4% who received azithromycin plus metronidazole discontinued therapy due to clinical side effects.

Clinical side effects leading to discontinuations from these studies were most commonly gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), and rashes; laboratory side effects leading to discontinuation were increases in transaminase levels and/or alkaline phosphatase levels.

Clinical:
Overall, the most common side effects associated with treatment in adult patients who received I.V./P.O. ZITHROMAX® in studies of community-acquired pneumonia were related to the gastrointestinal system with diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%) being the most frequently reported. Approximately 12% of patients experienced a side effect related to the intravenous infusion; most common were pain at the injection site (6.5%) and local inflammation (3.1%).

The most common side effects associated with treatment in adult women who received I.V./P.O. ZITHROMAX® in studies of pelvic inflammatory disease were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most commonly reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was co-administered with metronidazole in these studies, a higher proportion of women

experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), application site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).

No other side effects occurred in patients on the multiple dose I.V./P.O. regimen of ZITHROMAX® in these studies with a frequency greater than 1%.

Side effects that occurred with a frequency of 1% or less included the following:

Gastrointestinal: dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis
Nervous System: headache, somnolence
Allergic: bronchospasm
Special Senses: taste perversion

Post-Marketing Experience:

Adverse events reported with orally administered azithromycin during the post-marketing period in adult and/or pediatric patients for which a causal relationship could not be established include:

Allergic: arthralgia, edema, urticaria, angioedema
Cardiovascular: arrhythmias, including ventricular tachycardia
Gastrointestinal: anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis and rare reports of tongue discoloration
General: asthenia, paresthesia and anaphylaxis (rarely fatal)
Genitourinary: interstitial nephritis and acute renal failure, moniliasis, vaginitis
Hematopoietic: thrombocytopenia
Liver/Biliary: abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death
Nervous System: convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, and agitation
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, rare reports of taste perversion

Laboratory Abnormalities:

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:
with an incidence of 4-6%, elevated ALT (SGPT), AST (SGOT), creatinine
with an incidence of 1-3%, elevated LDH, bilirubin
with an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase

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

In multiple-dose clinical trials involving more than 750 patients treated with ZITHROMAX® (I.V./P.O.), less than 2% of patients discontinued azithromycin therapy because of treatment-related liver enzyme abnormalities.

DOSAGE AND ADMINISTRATION
(See INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY.)

The recommended dose of ZITHROMAX® (azithromycin for injection) for the treatment of adult patients with community-acquired pneumonia due to the indicated organisms is: 500 mg as a single daily dose by the intravenous route for at least two days. Intravenous therapy should be followed by azithromycin by the oral route at a single, daily dose of 500 mg, administered as two 250-mg tablets to complete a 7- to 10-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

The recommended dose of ZITHROMAX® (azithromycin) for the treatment of adult patients with pelvic inflammatory disease due to the indicated organisms is: 500 mg as a single daily dose by the intravenous route for one or two days. Intravenous therapy should be followed by azithromycin by the oral route at a single, daily dose of 250 mg to complete a 7-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with ZITHROMAX®.

The infusate concentration and rate of infusion for ZITHROMAX® (azithromycin for injection) should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour.

Preparation of the solution for intravenous administration is as follows:
Reconstitution

Prepare the initial solution of ZITHROMAX® (azithromycin for injection) by adding 4.8 mL of Sterile Water For Injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since ZITHROMAX® (azithromycin for injection) is supplied under vacuum, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of Sterile Water is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin. Reconstituted solution is stable for 24 hours when stored below 30°C or 86°F.

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

Dilute this solution further prior to administration as instructed below.

Dilution

To provide azithromycin over a concentration range of 1.0-2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:

Normal Saline (0.9% sodium chloride)
1/2 Normal Saline (0.45% sodium chloride)
5% Dextrose in Water
Lactated Ringer's Solution
5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride) with 20 mEq KCl
5% Dextrose in Lactated Ringer's Solution
5% Dextrose in 1/3 Normal Saline (0.3% sodium chloride)
5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride)
Normosol®-M in 5% Dextrose
Normosol®-R in 5% Dextrose

Final Infusion Solution Concentration (mg/mL)	Amount of Diluent (mL)
1.0 mg/mL	500 mL
2.0 mg/mL	250 mL

It is recommended that a 500-mg dose of ZITHROMAX® (azithromycin for injection), diluted as above, be infused over a period of not less than 60 minutes.

ZITHROMAX® (azithromycin for injection) should not be given as a bolus or as an intramuscular injection.

Storage

When diluted according to the instructions (1.0 mg/mL to 2.0 mg/mL), ZITHROMAX® (azithromycin for injection) is stable for 24 hours at or below room temperature (30°C or 86°F), or for 7 days if stored under refrigeration (5°C or 41°F).

