

# ZITHROMAX<sup>®</sup>

(azithromycin tablets)

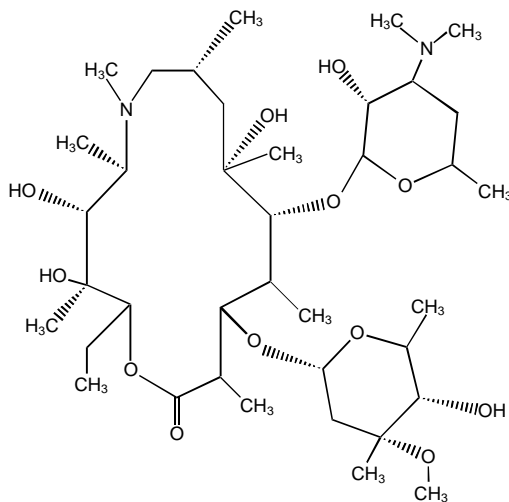
and

(azithromycin for oral suspension)

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

## DESCRIPTION

ZITHROMAX (azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (2*R*,3*S*,4*R*,5*R*,8*R*, 10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- $\alpha$ -*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)- $\beta$ -*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<sub>38</sub>H<sub>72</sub>N<sub>2</sub>O<sub>12</sub>, 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 is supplied for oral administration as film-coated, modified capsular shaped tablets containing azithromycin dihydrate equivalent to either 250 mg or 500 mg azithromycin and the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hypromellose, lactose, titanium dioxide, triacetin and D&C Red #30 aluminum lake.

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

### Pharmacokinetics

Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were  $AUC_{0-72} = 4.3 (1.2) \mu\text{g}\cdot\text{h/mL}$ ;  $C_{\text{max}} = 0.5 (0.2) \mu\text{g/mL}$ ;  $T_{\text{max}} = 2.2 (0.9)$  hours.

With a regimen of 500 mg (two 250 mg capsules\*) on day 1, followed by 250 mg daily (one 250 mg capsule) on days 2 through 5, the pharmacokinetic parameters of azithromycin in plasma in healthy young adults (18-40 years of age) are portrayed in the chart below.  $C_{\text{min}}$  and  $C_{\text{max}}$  remained essentially unchanged from day 2 through day 5 of therapy.

Pharmacokinetic Parameters (Mean)	Total n=12	
	<u>Day 1</u>	<u>Day 5</u>
$C_{\text{max}}$ ( $\mu\text{g/mL}$ )	0.41	0.24
$T_{\text{max}}$ (h)	2.5	3.2
$AUC_{0-24}$ ( $\mu\text{g}\cdot\text{h/mL}$ )	2.6	2.1
$C_{\text{min}}$ ( $\mu\text{g/mL}$ )	0.05	0.05
Urinary Excret. (% dose)	4.5	6.5

\*Azithromycin 250 mg tablets are bioequivalent to 250 mg capsules in the fasted state. Azithromycin 250 mg capsules are no longer commercially available.

In a two-way crossover study, 12 adult healthy volunteers (6 males, 6 females) received 1,500 mg of azithromycin administered in single daily doses over either 5 days (two 250 mg tablets on day 1, followed by one 250 mg tablet on days 2-5) or 3 days (500 mg per day for days 1-3). Due to limited serum samples on day 2 (3-day regimen) and days 2-4 (5-day regimen), the serum concentration-time profile of each subject was fit to a 3-compartment model and the  $AUC_{0-\infty}$  for the fitted concentration profile was comparable between the 5-day and 3-day regimens.

Pharmacokinetic Parameter [mean (SD)]	3-Day Regimen		5-Day Regimen	
	Day 1	Day 3	Day 1	Day 5
$C_{max}$ (serum, $\mu\text{g/mL}$ )	0.44 (0.22)	0.54 (0.25)	0.43 (0.20)	0.24 (0.06)
Serum $AUC_{0-\infty}$ ( $\mu\text{g}\cdot\text{hr/mL}$ )	17.4 (6.2)*		14.9 (3.1)*	
Serum $T_{1/2}$	71.8 hr		68.9 hr	

\*Total AUC for the entire 3-day and 5-day regimens

Median azithromycin exposure ( $AUC_{0-288}$ ) in mononuclear (MN) and polymorphonuclear (PMN) leukocytes following either the 5-day or 3-day regimen was more than a 1000-fold and 800-fold greater than in serum, respectively. Administration of the same total dose with either the 5-day or 3-day regimen may be expected to provide comparable concentrations of azithromycin within MN and PMN leukocytes.

Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.

#### Absorption

The absolute bioavailability of azithromycin 250 mg capsules is 38%.

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase  $C_{max}$  by 23% but had no effect on AUC.

When azithromycin suspension was administered with food to 28 adult healthy male subjects,  $C_{max}$  increased by 56% and AUC was unchanged.

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

#### Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02  $\mu\text{g/mL}$  to 7% at 2  $\mu\text{g/mL}$ .

Following oral administration, azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg. Greater azithromycin concentrations in tissues than in plasma or serum were observed. High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of azithromycin is pH related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

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

AZITHROMYCIN CONCENTRATIONS FOLLOWING  
A 500 mg DOSE (TWO 250 mg CAPSULES) IN ADULTS<sup>1</sup>

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (µg/g or µg/mL)	CORRESPONDING PLASMA OR SERUM LEVEL (µg/mL)	TISSUE (FLUID) PLASMA (SERUM) RATIO
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

<sup>1</sup> Azithromycin tissue concentrations were originally determined using 250 mg capsules.

- \* Sample was obtained 2-4 hours after the first dose.
- \*\* Sample was obtained 10-12 hours after the first dose.
- \*\*\* Dosing regimen of two 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 importance 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.

#### Metabolism

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

#### Elimination

Plasma concentrations of azithromycin following single 500 mg oral and i.v. doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues.

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.

### Special Populations

#### Renal Insufficiency

Azithromycin pharmacokinetics were investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1,000 mg dose of azithromycin, mean  $C_{max}$  and  $AUC_{0-120}$  increased by 5.1% and 4.2%, respectively in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean  $C_{max}$  and  $AUC_{0-120}$  increased 61% and 35%, respectively in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). (See **DOSAGE AND ADMINISTRATION.**)

#### Hepatic Insufficiency

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

#### Gender

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

#### Geriatric Patients

When studied in healthy elderly subjects aged 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.

#### Pediatric Patients

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 pediatric patients (aged 1-5 years and 5-15 years, respectively). The mean pharmacokinetic parameters on day 5 were  $C_{max}=0.216$   $\mu\text{g/mL}$ ,  $T_{max}=1.9$  hours, and  $AUC_{0-24}=1.822$   $\mu\text{g}\cdot\text{hr/mL}$  for the 1- to 5-year-old group and were  $C_{max}=0.383$   $\mu\text{g/mL}$ ,  $T_{max}=2.4$  hours, and  $AUC_{0-24}=3.109$   $\mu\text{g}\cdot\text{hr/mL}$  for the 5- to 15-year-old group.

Two clinical studies were conducted in 68 pediatric patients aged 3-16 years to determine the pharmacokinetics and safety of azithromycin for oral suspension. Azithromycin was administered following a low-fat breakfast.

The first study consisted of 35 pediatric patients treated with 20 mg/kg/day (maximum daily dose 500 mg) for 3 days of whom 34 patients were evaluated for pharmacokinetics.

In the second study, 33 pediatric patients received doses of 12 mg/kg/day (maximum daily dose 500 mg) for 5 days of whom 31 patients were evaluated for pharmacokinetics.