HOW SUPPLIED

ZITHROMAX® (azithromycin for injection) is supplied in lyophilized form under a vacuum in a 10-mL vial equivalent to 500 mg of azithromycin for intravenous administration. Each vial also contains sodium hydroxide and 413.6 mg citric acid.

These are packaged as follows:

10 vials of 500 mg NDC 0069-3150-83

CLINICAL STUDIES

Community-Acquired Pneumonia

In a controlled study of community-acquired pneumonia performed in the U.S., azithromycin (500 mg as a single daily dose by the intravenous route for 2-5 days, followed by 500 mg/day by the oral route to complete 7-10 days therapy) was compared to cefuroxime (2250 mg/day in three divided doses by the intravenous route for 2-5 days followed by 1000 mg/day in two divided doses by the oral route to complete 7-10 days therapy), with or without erythromycin. For the 291 patients who were evaluable for clinical efficacy, the clinical outcome rates, i.e., cure, improved, and success (cure + improved) among the 277 patients seen at 10-14 days post-therapy were as follows:

Clinical Outcome	Azithromycin	Comparator
Cure	46%	44%
Improved	32%	30%
Success (Cure + Improved)	78%	74%

In a separate, uncontrolled clinical and microbiological trial performed in the U.S., 94 patients with community-acquired pneumonia who received azithromycin in the same regimen were evaluable for clinical efficacy. The clinical outcome rates, i.e., cure, improved, and success (cure + improved) among the 84 patients seen at 10-14 days post-therapy were as follows:

Clinical Outcome	Azithromycin
Cure	60%
Improved	29%
Success (Cure + Improved)	89%

Microbiological determinations in both trials were made at the pre-treatment visit and, where applicable, were reassessed at later visits. Serological testing was done on baseline and final visit specimens. The following combined presumptive bacteriological eradication rates were obtained from the evaluable groups:

Combined Bacteriological Eradication Rates for Azithromycin:

(at last completed visit)	Azithromycin
S. pneumoniae	64/67 (96%)[a]
H. influenzae	41/43 (95%)
M. catarrhalis	9/10
S. aureus	9/10

[a] Nineteen of twenty-four patients (79%) with positive blood cultures for *S. pneumoniae* were cured (intent to treat analysis) with eradication of the pathogen.

The presumed bacteriological outcomes at 10-14 days post-therapy for patients treated with azithromycin with evidence (serology and/or culture) of atypical pathogens for both trials were as follows:

Evidence of Infection	Total	Cure	Improved	Cure + Improved
Mycoplasma pneumoniae	18	11 (61%)	5 (28%)	16 (89%)
Chlamydia pneumoniae	34	15 (44%)	13 (38%)	28 (82%)
Legionella pneumophila	16	5 (31%)	8 (50%)	13 (81%)

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 pancreas) in dogs treated with azithromycin at doses which, expressed on a mg/kg basis, are only 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. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_{max} value of 1.3 μg/mL (6 times greater than the observed C_{max} of 0.216 μg/mL at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 μg/mL (7 times greater than the observed same C_{max} and drug dose in the studied pediatric population). On mg/m^2 basis, 30 mg/kg dose in the rat (135 mg/m^2) and 10 mg/kg dose in the dog (79 mg/m^2) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

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1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

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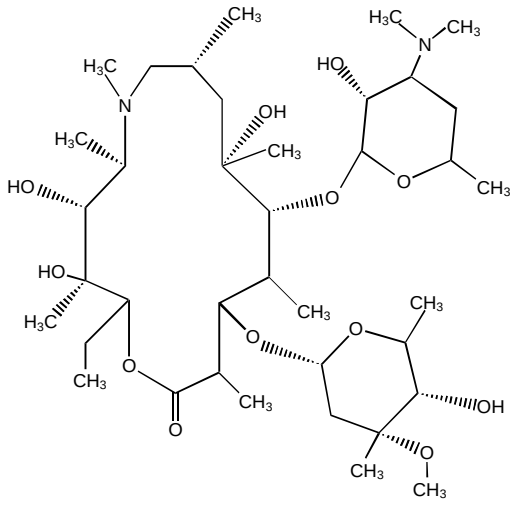
ZITHROMAX®
(azithromycin tablets)
(azithromycin capsules)
and
(azithromycin for oral suspension)

DESCRIPTION

ZITHROMAX® (azithromycin tablets, azithromycin capsules 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 749.00. 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® is supplied for oral administration as film-coated, modified capsular shaped tablets containing azithromycin dihydrate equivalent to 250 mg azithromycin and the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hydroxypropyl methylcellulose, lactose, titanium dioxide, triacetin and D&C Red #30 aluminum lake.

ZITHROMAX® capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C Red #40). They also contain the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and sodium lauryl sulfate.

It is also supplied as a powder for oral suspension.

ZITHROMAX® for oral suspension is supplied in bottles containing azithromycin dihydrate powder equivalent to 300 mg, 600 mg, 900 mg, or 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate, tribasic, anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C Red #40; and spray dried artificial cherry, creme de vanilla and banana flavors. After constitution, each 5 mL of suspension contains 100 mg or 200 mg of azithromycin.

CLINICAL PHARMACOLOGY

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

The pharmacokinetic parameters of azithromycin capsules in plasma after a loading dose of 500 mg (2–250 mg capsules) on day one followed by 250 mg (1–250 mg capsule) q.d. on days two through five in healthy young adults (age 18-40 years old) are portrayed in the following chart:

Pharmacokinetic Parameters (Mean)	Total n=12	
	Day 1	Day 5
C_{max} (μg/mL)	0.41	0.24
T_{max} (h)	2.5	3.2
AUC_{0-24} (μg·h/mL)	2.6	2.1
C_{min} (μg/mL)	0.05	0.05
Urinary Excret. (% dose)	4.5	6.5

In this study, 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 an open, randomized, two-way crossover study, pharmacokinetic parameters (AUC_{0-72}, C_{max}, T_{max}) determined from 36 fasted healthy male volunteers who received two 250-mg commercial capsules and two 250-mg tablets were:

	Capsule	Tablet	90% CI
AUC_{0-72} (μg·h/mL)	4.1 (1.2)	4.3 (1.2)	(99-113%)
C_{max} (μg/mL)	0.5 (0.2)	0.5 (0.2)	(96-121%)
T_{max} (hours)	2.1 (0.8)	2.2 (0.9)	

When azithromycin capsules were administered with food to 11 adult healthy male subjects, the rate of absorption (C_{max}) of azithromycin from the capsule formulation was reduced by 52% and the extent of absorption (AUC) by 43%.

In an open label, randomized, two-way crossover study in 12 healthy subjects to assess the effect of a high fat standard meal on the serum concentrations of azithromycin resulting from the oral administration of two 250-mg film-coated tablets, it was shown that food increased C_{max} by 23% while there was no change in AUC.

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

The AUC of azithromycin was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide with ZITHROMAX® capsules (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 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.

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.

There are no pharmacokinetic data available from studies in hepatically- or renally-impaired individuals.

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**.)

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

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

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (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.

Pediatric Pharmacokinetics:
In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 to two groups of children (aged 1-5 years and 5-15 years, respectively). The mean pharmacokinetic parameters at Day 5 were C_{max}=0.216 μg/mL, T_{max}=1.9 hours, and AUC_{0-24}=1.822 μg·hr/mL for the 1- to 5-year-old group and were C_{max}=0.383 μg/mL, T_{max}=2.4 hours, and AUC_{0-24}=3.109 μg·hr/mL for the 5- to 15-year-old group.

There are no pharmacokinetic data on azithromycin suspension when administered at a dose of 12 mg/kg/day in the presence or absence of food. (For the pediatric pharyngitis/tonsillitis dose, see **DOSAGE AND ADMINISTRATION.**)

Microbiology: 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.

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 ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

"Other" microorganisms
Chlamydia pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

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

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

Azithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 0.5 µg/mL or less against most (≥90%) strains of streptococci and MIC's of 2.0 µg/mL or less against most (≥90%) strains of other listed 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
Legionella pneumophila

Anaerobic microorganisms
Peptostreptococcus species
Prevotella bivia

"Other" microorganisms
Ureaplasma urealyticum

Susceptibility Tests
Azithromycin can be solubilized for *in vitro* susceptibility testing using dilution techniques by dissolving in a minimum amount of 95% ethanol and diluting to the working stock concentration with broth. Further dilutions may be made in water.

Dilution Techniques:
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MIC's). These MIC's provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC's should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus* species, *Neisseria gonorrhoeae*, and streptococci:

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

For testing *Haemophilus* species:[a]

MIC (µg/mL)	Interpretation
≤ 4	Susceptible (S)

[a]These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus* species using Haemophilus Test Medium.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing Streptococci including *S. pneumoniae*:[b]

MIC (µg/mL)	Interpretation
≤ 0.5	Susceptible (S)
1	Intermediate (I)
≥ 2	Resistant (R)

[b]These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

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

A report of "Susceptible" indicates that the pathogen is likely to respond to monotherapy with azithromycin. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that achievable drug concentrations are unlikely to be inhibitory; other therapy should be selected.