In both studies, azithromycin concentrations were determined over a 24 hour period following the last daily dose. Patients weighing above 25.0 kg in the 3-day study or 41.7 kg in the 5-day study received the maximum adult daily dose of 500 mg. Eleven patients (weighing 25.0 kg or less) in the first study and 17 patients (weighing 41.7 kg or less) in the second study received a total dose of 60 mg/kg. The following table shows pharmacokinetic data in the subset of pediatric patients who received a total dose of 60 mg/kg.

Pharmacokinetic Parameter [mean (SD)]	3-Day Regimen (20 mg/kg x 3 days)	5-Day Regimen (12 mg/kg x 5 days)
n	11	17
C <sub>max</sub> (µg/mL)	1.1 (0.4)	0.5 (0.4)
T <sub>max</sub> (hr)	2.7 (1.9)	2.2 (0.8)
AUC <sub>0-24</sub> (µg·hr/mL)	7.9 (2.9)	3.9 (1.9)

The similarity of the overall exposure (AUC<sub>0-∞</sub>) between the 3-day and 5-day regimens in pediatric patients is unknown.

Single dose pharmacokinetics in pediatric patients given doses of 30 mg/kg have not been studied. (See **DOSAGE AND ADMINISTRATION.**)

#### Drug-Drug Interactions

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

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

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the C<sub>max</sub> and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 2. (See **PRECAUTIONS - Drug Interactions.**)

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

Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (with/without azithromycin) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00	
				Mean C <sub>max</sub>	Mean AUC
Atorvastatin	10 mg/day × 8 days	500 mg/day PO on days 6-8	12	0.83 (0.63 to 1.08)	1.01 (0.81 to 1.25)
Carbamazepine	200 mg/day × 2 days, then 200 mg BID × 18 days	500 mg/day PO for days 16-18	7	0.97 (0.88 to 1.06)	0.96 (0.88 to 1.06)
Cetirizine	20 mg/day × 11 days	500 mg PO on day 7, then 250 mg/day on days 8-11	14	1.03 (0.93 to 1.14)	1.02 (0.92 to 1.13)
Didanosine	200 mg PO BID × 21 days	1,200 mg/day PO on days 8-21	6	1.44 (0.85 to 2.43)	1.14 (0.83 to 1.57)
Efavirenz	400 mg/day × 7 days	600 mg PO on day 7	14	1.04*	0.95*
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	1.04 (0.98 to 1.11)	1.01 (0.97 to 1.05)
Indinavir	800 mg TID × 5 days	1,200 mg PO on day 5	18	0.96 (0.86 to 1.08)	0.90 (0.81 to 1.00)
Midazolam	15 mg PO on day 3	500 mg/day PO × 3 days	12	1.27 (0.89 to 1.81)	1.26 (1.01 to 1.56)
Nelfinavir	750 mg TID × 11 days	1,200 mg PO on day 9	14	0.90 (0.81 to 1.01)	0.85 (0.78 to 0.93)
Rifabutin	300 mg/day × 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	See footnote below	NA
Sildenafil	100 mg on days 1 and 4	500 mg/day PO × 3 days	12	1.16 (0.86 to 1.57)	0.92 (0.75 to 1.12)
Theophylline	4 mg/kg IV on days 1, 11, 25	500 mg PO on day 7, 250 mg/day on days 8-11	10	1.19 (1.02 to 1.40)	1.02 (0.86 to 1.22)
Theophylline	300 mg PO BID × 15 days	500 mg PO on day 6, then 250 mg/day on days 7-10	8	1.09 (0.92 to 1.29)	1.08 (0.89 to 1.31)
Triazolam	0.125 mg on day 2	500 mg PO on day 1, then 250 mg/day on day 2	12	1.06*	1.02*
Trimethoprim/Sulfamethoxazole	160 mg/800 mg/day PO × 7 days	1,200 mg PO on day 7	12	0.85 (0.75 to 0.97)/ 0.90 (0.78 to 1.03)	0.87 (0.80 to 0.95)/ 0.96 (0.88 to 1.03)
Zidovudine	500 mg/day PO × 21 days	600 mg/day PO × 14 days	5	1.12 (0.42 to 3.02)	0.94 (0.52 to 1.70)
Zidovudine	500 mg/day PO × 21 days	1,200 mg/day PO × 14 days	4	1.31 (0.43 to 3.97)	1.30 (0.69 to 2.43)

NA - Not Available

\* - 90% Confidence interval not reported

Mean rifabutin concentrations one-half day after the last dose of rifabutin were 60 ng/mL when co-administered with azithromycin and 71 ng/mL when co-administered with placebo.

Table 2. Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs (See **PRECAUTIONS - Drug Interactions.**)

Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (with/without co-administered drug) of Azithromycin Pharmacokinetic Parameters (90% CI); No Effect = 1.00	
				Mean C <sub>max</sub>	Mean AUC
Efavirenz	400 mg/day × 7 days	600 mg PO on day 7	14	1.22 (1.04 to 1.42)	0.92*
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	0.82 (0.66 to 1.02)	1.07 (0.94 to 1.22)
Nelfinavir	750 mg TID × 11 days	1,200 mg PO on day 9	14	2.36 (1.77 to 3.15)	2.12 (1.80 to 2.50)
Rifabutin	300 mg/day × 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	See footnote below	NA

NA – Not available

\* - 90% Confidence interval not reported

Mean azithromycin concentrations one day after the last dose were 53 ng/mL when coadministered with 300 mg daily rifabutin and 49 ng/mL when coadministered with placebo.

## Microbiology

### Mechanism of Action

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

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. 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.

### Mechanism of Resistance

The most frequently encountered mechanism of resistance to azithromycin is modification of the 23S rRNA at positions corresponding to A2058 and A2059 in the *Escherichia coli* numbering system. In addition to cross resistance with other macrolides (erythromycin and clarithromycin), ribosomal modification may determine resistance to other antibiotic classes (lincosamides and streptogramins B) that bind to overlapping ribosomal sites.

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



**Gram-positive bacteria**

*Staphylococcus aureus*  
*Streptococcus agalactiae*  
*Streptococcus pneumoniae*  
*Streptococcus pyogenes*

**Gram-negative bacteria**

*Haemophilus ducreyi*  
*Haemophilus influenzae*  
*Moraxella catarrhalis*  
*Neisseria gonorrhoeae*

**“Other” bacteria**

*Chlamydia pneumoniae*  
*Chlamydia trachomatis*  
*Mycoplasma pneumoniae*

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

At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the azithromycin susceptible breakpoint of  $\leq 4\text{mcg/mL}$ . However, safety and effectiveness of azithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

**Gram-positive bacteria**

Beta-hemolytic streptococci (Groups C, F, G)  
Viridans group streptococci

**Gram-negative bacteria**

*Bordetella pertussis*

**Anaerobic bacteria**

*Peptostreptococcus* species  
*Prevotella bivia*

**“Other” bacteria**

*Ureaplasma urealyticum*  
*Legionella pneumophila*

**Susceptibility Testing Methods**

When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports may differ from susceptibility data obtained from outpatient use, but could aid the physician in selecting the most effective antimicrobial.

### **Dilution Techniques:**

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1,2</sup> (broth or agar) or equivalent with standardized inoculum concentration and standardized concentration of azithromycin powder. The MIC values should be interpreted according to criteria provided in Table 3.

### **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<sup>2,3</sup> requires the use of standardized inoculum concentration. This procedure uses paper disks impregnated with 15-mcg azithromycin to test the susceptibility of bacteria to azithromycin. The disk diffusion interpretive criteria are provided in Table 3.

**Table 3. Susceptibility Test Interpretive Criteria for Azithromycin**  
**Susceptibility Test Result Interpretive Criteria**

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R	S	I	R
<i>Haemophilus influenzae</i> <sup>a</sup>	≤ 4	--	--	≥ 12	--	--
<i>Staphylococcus aureus</i>	≤ 2	4	≥ 8	≥ 18	14-17	≤ 13
Streptococci including <i>S. pneumoniae</i>	≤ 0.5	1	≥ 2	≥ 18	14-17	≤ 13

Susceptibility to azithromycin must be tested in ambient air.