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

Microorganism	MIC (µg/mL)
Haemophilus influenzae ATCC 49247[a]	1.0-4.0
Staphylococcus aureus ATCC 29213	0.5-2.0
Streptococcus pneumoniae ATCC 49619[b]	0.06-0.25

[a]This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).[1]

[b]This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

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

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] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-µg azithromycin to test the susceptibility of microorganisms to 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:

For testing aerobic microorganisms (including streptococci)[a] except *Haemophilus* species and *Neisseria gonorrhoeae:*

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

[a]These zone diameter standards for streptococci apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

For testing *Haemophilus* species:[b]

Zone Diameter (mm)	Interpretation
≥ 12	Susceptible (S)

[b]These zone diameter standards apply only to tests with *Haemophilus* species using Haemophilus Test Medium (HTM).[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

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

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for azithromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 15-μg azithromycin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49247[a]	13-21
Staphylococcus aureus ATCC 25923	21-26
Streptococcus pneumoniae ATCC 49619[b]	19-25

[a]These quality control limits apply only to tests conducted with *H. influenzae* ATCC 49247 using Haemophilus Test Medium (HTM).[2]

[b]These quality control limits apply only to tests conducted with *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

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. As recommended dosages, durations of therapy, and applicable patient populations vary among these infections, please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

Adults:
Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae*.

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,
patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization,
elderly or debilitated patients, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX®. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Uncomplicated skin and skin structure infections due to *Staphylococcus aureus, Streptococcus pyogenes,* or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

ZITHROMAX®, at the recommended dose, should not be relied upon to treat 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 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.

Children: (See **Pediatric Use** and **CLINICAL STUDIES IN PEDIATRIC PATIENTS**.)

Acute otitis media caused by *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae*. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**.)

Community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**.)

NOTE: Azithromycin should not be used in pediatric patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following:

patients with cystic fibrosis,
patients with nosocomially acquired infections,
patients with known or suspected bacteremia,
patients requiring hospitalization, or
patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy. (For specific dosage recommendation, see **DOSAGE AND ADMINISTRATION**.)

NOTE: Penicillin by the intramuscular route is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to ZITHROMAX®, susceptibility tests should be performed when patients are treated with ZITHROMAX®. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

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.

CONTRAINDICATIONS

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

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to *Chlamydia pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients.

The following adverse events have not been reported in clinical trials with azithromycin, an azalide; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsade de pointes*, in individuals with prolonged QT intervals.

There has been a spontaneous report from the post-marketing experience of a patient with previous history of arrhythmias who experienced *torsade de pointes* and subsequent myocardial infarction following a course of azithromycin therapy.

Information for Patients:
Patients should be cautioned to take ZITHROMAX® capsules and ZITHROMAX® suspension at least one hour prior to a meal or at least two hours after a meal. These medications should not be taken with food.

ZITHROMAX® tablets can be taken with or without 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.

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

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

Azithromycin 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.

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

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, terfenadine, 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. No evidence of impaired fertility due to azithromycin was found.

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. 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.

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: (See **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE,** and **DOSAGE AND ADMINISTRATION**.)

Acute Otitis Media (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with otitis media under 6 months of age have not been established.

Community-Acquired Pneumonia (dosage regimen: 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5): Safety and effectiveness in the treatment of children with community-acquired pneumonia under 6 months of age have not been established. Safety and effectiveness for pneumonia due to *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* were documented in pediatric clinical trials. Safety and effectiveness for pneumonia due to *Haemophilus influenzae* and *Streptococcus pneumoniae* were not documented bacteriologically in the pediatric clinical trial due to difficulty in obtaining specimens. Use of azithromycin for these two microorganisms is supported, however, by evidence from adequate and well-controlled studies in adults.

Pharyngitis/Tonsillitis (dosage regimen: 12 mg/kg on Days 1-5): Safety and effectiveness in the treatment of children with pharyngitis/tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted. (See CLINICAL PHARMACOLOGY and ANIMAL TOXICOLOGY.)

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**.)

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 (adults and children) 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. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely.

Clinical:
Adults:
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.

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%).

Single 2-gram dose regimen: Overall, the most common side effects in patients receiving a single 2-gram dose of ZITHROMAX® were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.

Children:
Multiple-dose regimens: The types of side effects in children were comparable to those seen in adults, with different incidence rates for the two dosage regimens recommended in children.

Acute Otitis Media: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (2%), abdominal pain (2%), vomiting (1%), and nausea (1%).

Community-Acquired Pneumonia: For the recommended dosage regimen of 10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (5.8%), abdominal pain, vomiting, and nausea (1.9% each), and rash (1.6%).

Pharyngitis/tonsillitis: For the recommended dosage regimen of 12 mg/kg on Days 1-5, the most frequent side effects attributed to treatment were diarrhea/loose stools (6%), vomiting (5%), abdominal pain (3%), nausea (2%), and headache (1%).