<sup>a</sup>Insufficient information is available to determine Intermediate or Resistant interpretive criteria. The ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues [see **Clinical Pharmacology**].

A report of “susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. 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 the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; other therapy should be selected.

## **Quality Control**

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test. Standard azithromycin powder should provide the following range of MIC values noted in Table 4. For the diffusion technique using the azithromycin 15 mcg disk, the criteria in Table 4 should be achieved.

**Table 4. Acceptable Quality Control Ranges for Azithromycin**

<b>QC Strain</b>	<b>Minimum Inhibitory Concentrations (mcg/mL)</b>	<b>Disk Diffusion (zone diameters in mm)</b>
<i>Haemophilus influenzae</i> ATCC* 49247	1.0-4.0	13-21
<i>Staphylococcus aureus</i> ATCC 29213	0.5-2.0	...
<i>Staphylococcus aureus</i> ATCC 25923	...	21-26
<i>Streptococcus pneumoniae</i> ATCC 49619	0.06-0.25	19-25

Susceptibility to azithromycin must be tested in ambient air.

\*ATCC = American Type Culture Collection

## **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*.

**Acute bacterial sinusitis** due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

**Community-acquired pneumonia** due to *Chlamydophila 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.

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

should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**Pediatric Patients:** (See **PRECAUTIONS—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 *Chlamydophila 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, any macrolide or ketolide antibiotic. Zithromax is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

## WARNINGS

### Hypersensitivity

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

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

### Hepatotoxicity

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

### Treatment of pneumonia

**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).**

### *Clostridium Difficile*-associated diarrhea

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

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

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

### **QT Prolongation**

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

## **PRECAUTIONS**

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

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

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

### **Information for Patients:**

ZITHROMAX tablets and oral suspension 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.

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

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

#### **Drug Interactions:**

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

Although, in a study of 22 healthy men, a 5-day course of azithromycin did not affect the prothrombin time from a subsequently administered dose of warfarin, spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. (See **CLINICAL PHARMACOLOGY-Drug-Drug Interactions**.) When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz, or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is coadministered with any of the above agents.

Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate



potential drug-drug interaction. 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 concentrations.

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

Terfenadine, cyclosporine, hexobarbital and phenytoin concentrations.

**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 concentrations (i.e., 200 mg/kg/day). These doses, based on a mg/m<sup>2</sup> 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 (total dosage regimen: 30 mg/kg, see **DOSAGE AND ADMINISTRATION**): Safety and effectiveness in the treatment of pediatric patients with otitis media under 6 months of age have not been established.

Acute Bacterial Sinusitis (dosage regimen: 10 mg/kg on Days 1-3): Safety and effectiveness in the treatment of pediatric patients with acute bacterial sinusitis under 6 months of age have not been established. Use of Zithromax for the treatment of acute bacterial sinusitis in pediatric patients (6 months of age or greater) is supported by adequate and well-controlled studies in adults, similar pathophysiology of acute sinusitis in adults and pediatric patients, and studies of acute otitis media in pediatric patients.

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 pediatric patients with community-acquired pneumonia under 6 months of age have not been established. Safety and

effectiveness for pneumonia due to *Chlamydophila 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 pediatric patients 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**.)

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

Elderly patients may be more susceptible to development of torsades de pointes arrhythmia than younger patients (See **WARNINGS**).

ZITHROMAX 250 mg tablets contain 0.9 mg of sodium per tablet.

ZITHROMAX 500 mg tablets contain 1.8 mg of sodium per tablet.

ZITHROMAX for oral suspension 100 mg/5 mL contains 3.7 mg of sodium per 5 mL of constituted solution.

ZITHROMAX for oral suspension 200 mg/5 mL contains 7.4 mg of sodium per 5 mL of constituted solution.

## 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. Potentially serious side effects of angioedema and cholestatic jaundice were reported rarely. Approximately 0.7% of the patients (adults and pediatric patients) from the 5-day multiple-dose clinical trials discontinued ZITHROMAX (azithromycin) therapy because of treatment-related side effects. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.6%. In clinical trials in pediatric patients given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related side effects was approximately 1%. (See **DOSAGE AND ADMINISTRATION**.) Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. (See **CLINICAL STUDIES IN PEDIATRIC PATIENTS**.)

### **Clinical:**

#### **Adults:**

*Multiple-dose regimens:* Overall, the most common treatment-related side effects in adult patients receiving multiple-dose regimens of ZITHROMAX were related to the gastrointestinal system with diarrhea/loose stools (4-5%), nausea (3%) and abdominal pain (2-3%) being the most frequently reported.

No other treatment-related side effects occurred in patients on the multiple-dose regimens 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, pruritus, 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.

**Pediatric Patients:**

*Single and Multiple-dose regimens:* The types of side effects in pediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in pediatric patients.

**Acute Otitis Media:** For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects ( $\geq 1\%$ ) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea and rash. (See **DOSAGE AND ADMINISTRATION** and **CLINICAL STUDIES IN PEDIATRIC PATIENTS**.)

The incidence, based on dosing regimen, is described in the table below:

Dosage Regimen	Diarrhea, %	Abdominal Pain, %	Vomiting, %	Nausea, %	Rash, %
1-day	4.3%	1.4%	4.9%	1.0%	1.0%
3-day	2.6%	1.7%	2.3%	0.4%	0.6%
5-day	1.8%	1.2%	1.1%	0.5%	0.4%

**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, abdominal pain, vomiting, nausea and rash.

The incidence is described in the table below:

Dosage Regimen	Diarrhea/Loose stools, %	Abdominal Pain, %	Vomiting, %	Nausea, %	Rash, %
5-day	5.8%	1.9%	1.9%	1.9%	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, vomiting, abdominal pain, nausea and headache.

The incidence is described in the table below:

Dosage Regimen	Diarrhea, %	Abdominal Pain, %	Vomiting, %	Nausea, %	Rash, %	Headache, %
5-day	5.4%	3.4%	5.6%	1.8%	0.7%	1.1%

With any of the treatment regimens, no other treatment-related side effects occurred in pediatric patients 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, enteritis, flatulence, gastritis, jaundice, loose stools and oral moniliasis.

**Hematologic and Lymphatic:** Anemia and leukopenia.

**Nervous System:** Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness and insomnia.

**General:** Fever, face edema, fatigue, fungal infection, malaise and pain.

**Allergic:** Rash and allergic reaction.

**Respiratory:** Cough increased, pharyngitis, pleural effusion and rhinitis.

**Skin and Appendages:** Eczema, fungal dermatitis, pruritus, sweating, urticaria and vesiculobullous rash.

**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 and angioedema.

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

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

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

**Genitourinary:** Interstitial nephritis and acute renal failure and vaginitis.

**Hematopoietic:** Thrombocytopenia.

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

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

**Psychiatric:** Aggressive reaction and anxiety.

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

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

### **Laboratory Abnormalities:**

#### **Adults:**

Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils and blood glucose; elevated serum creatine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline.

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

In multiple-dose clinical trials involving more than 5000 patients, four patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

### **Pediatric Patients:**

#### **One, Three and Five Day Regimens**

Laboratory data collected from comparative clinical trials employing two 3-day regimens (30 mg/kg or 60 mg/kg in divided doses over 3 days), or two 5-day regimens (30 mg/kg or 60 mg/kg in divided doses over 5 days) were similar for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1-5%. Laboratory data for patients receiving 30 mg/kg as a single dose were collected in one single center trial. In that trial, an absolute neutrophil count between 500-1500 cells/mm<sup>3</sup> was observed in 10/64 patients receiving 30 mg/kg as a single dose, 9/62 patients receiving 30 mg/kg given over 3 days, and 8/63 comparator patients. No patient had an absolute neutrophil count <500 cells/mm<sup>3</sup>. (See **DOSAGE AND ADMINISTRATION**.)