With either treatment regimen, no other side effects occurred in children treated with ZITHROMAX® with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

Cardiovascular: Chest pain.
Gastrointestinal: Dyspepsia, constipation, anorexia, flatulence, and gastritis.
Nervous System: Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness, insomnia.
General: Fever, fatigue, malaise.
Allergic: Rash.
Skin and Appendages: Pruritus, urticaria.
Special Senses: Conjunctivitis.

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.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis and rare reports of tongue discoloration.
General: Asthenia, paresthesia and anaphylaxis (rarely fatal).
Genitourinary: Interstitial nephritis and acute renal failure, moniliasis, vaginitis.
Hematopoietic: Thrombocytopenia.
Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death.
Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, and agitation.
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, rare reports of taste perversion.

Laboratory Abnormalities:
Adults:
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.

Children:
Significant abnormalities (irrespective of drug relationship) occurring during clinical trials were all reported at a frequency of less than 1%, but were similar in type to the adult pattern.

In multiple-dose clinical trials involving almost 3300 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

DOSAGE AND ADMINISTRATION
(See INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY.)

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

ZITHROMAX® capsules should be given at least 1 hour before or 2 hours after a meal. ZITHROMAX® capsules should not be taken with food.

ZITHROMAX® tablets can be taken with or without food.

The recommended dose of ZITHROMAX® for the treatment of genital ulcer disease due to *Haemophilus ducreyi* (chancroid), non-gonococcal urethritis and cervicitis due to *C. trachomatis* is: a single 1 gram (1000 mg) dose of ZITHROMAX®.

The recommended dose of ZITHROMAX® for the treatment of urethritis and cervicitis due to *Neisseria gonorrhoeae* is a single 2 gram (2000 mg) dose of ZITHROMAX®.

Children:
Acute Otitis Media and Community-Acquired Pneumonia: The recommended dose of ZITHROMAX® for oral suspension for the treatment of children with acute otitis media and community-acquired pneumonia is 10 mg/kg as a single dose on the first day (not to exceed 500 mg/day) followed by 5 mg/kg on days 2 through 5 (not to exceed 250 mg/day). (See chart below.)

ZITHROMAX® for oral suspension should be given at least 1 hour before or 2 hours after a meal.

ZITHROMAX® for oral suspension should not be taken with food.

PEDIATRIC DOSAGE GUIDELINES FOR OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA
(Age 6 months and above, see Pediatric Use.)
Based on Body Weight

OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA

Dosing Calculated on 10 mg/kg on Day 1 dose, followed by 5 mg/kg on Days 2 to 5.

Weight		100 mg/5 mL Suspension		200 mg/5 mL Suspension		
Kg	lbs	Day 1	Days 2-5	Day 1	Days 2-5	Total mL per Treatment Course
10	22	5 mL (1 tsp)	2.5 mL (½ tsp)			15 mL
20	44			5 mL (1 tsp)	2.5 mL (½ tsp)	15 mL
30	66			7.5 mL (1½ tsp)	3.75 mL (¾ tsp)	22.5 mL
40	88			10 mL (2 tsp)	5 mL (1 tsp)	30 mL

Pharyngitis/Tonsillitis: The recommended dose for children with pharyngitis/tonsillitis is 12 mg/kg once a day for 5 days (not to exceed 500 mg/day). (See chart below.)

ZITHROMAX® for oral suspension should be given at least 1 hour before or 2 hours after a meal.

ZITHROMAX® for oral suspension should not be taken with food.

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS/TONSILLITIS
(Age 2 years and above, see Pediatric Use.)
Based on Body Weight

PHARYNGITIS/TONSILLITIS

Dosing Calculated on 12 mg/kg once daily Days 1 to 5.

Weight		200 mg/5 mL Suspension	
Kg	lbs	Day 1-5	Total mL per Treatment Course
8	18	2.5 mL (½ tsp)	12.5 mL
17	37	5 mL (1 tsp)	25 mL
25	55	7.5 mL (1½ tsp)	37.5 mL
33	73	10 mL (2 tsp)	50 mL
40	88	12.5 mL (2½ tsp)	62.5 mL

Constituting instructions for ZITHROMAX® Oral Suspension, 300, 600, 900, 1200 mg bottles. The table below indicates the volume of water to be used for constitution:

Amount of water to be added	Total volume after constitution (azithromycin content)	Azithromycin concentration after constitution
9 mL (300 mg)	15 mL (300 mg)	100 mg/5 mL
9 mL (600 mg)	15 mL (600 mg)	200 mg/5 mL
12 mL (900 mg)	22.5 mL (900 mg)	200 mg/5 mL
15 mL (1200 mg)	30 mL (1200 mg)	200 mg/5 mL

Shake well before each use. Oversized bottle provides shake space. Keep tightly closed.

After mixing, store at 5° to 30°C (41° to 86°F) and use within 10 days. Discard after full dosing is completed.

HOW SUPPLIED

ZITHROMAX® tablets are supplied as red modified capsular shaped, engraved, film-coated tablets containing azithromycin dihydrate equivalent to 250 mg of azithromycin. ZITHROMAX® tablets are engraved with "PFIZER" on one side and "306" on the other. These are packaged in bottles and blister cards of 6 tablets (Z-PAKS®) as follows:

Bottles of 30	NDC 0069-3060-30
Boxes of 3 (Z-PAKS® of 6)	NDC 0069-3060-75
Unit Dose package of 50	NDC 0069-3060-86

ZITHROMAX® tablets should be stored between 15° to 30°C (59° to 86°F).

ZITHROMAX® for oral suspension after constitution contains a flavored suspension. ZITHROMAX® for oral suspension is supplied in bottles with accompanying calibrated dropper as follows:

Azithromycin contents per bottle	NDC
300 mg	0069-3110-19
600 mg	0069-3120-19
900 mg	0069-3130-19
1200 mg	0069-3140-19

Storage: Store dry powder below 30°C (86°F). Store constituted suspension between 5° to 30°C (41° to 86°F) and discard when full dosing is completed.

CLINICAL STUDIES IN PEDIATRIC PATIENTS
(See INDICATIONS AND USAGE and Pediatric Use.)

From the perspective of evaluating pediatric clinical trials, Days 11-14 (6-9 days after completion of the five-day regimen) were considered on-therapy evaluations because of the extended half-life of azithromycin. Day 11-14 data are provided for clinical guidance. Day 30 evaluations were considered the primary test of cure endpoint.

Acute Otitis Media

Efficacy Protocol 1

In a double-blind, controlled clinical study of acute otitis media performed in the United States, azithromycin (10 mg/kg on Day 1 followed by 5 mg/kg on Days 2-5) was compared to an antimicrobial/beta-lactamase inhibitor. In this study, very strict evaluability criteria were used to determine clinical response and safety results were obtained. For the 553 patients who were evaluated for clinical efficacy, the clinical success rate (i.e., cure plus improvement) at the Day 11 visit was 88% for azithromycin and 88% for the control agent. For the 521 patients who were evaluated at the Day 30 visit, the clinical success rate was 73% for azithromycin and 71% for the control agent.

In the safety analysis of the above study, the incidence of adverse events, primarily gastrointestinal, in all patients treated was 9% with azithromycin and 31% with the control agent. The most common side effects were diarrhea/loose stools (4% azithromycin vs. 20% control), vomiting (2% azithromycin vs. 7% control), and abdominal pain (2% azithromycin vs. 5% control).

Efficacy Protocol 2
In a noncomparative clinical and microbiologic trial performed in the United States, where significant rates of beta-lactamase producing organisms (35%) were found, 131 patients were evaluable for clinical efficacy. The combined clinical success rate (i.e., cure and improvement) at the Day 11 visit was 84% for azithromycin. For the 122 patients who were evaluated at the Day 30 visit, the clinical success rate was 70% for azithromycin.

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

Bacteriologic Eradication:

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

In the safety analysis of this study, the incidence of adverse events, primarily gastrointestinal, in all patients treated was 9%. The most common side effect was diarrhea (4%).

Efficacy Protocol 3
In another controlled comparative clinical and microbiologic study of otitis media performed in the United States, azithromycin was compared to an antimicrobial/beta-lactamase inhibitor. This study utilized two of the same investigators as Efficacy Protocol 2 (above), and these two investigators enrolled 90% of the patients in Efficacy Protocol 3. For this reason, Efficacy Protocol 3 was not considered to be an independent study. Significant rates of beta-lactamase producing organisms (20%) were found. Ninety-two (92) patients were evaluable for clinical and microbiologic efficacy. The combined clinical success rate (i.e., cure and improvement) of those patients with a baseline pathogen at the Day 11 visit was 88% for azithromycin vs. 100% for control; at the Day 30 visit, the clinical success rate was 82% for azithromycin vs. 80% for control.

Microbiologic determinations were made at the pre-treatment visit. Microbiology was not reassessed at later visits. At the Day 11 and Day 30 visits, the following presumptive bacterial/clinical cure outcomes (i.e., clinical success) were obtained from the evaluable group:

Bacteriologic Eradication:

	Day 11		Day 30	
	Azithromycin	Control	Azithromycin	Control
S. pneumoniae	25/29 (86%)	26/26 (100%)	22/28 (79%)	18/22 (82%)
H. influenzae	9/11 (82%)	9/9	8/10 (80%)	6/8
M. catarrhalis	7/7	5/5	5/5	2/3
S. pyogenes	2/2	5/5	2/2	4/4
Overall	43/49 (88%)	45/45 (100%)	37/45 (82%)	30/37 (81%)

In the safety analysis of the above study, the incidence of adverse events, primarily gastrointestinal, in all patients treated was 4% with azithromycin and 31% with the control agent. The most common side effect was diarrhea/loose stools (2% azithromycin vs. 29% control).