In multiple-dose clinical trials involving approximately 4700 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

## DOSAGE AND ADMINISTRATION

(See **INDICATIONS AND USAGE** and **CLINICAL PHARMACOLOGY**.)

### Adults:

Infection*	Recommended Dose/Duration of Therapy
Community-acquired pneumonia (mild severity) Pharyngitis/tonsillitis (second line therapy) Skin/skin structure (uncomplicated)	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Acute bacterial exacerbations of chronic obstructive pulmonary disease (mild to moderate)	500 mg QD x 3 days OR 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5.
Acute bacterial sinusitis	500 mg QD x 3 days
Genital ulcer disease (chancroid)	One single 1 gram dose
Non-gonococcal urethritis and cervicitis	One single 1 gram dose
Gonococcal urethritis and cervicitis	One single 2 gram dose
<b>*DUE TO THE INDICATED ORGANISMS (See INDICATIONS AND USAGE.)</b>	

ZITHROMAX tablets can be taken with or without food.

#### Renal Insufficiency:

No dosage adjustment is recommended for subjects with renal impairment (GFR  $\leq$ 80 mL/min). The mean AUC<sub>0-120</sub> was similar in subjects with GFR 10-80 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR <10 mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment. (See **CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency**.)

#### Hepatic Insufficiency:

The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function (See **CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency**.)

No dosage adjustment is recommended based on age or gender. (See **CLINICAL PHARMACOLOGY, Special Populations**.)

#### Pediatric Patients:

ZITHROMAX for oral suspension can be taken with or without food.

**Acute Otitis Media:** The recommended dose of ZITHROMAX for oral suspension for the treatment of pediatric patients with acute otitis media is 30 mg/kg given as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on Days 2 through 5. (See chart below.)

**Acute Bacterial Sinusitis:** The recommended dose of ZITHROMAX for oral suspension for the treatment of pediatric patients with acute bacterial sinusitis is 10 mg/kg once daily for 3 days. (See chart below.)

**Community-Acquired Pneumonia:** The recommended dose of ZITHROMAX for oral suspension for the treatment of pediatric patients with community-acquired pneumonia is 10 mg/kg as a single dose on the first day followed by 5 mg/kg on Days 2 through 5. (See chart below.)

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

<b>OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA: (5-Day Regimen)*</b>							
<b>Dosing Calculated on 10 mg/kg/day Day 1 and 5 mg/kg/day Days 2 to 5.</b>							
<b>Weight</b>		<b>100 mg/5 mL</b>		<b>200 mg/5 mL</b>		<b>Total mL per Treatment Course</b>	<b>Total mg per Treatment Course</b>
<b>Kg</b>	<b>Lbs.</b>	<b>Day 1</b>	<b>Days 2-5</b>	<b>Day 1</b>	<b>Days 2-5</b>		
5	11	2.5 mL (½ tsp)	1.25 mL (¼ tsp)			7.5 mL	150 mg
10	22	5 mL (1 tsp)	2.5 mL (½ tsp)			15 mL	300 mg
20	44			5 mL (1 tsp)	2.5 mL (½ tsp)	15 mL	600 mg
30	66			7.5 mL (1½ tsp)	3.75 mL (¾ tsp)	22.5 mL	900 mg
40	88			10 mL (2 tsp)	5 mL (1 tsp)	30 mL	1200 mg
50 and above	110 and above			12.5 mL (2½ tsp)	6.25 mL (1¼ tsp)	37.5 mL	1500 mg

\* Effectiveness of the 3-day or 1-day regimen in pediatric patients with community-acquired pneumonia has not been established.



<b>OTITIS MEDIA AND ACUTE BACTERIAL SINUSITIS: (3-Day Regimen)*</b>					
<b>Dosing Calculated on 10 mg/kg/day</b>					
<b>Weight</b>		<b>100 mg/5 mL</b>	<b>200 mg/5 mL</b>	<b>Total mL per Treatment Course</b>	<b>Total mg per Treatment Course</b>
<b>Kg</b>	<b>Lbs.</b>	<b>Day 1-3</b>	<b>Day 1-3</b>		
5	11	2.5 mL (1/2 tsp)		7.5 mL	150 mg
10	22	5 mL (1 tsp)		15 mL	300 mg
20	44		5 mL (1 tsp)	15 mL	600 mg
30	66		7.5 mL (1 ½ tsp)	22.5 mL	900 mg
40	88		10 mL (2 tsp)	30 mL	1200 mg
50 and above	110 and above		12.5 mL (2 ½ tsp)	37.5 mL	1500 mg

\*Effectiveness of the 5-day or 1-day regimen in pediatric patients with acute bacterial sinusitis has not been established.

<b>OTITIS MEDIA: (1-Day Regimen)</b>				
<b>Dosing Calculated on 30 mg/kg as a single dose</b>				
<b>Weight</b>		<b>200 mg/5 mL</b>	<b>Total mL per Treatment Course</b>	<b>Total mg per Treatment Course</b>
<b>Kg</b>	<b>Lbs.</b>	<b>Day 1</b>		
5	11	3.75 mL (3/4 tsp)	3.75 mL	150 mg
10	22	7.5 mL (1 ½ tsp)	7.5 mL	300 mg
20	44	15 mL (3 tsp)	15 mL	600 mg
30	66	22.5 mL (4 ½ tsp)	22.5 mL	900 mg
40	88	30 mL (6 tsp)	30 mL	1200 mg
50 and above	110 and above	37.5 mL (7 ½ tsp)	37.5 mL	1500 mg

The safety of re-dosing azithromycin in pediatric patients who vomit after receiving 30 mg/kg as a single dose has not been established. In clinical studies involving 487 patients with acute otitis media given a single 30 mg/kg dose of azithromycin, eight patients who vomited within 30 minutes of dosing were re-dosed at the same total dose.

**Pharyngitis/Tonsillitis:** The recommended dose of ZITHROMAX for children with pharyngitis/tonsillitis is 12 mg/kg once daily for 5 days. (See chart below.)

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

<b>PHARYNGITIS/TONSILLITIS: (5-Day Regimen)</b>				
<b>Dosing Calculated on 12 mg/kg/day for 5 days.</b>				
<b>Weight</b>		<b>200 mg/5 mL</b>	<b>Total mL per Treatment Course</b>	<b>Total mg per Treatment Course</b>
<b>Kg</b>	<b>Lbs.</b>	<b>Day 1-5</b>		
8	18	2.5 mL (½ tsp)	12.5 mL	500 mg
17	37	5 mL (1 tsp)	25 mL	1000 mg
25	55	7.5 mL (1½ tsp)	37.5 mL	1500 mg
33	73	10 mL (2 tsp)	50 mL	2000 mg
40	88	12.5 mL (2½ tsp)	62.5 mL	2500 mg

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:

<u>Amount of water to be added</u>	<u>Total volume after constitution (azithromycin content)</u>	<u>Azithromycin concentration after constitution</u>
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 suspension at 5° to 30°C (41° to 86°F) and use within 10 days. Discard after full dosing is completed.

**HOW SUPPLIED**

ZITHROMAX 250 mg tablets are supplied as pink modified capsular shaped, engraved, film-coated tablets containing azithromycin dihydrate equivalent to 250 mg of azithromycin. ZITHROMAX 250 mg 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<sup>®</sup>) as follows:

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

ZITHROMAX 500 mg tablets are supplied as pink modified capsular shaped, engraved, film-coated tablets containing azithromycin dihydrate equivalent to 500 mg of azithromycin. ZITHROMAX 500 mg tablets are engraved with “Pfizer” on one side and “ZTM500” on the other. These are packaged in bottles and blister cards of 3 tablets (TRI-PAKS™) as follows:

Bottles of 30	NDC 0069-3070-30
Boxes of 3 (TRI-PAKS™ of 3 tablets)	NDC 0069-3070-75
Unit Dose package of 50	NDC 0069-3070-86

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 to provide 100 mg/5 mL or 200 mg/5 mL suspension in bottles as follows:

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

See **DOSAGE AND ADMINISTRATION** for constitution instructions with each bottle type.

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 (See INDICATIONS AND USAGE and Pediatric Use.)**

### **Pediatric Patients**

From the perspective of evaluating pediatric clinical trials, Days 11-14 were considered on-therapy evaluations because of the extended half-life of azithromycin. Day 11-14 data are provided for clinical guidance. Day 24-32 evaluations were considered the primary test of cure endpoint.

## Acute Otitis Media

### Safety and efficacy using azithromycin 30 mg/kg given over 5 days

#### 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 amoxicillin/clavulanate potassium (4:1). 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 treatment-related 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).

#### Protocol 2

In a non-comparative 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:

#### Presumed Bacteriologic Eradication

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

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

#### Protocol 3

In another controlled comparative clinical and microbiologic study of otitis media performed in the United States, azithromycin was compared to amoxicillin/clavulanate potassium (4:1). This study utilized two of the same investigators as Protocol 2 (above), and these two investigators enrolled 90% of the patients in Protocol 3. For this reason, 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:

#### Presumed Bacteriologic Eradication

	Day 11		Day 30	
	Azithromycin	Control	Azithromycin	Control
<i>S. pneumoniae</i>	25/29 (86%)	26/26 (100%)	22/28 (79%)	18/22 (82%)
<i>H. influenzae</i>	9/11 (82%)	9/9	8/10 (80%)	6/8
<i>M. catarrhalis</i>	7/7	5/5	5/5	2/3
<i>S. pyogenes</i>	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 treatment-related 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).

#### **Safety and efficacy using azithromycin 30 mg/kg given over 3 days**

##### Protocol 4

In a double-blind, controlled, randomized clinical study of acute otitis media in pediatric patients from 6 months to 12 years of age, azithromycin (10 mg/kg per day for 3 days) was compared to amoxicillin/clavulanate potassium (7:1) in divided doses q12h for 10 days. Each patient received active drug and placebo matched for the comparator.

For the 366 patients who were evaluated for clinical efficacy at the Day 12 visit, the clinical success rate (i.e., cure plus improvement) was 83% for azithromycin and 88% for the control agent. For the 362 patients who were evaluated at the Day 24-28 visit, the clinical success rate was 74% for azithromycin and 69% for the control agent.

In the safety analysis of the above study, the incidence of treatment-related adverse events, primarily gastrointestinal, in all patients treated was 10.6% with azithromycin and 20.0% with the control agent. The most common side effects were diarrhea/loose stools (5.9% azithromycin vs. 14.6% control), vomiting (2.1% azithromycin vs. 1.1% control), and rash (0.0% azithromycin vs. 4.3% control).

#### **Safety and efficacy using azithromycin 30 mg/kg given as a single dose**

##### Protocol 5

A double blind, controlled, randomized trial was performed at nine clinical centers. Pediatric patients from 6 months to 12 years of age were randomized 1:1 to treatment with either azithromycin (given at 30 mg/kg as a single dose on Day 1) or amoxicillin/clavulanate potassium (7:1), divided q12h for 10 days. Each child received active drug, and placebo matched for the comparator.

Clinical response (Cure, Improvement, Failure) was evaluated at End of Therapy (Day 12-16) and Test of Cure (Day 28-32). Safety was evaluated throughout the trial for all treated subjects. For the 321 subjects who were evaluated at End of Treatment, the clinical success rate (cure plus improvement) was 87% for azithromycin, and 88% for the comparator. For the 305 subjects who were evaluated at Test of Cure, the clinical success rate was 75% for both azithromycin and the comparator.

In the safety analysis, the incidence of treatment-related adverse events, primarily gastrointestinal, was 16.8% with azithromycin, and 22.5% with the comparator. The most common side effects were diarrhea (6.4% with azithromycin vs. 12.7% with the comparator), vomiting (4% with each agent), rash (1.7% with azithromycin vs. 5.2% with the comparator) and nausea (1.7% with azithromycin vs. 1.2% with the comparator).

#### Protocol 6

In a non-comparative clinical and microbiological trial, 248 patients from 6 months to 12 years of age with documented acute otitis media were dosed with a single oral dose of azithromycin (30 mg/kg on Day 1).

For the 240 patients who were evaluable for clinical modified Intent-to-Treat (MITT) analysis, the clinical success rate (i.e., cure plus improvement) at Day 10 was 89% and for the 242 patients evaluable at Day 24-28, the clinical success rate (cure) was 85%.

#### Presumed Bacteriologic Eradication

	Day 10	Day 24-28
<i>S. pneumoniae</i>	70/76 (92%)	67/76 (88%)
<i>H. influenzae</i>	30/42 (71%)	28/44 (64%)
<i>M. catarrhalis</i>	10/10 (100%)	10/10 (100%)
Overall	110/128 (86%)	105/130 (81%)

In the safety analysis of this study, the incidence of treatment-related adverse events, primarily gastrointestinal, in all the subjects treated was 12.1%. The most common side effects were vomiting (5.6%), diarrhea (3.2%), and abdominal pain (1.6%).

#### Pharyngitis/Tonsillitis

In three 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  $\beta$ -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 treatment-related 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).

**Adult Patients**

**Acute Bacterial Exacerbations of Chronic Obstructive Pulmonary Disease**

In a randomized, double-blind controlled clinical trial of acute exacerbation of chronic bronchitis (AECB), azithromycin (500 mg once daily for 3 days) was compared with clarithromycin (500 mg twice daily for 10 days). The primary endpoint of this trial was the clinical cure rate at Day 21- 24. For the 304 patients analyzed in the modified intent to treat analysis at the Day 21-24 visit, the clinical cure rate for 3 days of azithromycin was 85% (125/147) compared to 82% (129/157) for 10 days of clarithromycin.

The following outcomes were the clinical cure rates at the Day 21-24 visit for the bacteriologically evaluable patients by pathogen:

<b>Pathogen</b>	<b>Azithromycin (3 Days)</b>	<b>Clarithromycin (10 Days)</b>
<i>S. pneumoniae</i>	29/32 (91%)	21/27 (78%)
<i>H. influenzae</i>	12/14 (86%)	14/16 (88%)
<i>M. catarrhalis</i>	11/12 (92%)	12/15 (80%)

In the safety analysis of this study, the incidence of treatment-related adverse events, primarily gastrointestinal, were comparable between treatment arms (25% with azithromycin and 29% with clarithromycin). The most common side effects were diarrhea, nausea and abdominal pain

with comparable incidence rates for each symptom of 5-9% between the two treatment arms. (See **ADVERSE REACTIONS**.)

### **Acute Bacterial Sinusitis**

In a randomized, double blind, double-dummy controlled clinical trial of acute bacterial sinusitis, azithromycin (500 mg once daily for 3 days) was compared with amoxicillin/clavulanate (500/125 mg tid for 10 days). Clinical response assessments were made at Day 10 and Day 28. The primary endpoint of this trial was prospectively defined as the clinical cure rate at Day 28. For the 594 patients analyzed in the modified intent to treat analysis at the Day 10 visit, the clinical cure rate for 3 days of azithromycin was 88% (268/303) compared to 85% (248/291) for 10 days of amoxicillin/clavulanate. For the 586 patients analyzed in the modified intent to treat analysis at the Day 28 visit, the clinical cure rate for 3 days of azithromycin was 71.5% (213/298) compared to 71.5% (206/288), with a 97.5% confidence interval of -8.4 to 8.3, for 10 days of amoxicillin/clavulanate.