Pharyngitis/Tonsillitis

In 3 double-blind controlled studies, conducted in the United States, azithromycin (12 mg/kg once a day for 5 days) was compared to penicillin V (250 mg three times a day for 10 days) in the treatment of pharyngitis due to documented Group A β-hemolytic streptococci (GABHS or *S. pyogenes*). Azithromycin was clinically and microbiologically statistically superior to penicillin at Day 14 and Day 30 with the following clinical success (i.e., cure and improvement) and bacteriologic efficacy rates (for the combined evaluable patient with documented GABHS):

Three U.S. Streptococcal Pharyngitis Studies
Azithromycin vs. Penicillin V
EFFICACY RESULTS

	Day 14	Day 30
Bacteriologic Eradication:		
Azithromycin	323/340 (95%)	255/330 (77%)
Penicillin V	242/332 (73%)	206/325 (63%)
Clinical Success (Cure plus improvement):		
Azithromycin	336/343 (98%)	310/330 (94%)
Penicillin V	284/338 (84%)	241/325 (74%)

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

The incidence of adverse events, primarily gastrointestinal, in all patients treated was 18% on azithromycin and 13% on penicillin. The most common side effects were diarrhea/loose stools (6% azithromycin vs. 2% penicillin), vomiting (6% azithromycin vs. 4% penicillin), and abdominal pain (3% azithromycin vs. 1% penicillin).

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 pancreas) in dogs treated with azithromycin at doses which, expressed on a mg/kg basis, are only 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. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed C_{max} value of 1.3 µg/mL (6 times greater than the observed C_{max} of 0.216 µg/mL at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed C_{max} value of 1.5 µg/mL (7 times greater than the observed same C_{max} and drug dose in the studied pediatric population). On mg/m^2 basis, 30 mg/kg dose in the rat (135 mg/m^2) and 10 mg/kg dose in the dog (79 mg/m^2) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically–Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December 1993.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests–Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.

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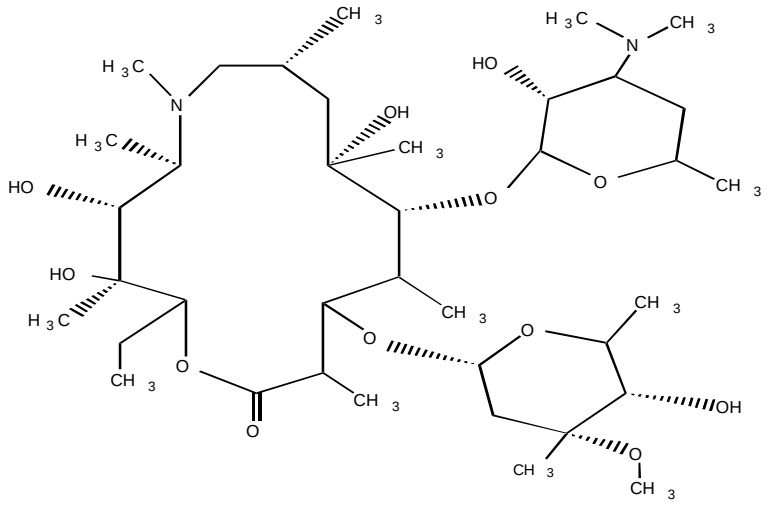
ZITHROMAX®
(azithromycin capsules)
(azithromycin tablets)
and
(azithromycin for oral suspension)

DESCRIPTION

ZITHROMAX® (azithromycin capsules, 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 $C_{38}H_{72}N_2O_{12}\cdot 2H_2O$ and a molecular weight of 785.0.

ZITHROMAX® capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C Red #40). They also contain the following inactive ingredients: anhydrous lactose, corn starch, magnesium stearate, and sodium lauryl sulfate.

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 hydroxypropyl methyl cellulose, 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 capsules.

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

MEAN (CV%) PK PARAMETER

DOSE/DOSAGE FORM	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 (62%)	2.5 (79%)	0.074 (49%)	6.8[b] (64%)	40 (33%)	–

[a]0-24 hr; [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.

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:

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.

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.

There are no pharmacokinetic data available from studies in hepatically- or renally-impaired individuals.

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 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

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 *M. avium* species from *M. intracellulare,* many studies only report 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, 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, 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 ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues.