In the safety analysis of this study, the overall incidence of treatment-related adverse events, primarily gastrointestinal, was lower in the azithromycin treatment arm (31%) than in the amoxicillin/clavulanate arm (51%). The most common side effects were diarrhea (17% in the azithromycin arm vs. 32% in the amoxicillin/clavulanate arm), and nausea (7% in the azithromycin arm vs. 12% in the amoxicillin/clavulanate arm). (See **ADVERSE REACTIONS**).

In an open label, noncomparative study requiring baseline transantral sinus punctures the following outcomes were the clinical success rates at the Day 7 and Day 28 visits for the modified intent to treat patients administered 500 mg of azithromycin once daily for 3 days with the following pathogens:

<b>Pathogen</b>	<b>Azithromycin</b>	
	<b>(500 mg per day for 3 Days)</b>	
	<b>Day 7</b>	<b>Day28</b>
<i>S. pneumoniae</i>	23/26 (88%)	21/25 (84%)
<i>H. influenzae</i>	28/32 (87%)	24/32 (75%)
<i>M. catarrhalis</i>	14/15 (93%)	13/15 (87%)

The overall incidence of treatment-related adverse events in the noncomparative study was 21% in modified intent to treat patients treated with azithromycin at 500 mg once daily for 3 days



with the most common side effects being diarrhea (9%), abdominal pain (4%) and nausea (3%). (See **ADVERSE REACTIONS**).

### **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 the basis of  $\text{mg}/\text{m}^2$ , are approximately equal to the recommended adult human dose, and in rats treated at doses approximately one-sixth of the recommended adult human dose. This effect has been shown to be 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  $C_{\text{max}}$  value of  $1.3 \mu\text{g}/\text{mL}$  (six times greater than the observed  $C_{\text{max}}$  of  $0.216 \mu\text{g}/\text{mL}$  at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed  $C_{\text{max}}$  value of  $1.5 \mu\text{g}/\text{mL}$  (seven times greater than the observed same  $C_{\text{max}}$  and drug dose in the studied pediatric population). On a  $\text{mg}/\text{m}^2$  basis, 30 mg/kg dose in the neonatal rat ( $135 \text{mg}/\text{m}^2$ ) and 10 mg/kg dose in the neonatal dog ( $79 \text{mg}/\text{m}^2$ ) are approximately 0.5 and 0.3 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. Phospholipidosis, 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:**

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2. CLSI, Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. CLSI document M100-S22. CLSI, Wayne, PA 19087, 2012.
3. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard - Eleventh Edition. CLSI document M02-A11. CLSI, Wayne, PA 19087, 2012.

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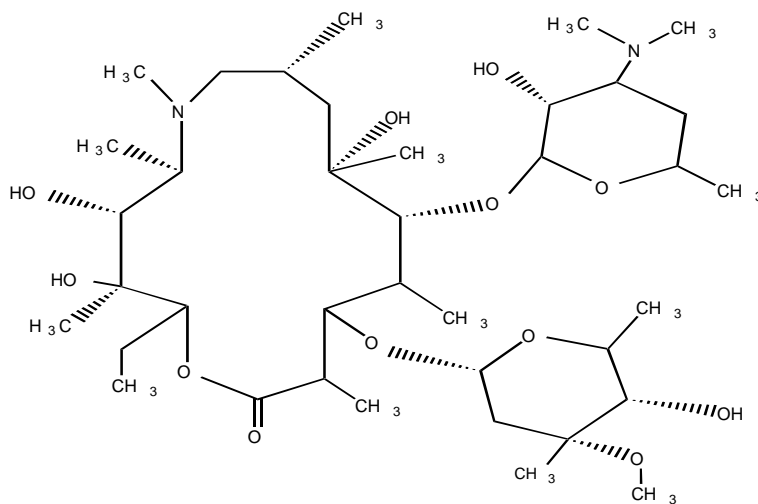
# ZITHROMAX<sup>®</sup>

## (azithromycin tablets) and (azithromycin for oral suspension)

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

### DESCRIPTION

ZITHROMAX (azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for oral administration. Azithromycin has the chemical name (2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl- $\alpha$ -*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)- $\beta$ -*D*-*xyl*o-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<sub>38</sub>H<sub>72</sub>N<sub>2</sub>O<sub>12</sub>, 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 tablets contain azithromycin dihydrate equivalent to 600 mg azithromycin. The tablets are supplied as white, modified oval-shaped, film-coated tablets. They also contain the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate and an aqueous film coat consisting of hypromellose, titanium dioxide, lactose and triacetin.

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

### CLINICAL PHARMACOLOGY

**Pharmacokinetics:** Following oral administration, azithromycin is rapidly absorbed and widely distributed throughout the body. Rapid distribution of azithromycin into tissues and high concentration within cells result in significantly higher azithromycin concentrations in tissues than in plasma or serum. The 1 g single dose packet is bioequivalent to four 250 mg azithromycin capsules.

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

MEAN (CV%) PK PARAMETER

<u>DOSE/DOSAGE FORM</u> (serum, except as indicated)	<u>Subjects</u>	<u>Day No.</u>	<u>C<sub>max</sub></u> ( <u>µg/mL</u> )	<u>T<sub>max</sub></u> ( <u>hr</u> )	<u>C<sub>24</sub></u> ( <u>µg/mL</u> )	<u>AUC</u> ( <u>µg•hr/mL</u> )	<u>T<sub>1/2</sub></u> ( <u>hr</u> )	<u>Urinary Excretion</u> ( <u>% of dose</u> )
500 mg/250 mg capsule	12	Day 1	0.41	2.5	0.05	2.6 <sup>a</sup>	–	4.5
and 250 mg on Days 2-5	12	Day 5	0.24	3.2	0.05	2.1 <sup>a</sup>	–	6.5
1200 mg/600 mg tablets	12	Day 1	0.66	2.5	0.074	6.8 <sup>b</sup>	40	–
%CV			(62%)	(79%)	(49%)	(64%)	(33%)	
600 mg tablet/day	7	1	0.33	2.0	0.039	2.4 <sup>a</sup>		
%CV			25%	(50%)	(36%)	(19%)		
	7	22	0.55	2.1	0.14	5.8 <sup>a</sup>	84.5	-
%CV			(18%)	(52%)	(26%)	(25%)		-
600 mg tablet/day (leukocytes)	7	22	252	10.9	146	4763 <sup>a</sup>	82.8	-
%CV			(49%)	(28%)	(33%)	(42%)	-	-

<sup>a</sup>AUC<sub>0-24</sub>; <sup>b</sup>0-last.

In these studies (500 mg Day 1, 250 mg Days 2-5), there was no significant difference in the disposition of azithromycin between male and female subjects. Plasma concentrations of azithromycin following single 500 mg oral and I.V. doses declined in a polyphasic pattern resulting in an average terminal half-life of 68 hours. With a regimen of 500 mg on Day 1 and 250 mg/day on Days 2-5,  $C_{\min}$  and  $C_{\max}$  remained essentially unchanged from Day 2 through Day 5 of therapy. However, without a loading dose, azithromycin  $C_{\min}$  levels required 5 to 7 days to reach steady-state.

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

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

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

The absolute bioavailability of two 600 mg tablets was 34% (CV=56%). Administration of two 600 mg tablets with food increased  $C_{\max}$  by 31% (CV=43%) while the extent of absorption (AUC) was unchanged (mean ratio of AUCs=1.00; CV=55%).

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

When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin (500 mg Day 1, 250 mg Days 2-5) in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30 to 50%) were observed, no significant accumulation occurred.

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

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

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION ( $\mu\text{g/g}$ or $\mu\text{g/mL}$ ) <sup>1</sup>	CORRESPONDING PLASMA OR SERUM LEVEL ( $\mu\text{g/mL}$ )	TISSUE (FLUID) PLASMA (SERUM) RATIO <sup>1</sup>
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

<sup>1</sup> 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  $\mu\text{g/mL}$ ) 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  $\mu\text{g/mL}$ . Concentrations remained above 32  $\mu\text{g/mL}$  for approximately 60 hr. The mean half-lives for 6 males and 6 females were 34 hr and 57 hr, respectively. Leukocyte to plasma  $C_{\text{max}}$  ratios for males and females were 258 ( $\pm 77\%$ ) and 175 ( $\pm 60\%$ ), respectively, and the AUC ratios were 804 ( $\pm 31\%$ ) and 541 ( $\pm 28\%$ ), respectively. The clinical relevance of these findings is unknown.

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

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

### **Renal Insufficiency**

Azithromycin pharmacokinetics was investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1.0 g dose of azithromycin (4 × 250 mg capsules), the mean  $C_{max}$  and  $AUC_{0-120}$  increased by 5.1% and 4.2%, respectively in subjects with GFR 10 to 80 mL/min compared to subjects with normal renal function (GFR >80 mL/min). The mean  $C_{max}$  and  $AUC_{0-120}$  increased 61% and 35%, respectively in subjects with end-stage renal disease (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). (See **DOSAGE AND ADMINISTRATION**.)

### **Hepatic Insufficiency**

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

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

### **Microbiology**

#### Mechanism of Action

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

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

#### Activity of Azithromycin Against *Mycobacterium avium* complex (MAC)

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

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

### Mechanism of Resistance

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

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

### Mycobacterium avium complex (MAC)

*Chlamydia trachomatis*

### Susceptibility Testing Methods

#### Susceptibility testing of *Mycobacterium avium* complex (MAC)

Susceptibility testing may be done following the methodology of the Clinical and Laboratory Standards Institute (CLSI)<sup>1</sup>

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

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

Susceptibility testing of *Chlamydia trachomatis*.

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

## INDICATIONS AND USAGE

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



ZITHROMAX (azithromycin) is indicated for the treatment of MAC infection and prophylaxis against MAC Infection (pneumonia: see WARNINGS) caused by susceptible isolates.

#### Treatment of Disseminated *Mycobacterium avium* complex (MAC) Disease

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

#### 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 MAC disease in persons with advanced HIV infection (See DOSAGE AND ADMINISTRATION, CLINICAL STUDIES).

#### **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.

### **CONTRAINDICATIONS**

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

### **WARNINGS**

#### **Hypersensitivity**

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

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

**Hepatotoxicity**

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

**Clostridium Difficile-associated diarrhea**

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

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

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

**QT Prolongation**

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

## PRECAUTIONS

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

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

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

### **Information for Patients:**

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

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

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

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

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

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

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

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

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

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

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

Coadministration of a single oral dose of 1200 mg azithromycin (2 x 600 mg ZITHROMAX<sup>®</sup> tablets) with steady-state nelfinavir (750 mg tid) to healthy adult subjects produced a decrease of approximately 15% in mean AUC<sub>0-8</sub> of nelfinavir and its M8 metabolite. Mean C<sub>max</sub> of nelfinavir and its M8 metabolite were not significantly affected. No dosage adjustment of nelfinavir is required when nelfinavir is coadministered with azithromycin.

Coadministration of nelfinavir (750 mg tid) at steady state with a single oral dose of 1200 mg azithromycin increased the mean AUC<sub>0-∞</sub> of azithromycin by approximately a factor of 2-times (range of up to 4 times) of that when azithromycin was given alone. The mean C<sub>max</sub> of azithromycin was also increased by approximately a factor of 2-times (range of up to 5 times) of that when azithromycin was given alone. Dose adjustment of azithromycin is not recommended. However, when administered in conjunction with nelfinavir, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted. (See ADVERSE REACTIONS.)

Following administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days to healthy adult subjects, coadministration of 1200 mg azithromycin (2 x 600 mg ZITHROMAX<sup>®</sup> tablets) on the 7<sup>th</sup> day had no significant effects on peak concentrations (C<sub>max</sub>), total exposure (AUC), and the urinary excretion of either trimethoprim or sulfamethoxazole.

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

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

Efavirenz, when administered at a dose of 400 mg for seven days produced a 22% increase in the C<sub>max</sub> of azithromycin administered as a 600 mg single oral dose, while the AUC of azithromycin was not affected.

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

Although, in a study of 22 healthy men, a 5-day course of azithromycin did not affect the prothrombin time from a subsequently administered dose of warfarin, spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Dose adjustments are not indicated when azithromycin and zidovudine are coadministered. When zidovudine (100 mg q3h x5) was coadministered with daily azithromycin (600 mg, n=5 or 1200 mg, n=7), mean  $C_{max}$ , AUC and Cl<sub>r</sub> 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<sup>450</sup> 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<sup>2</sup> 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<sup>2</sup>/day basis, the doses in rats and mice are approximately 3.3 and 1.7 times the human dose, respectively.

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

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

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

#### **Pediatric Use:**

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

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

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

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

Elderly patients may be more susceptible to development of torsades de pointes arrhythmia than younger patients (See **WARNINGS**).

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

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

### ADVERSE REACTIONS

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Approximately 0.7% of the patients from the multiple-dose clinical trials discontinued ZITHROMAX (azithromycin) therapy because of treatment-related side effects. Most of the side effects leading to discontinuation were related to

the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain. Rarely but potentially serious side effects were angioedema and cholestatic jaundice.

**Clinical:**

*Multiple-dose regimen:*

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

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

**Cardiovascular:** Palpitations, chest pain.

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

**Genitourinary:** Monilia, vaginitis, and nephritis.

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

**General:** Fatigue.

**Allergic:** Rash, photosensitivity, and angioedema.

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

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

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

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

**Post-Marketing Experience:**



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

**Allergic:** Arthralgia, edema, urticaria, angioedema.

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

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

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

**Genitourinary:** Interstitial nephritis and acute renal failure, vaginitis.

**Hematopoietic:** Thrombocytopenia.

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

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

**Psychiatric:** Aggressive reaction and anxiety.

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

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

#### **Laboratory Abnormalities:**

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

With an incidence of 1-2%, 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<sup>3</sup>).

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

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

### **DOSAGE AND ADMINISTRATION** (See INDICATIONS AND USAGE.)

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

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

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

#### **Prevention of Disseminated MAC Infections**

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

#### **Treatment of Disseminated MAC Infections**

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

**DIRECTIONS FOR ADMINISTRATION OF ZITHROMAX for oral suspension in the single dose packet (1 g):** The entire contents of the packet should be mixed thoroughly with two ounces (approximately 60 mL) of water. Drink the entire contents immediately; add an additional two ounces of water, mix, and drink to assure complete consumption of dosage. **The**

**single dose packet should not be used to administer doses other than 1000 mg of azithromycin. This packet not for pediatric use.**

Renal Insufficiency: No dosage adjustment is recommended for subjects with renal impairment ( $GFR \leq 80 \text{ mL/min}$ ). The mean  $AUC_{0-120}$  was similar in subjects with  $GFR$  10-80 mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with  $GFR < 10 \text{ mL/min}$  compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment. (See **CLINICAL PHARMACOLOGY-Renal Insufficiency**.)