A cross resistance relationship between azithromycin and clarithromycin has been observed with some *Mycobacterium avium* complex (MAC) isolates. The various mechanisms of cross resistance between azithromycin and clarithromycin for *M. avium*

complex organisms have not been fully characterized. The clinical significance of azithromycin and clarithromycin cross resistance is unknown.

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 established 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 to azithromycin have not been established.

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.

Lower Respiratory Tract:
Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

Community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy.

NOTE: Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following:

- **patients with nosocomially acquired infections,**
- **patients with known or suspected bacteremia,**
- **patients requiring hospitalization,**
- **elderly or debilitated patients, or**
- **patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).**

Upper Respiratory Tract:
Streptococcal pharyngitis/tonsillitis–As an alternative to first line therapy of acute pharyngitis/tonsillitis due to *Streptococcus pyogenes* occurring in individuals who cannot use first line therapy.

NOTE: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infection and the prophylaxis of rheumatic fever. ZITHROMAX® is often effective in the

eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available.

Skin and Skin Structure
Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

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.

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 Clinical Trials section.)

CONTRAINDICATIONS

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

WARNINGS

Rare serious allergic reactions, including angioedema and anaphylaxis, have been reported rarely in patients on azithromycin therapy. (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.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* **or** *Haemophilus influenzae* **in patients appropriate for outpatient oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia). Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.**

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* **is a primary cause of "antibiotic-associated colitis."**

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* **colitis.**

PRECAUTIONS

General: Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function. There are no data regarding azithromycin usage in patients with renal impairment; thus, caution should be exercised when prescribing azithromycin in these patients.

The following adverse events have not been reported in clinical trials with azithromycin, an azalide; however, they have been reported with macrolide products: ventricular arrhythmias, including ventricular tachycardia and *torsade de pointes***, in individuals with prolonged QT intervals.**

Information for Patients:
Patients should be cautioned to take ZITHROMAX® capsules at least one hour prior to a meal or at least two hours after a meal. Azithromycin capsules should not be taken with food.

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.

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.

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.

Azithromycin (500 mg Day 1, 250 mg Days 2-5) did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.

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 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.

Prevention of Disseminated *Mycobacterium avium* complex (MAC) Disease: Safety and efficacy of azithromycin for the prevention of MAC in children have not been established. Limited safety data are available for 24 children 5 months to 14 years of age (mean 4.6 years) who received azithromycin for treatment of opportunistic infections. The mean duration of therapy was 186.7 days (range 13-710 days) at doses of <5 to 20 mg/kg/day. Three children were treated for 6 months or more and 4 children were treated for 1 month or more with a dose of >10 mg/kg/day. Adverse events were similar to those observed in the adult population, most of which involved the gastrointestinal tract. While none of these children prematurely discontinued treatment due to a side effect, one child discontinued due to a laboratory abnormality (eosinophilia). The protocols upon which these data are based specified a daily dose of 10-20 mg/kg/day 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.)

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 TRIALS.)**

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.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis and rare reports of tongue discoloration.
General: Asthenia, paresthesia and anaphylaxis (rarely fatal).
Genitourinary: Interstitial nephritis and acute renal failure, moniliasis, vaginitis.
Hematopoietic: Thrombocytopenia.
Liver/Biliary: Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death.
Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, and agitation.
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, rare reports of taste perversion.

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 TRIALS section.

DOSAGE AND ADMINISTRATION
(See INDICATIONS AND USAGE.)

ZITHROMAX® capsules should be given at least 1 hour before or 2 hours after a meal. ZITHROMAX® capsules should not be mixed with or taken with food.

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

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.

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 four 250 mg capsules or as one single dose packet (1 g).

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.

HOW SUPPLIED

ZITHROMAX® capsules (imprinted with "Pfizer 305") are supplied in red opaque hard-gelatin capsules containing azithromycin dihydrate equivalent to 250 mg of azithromycin. These are packaged in bottles and blister cards of 6 capsules (Z-PAKS™) as follows:

Bottles of 50	**NDC 0069-3050-50**
Boxes of 3 (Z-PAKS™ of 6)	**NDC 0069-3050-34**
Unit Dose package of 50	**NDC 0069-3050-86**

Store capsules below 30°C (86°F).

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 OF DISEASE DUE TO DISSEMINATED *MYCOBACTERIUM AVIUM* COMPLEX (MAC) (See INDICATIONS AND USAGE):

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* 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. (*Methodology per Inderlied CB, et al. Determination of *In Vitro* Susceptibility of *Mycobacterium avium* Complex Isolates to Antimicrobial Agents by Various Methods. Antimicrob. Agents Chemother 1987; 31: 1697-1702.)

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**

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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2. **National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests–Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December 1993.**

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