Hepatic Insufficiency:

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

### **HOW SUPPLIED**

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

Bottles of 30

NDC 0069-3080-30

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

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

Boxes of 10 Single Dose Packets (1 g)

NDC 0069-3051-07

Boxes of 3 Single Dose Packets (1 g)

NDC 0069-3051-75

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

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

#### **Prevention of Disseminated MAC Disease**

Two randomized, double blind clinical trials were performed in patients with CD4 counts  $< 100 \text{ cells}/\mu\text{L}$ . The first study (155) compared azithromycin (1200 mg once weekly) to placebo and enrolled 182 patients with a mean CD4 count of 35  $\text{cells}/\mu\text{L}$ . The second study (174) randomized 723 patients to either azithromycin (1200 mg once weekly), rifabutin (300 mg daily)

or the combination of both. The mean CD4 count was 51 cells/ $\mu$ L. The primary endpoint in these studies was disseminated MAC disease. Other endpoints included the incidence of clinically significant MAC disease and discontinuations from therapy for drug-related side effects.

#### *MAC bacteremia*

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

Cumulative Incidence Rate, %: Placebo (n=89)				
Month	MAC Free and Alive	MAC	Adverse Experience	Lost to Follow-up
6	69.7	13.5	6.7	10.1
12	47.2	19.1	15.7	18.0
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<sup>4</sup> was performed on all available MAC isolates from subjects randomized to either azithromycin, rifabutin or the combination. The distribution of MIC values for azithromycin from susceptibility testing of the breakthrough isolates was similar between study arms. As the efficacy of azithromycin in the treatment of disseminated MAC has not been established, the clinical relevance of these *in vitro* MICs as an indicator of susceptibility or resistance is not known.

#### *Clinically Significant Disseminated MAC Disease*

In association with the decreased incidence of bacteremia, patients in the groups randomized to either azithromycin alone or azithromycin in combination with rifabutin showed reductions in the signs and symptoms of disseminated MAC disease, including fever or night sweats, weight loss and anemia.

#### *Discontinuations From Therapy For Drug-Related Side Effects*

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

discontinued from the combination of azithromycin and rifabutin (22.7%) than from azithromycin alone (13.5%; p=0.026) or rifabutin alone (15.9%; p=0.209).

### Safety

As these patients with advanced HIV disease were taking multiple concomitant medications and experienced a variety of intercurrent illnesses, it was often difficult to attribute adverse events to study medication. Overall, the nature of side effects seen on the weekly dosage regimen of azithromycin over a period of approximately one year in patients with advanced HIV disease was similar to that previously reported for shorter course therapies.

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

	Study 155		Study 174		
	Placebo (N=91)	Azithromycin 1200 mg weekly (N=89)	Azithromycin 1200 mg weekly (N=233)	Rifabutin 300 mg daily (N=236)	Azithromycin + Rifabutin (N=224)
Mean Duration of Therapy (days)	303.8	402.9	315	296.1	344.4
Discontinuation of Therapy	2.3	8.2	13.5	15.9	22.7
Autonomic Nervous System					
Mouth Dry	0	0	0	3.0	2.7
Central Nervous System					
Dizziness	0	1.1	3.9	1.7	0.4
Headache	0	0	3.0	5.5	4.5
Gastrointestinal					
Diarrhea	15.4	52.8	50.2	19.1	50.9
Loose Stools	6.6	19.1	12.9	3.0	9.4
Abdominal Pain	6.6	27	32.2	12.3	31.7
Dyspepsia	1.1	9	4.7	1.7	1.8
Flatulence	4.4	9	10.7	5.1	5.8
Nausea	11	32.6	27.0	16.5	28.1
Vomiting	1.1	6.7	9.0	3.8	5.8
General					
Fever	1.1	0	2.1	4.2	4.9
Fatigue	0	2.2	3.9	2.1	3.1
Malaise	0	1.1	0.4	0	2.2
Musculoskeletal					
Arthralgia	0	0	3.0	4.2	7.1
Psychiatric					
Anorexia	1.1	0	2.1	2.1	3.1
Skin & Appendages					
Pruritus	3.3	0	3.9	3.4	7.6
Rash	3.2	3.4	8.1	9.4	11.1
Skin discoloration	0	0	0	2.1	2.2
Special Senses					
Tinnitus	4.4	3.4	0.9	1.3	0.9
Hearing Decreased	2.2	1.1	0.9	0.4	0
Uveitis	0	0	0.4	1.3	1.8
Taste Perversion	0	0	1.3	2.5	1.3

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

\*\* >2% adverse event rates for any group (except uveitis).

Side effects related to the gastrointestinal tract were seen more frequently in patients receiving azithromycin than in those receiving placebo or rifabutin. In Study 174, 86% of diarrheal episodes were mild to moderate in nature with discontinuation of therapy for this reason occurring in only 9/233 (3.8%) of patients.

#### *Changes in Laboratory Values*

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

#### Prophylaxis Against Disseminated MAC Abnormal Laboratory Values\*

		Placebo	Azithromycin 1200 mg weekly	Rifabutin 300 mg daily	Azithromycin & Rifabutin
Hemoglobin	<8 g/dl	1/51 2%	4/170 2%	4/114 4%	8/107 8%
Platelet Count	<50 × 10 <sup>3</sup> /mm <sup>3</sup>	1/71 1%	4/260 2%	2/182 1%	6/181 3%
WBC Count	<1 × 10 <sup>3</sup> /mm <sup>3</sup>	0/8 0%	2/70 3%	2/47 4%	0/43 0%
Neutrophils	<500/mm <sup>3</sup>	0/26 0%	4/106 4%	3/82 4%	2/78 3%
SGOT	>5 × ULN <sup>a</sup>	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%

<sup>a</sup>=Upper Limit of Normal

\*excludes subjects outside of the relevant normal range at baseline

#### **Treatment of Disseminated MAC Disease**

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

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

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

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

Response to therapy of patients taking ethambutol and either azithromycin 600 mg qd or clarithromycin 500 mg bid			
	Azithromycin 600 mg qd	Clarithromycin 500 mg bid	**95.1% CI on difference
Patients with positive culture at baseline	68	57	
Week 24			
Two consecutive negative blood cultures*	31/68 (46%)	32/57 (56%)	[-28, 7]
Mortality	16/68 (24%)	15/57 (26%)	[-18, 13]
* Primary endpoint			
** [95% confidence interval] on difference in rates (azithromycin-clarithromycin)			

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

#### **Sterilization by Baseline Colony Count**

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

	Azithromycin 600 mg (N=68)	Clarithromycin 500 mg bid (N=57)
Groups Stratified by MAC Colony Counts at Baseline	No. (%) Subjects in Stratified Group Sterile at Week 24	No. (%) Subjects in Stratified Group Sterile at Week 24
≤ 10 cfu/mL	10/15 (66.7%)	12/17 (70.6%)
11-100 cfu/mL	13/28 (46.4%)	13/19 (68.4%)
101-1,000 cfu/mL	7/19 (36.8%)	5/13 (38.5%)
1,001-10,000 cfu/mL	1/5 (20.0%)	1/5 (20%)
>10,000 cfu/mL	0/1 (0.0%)	1/3 (33.3%)

#### **Susceptibility Pattern of MAC Isolates:**

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

During study treatment and post-treatment follow up for up to 3.7 years (median: 9 months) in study 189, a total of 6/68 (9%) and 6/57 (11%) of the patients randomized to azithromycin 600



mg daily and clarithromycin 500 mg bid, respectively, developed MAC blood culture isolates that had a sharp increase in MIC values. All twelve MAC isolates had azithromycin MIC's  $\geq 256$   $\mu\text{g/mL}$  and clarithromycin MIC's  $> 32$   $\mu\text{g/mL}$ . These high MIC values suggest development of drug resistance. However, at this time, specific breakpoints for separating susceptible and resistant MAC isolates have not been established for either macrolide.

### ANIMAL TOXICOLOGY

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

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