

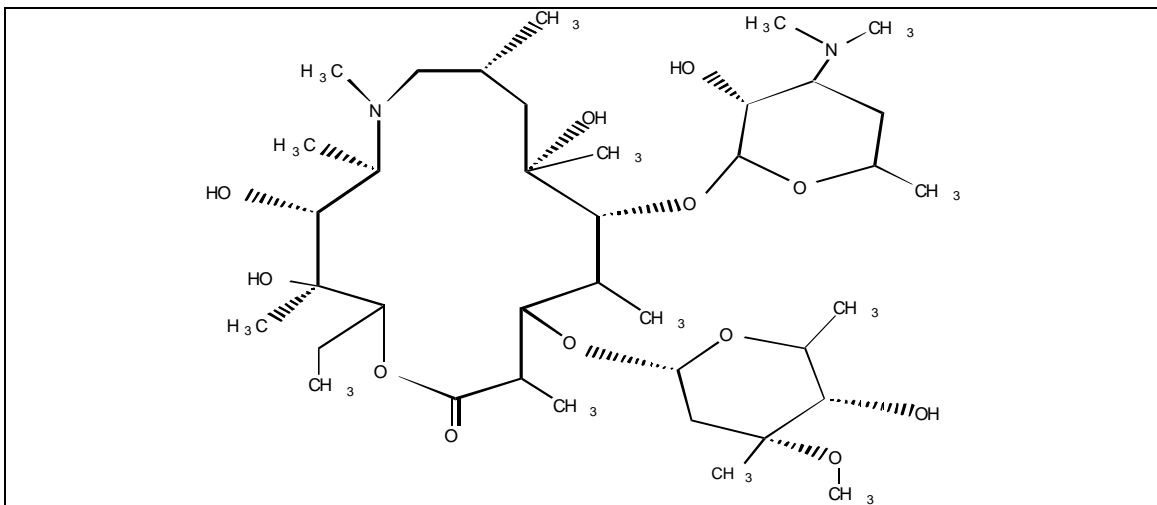
NDA 50-733/S-005

Page 4

**ZITHROMAX<sup>®</sup>**  
**(azithromycin for injection)**  
***For IV infusion only***

**DESCRIPTION**

ZITHROMAX<sup>®</sup> (azithromycin for injection) contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for intravenous injection. 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<sub>38</sub>H<sub>72</sub>N<sub>2</sub>O<sub>12</sub> · 2H<sub>2</sub>O and a molecular weight of 785.0.

ZITHROMAX<sup>®</sup> (azithromycin for injection) consists of azithromycin dihydrate and the following inactive ingredients: citric acid and sodium hydroxide. ZITHROMAX<sup>®</sup> (azithromycin for injection) is supplied in lyophilized form in a 10-mL vial equivalent to 500 mg of azithromycin for intravenous administration. Reconstitution, according to label directions, results in approximately 5 mL of ZITHROMAX<sup>®</sup> for intravenous injection with each mL containing azithromycin dihydrate equivalent to 100 mg of azithromycin.

NDA 50-733/S-005

Page 5

## CLINICAL PHARMACOLOGY

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

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

Plasma concentrations ( $\mu\text{g/mL} \pm S.D.$ ) after the last daily intravenous infusion of 500 mg azithromycin

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

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

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

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

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

Following single oral doses of 500 mg azithromycin to 12 healthy volunteers,  $C_{max}$ , trough level, and  $AUC_{24}$  were reported to be  $0.41 \mu\text{g/mL}$ ,  $0.05 \mu\text{g/mL}$ , and  $2.6 \mu\text{g}\cdot\text{h/mL}$ , respectively. These oral values are approximately 38%, 83%, and 52% of the values observed following a single 500-mg I.V. 3-hour infusion ( $C_{max}$ :  $1.08 \mu\text{g/mL}$ , trough:  $0.06 \mu\text{g/mL}$ , and  $AUC_{24}$ :  $5.0 \mu\text{g}\cdot\text{h/mL}$ ). Thus, plasma concentrations are higher following the intravenous regimen throughout the 24-hour interval. The pharmacokinetic parameters on day 5 of azithromycin 250-mg capsules following a 500-mg oral loading dose to healthy young adults (age 18-40 years old) were as follows:  $C_{max}$ :  $0.24 \mu\text{g/mL}$ ,  $AUC_{24}$ :  $2.1 \mu\text{g}\cdot\text{h/mL}$ . Tissue levels have not been obtained following intravenous infusions of azithromycin. Selected tissue (or fluid) concentration and tissue (or fluid) to

NDA 50-733/S-005

Page 6

plasma/serum concentration ratios following oral administration of azithromycin are shown in the following table:

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

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

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

In a multiple-dose study in 12 normal volunteers utilizing a 500-mg (1 mg/mL) one-hour intravenous-dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the 1st dose and 14% after the 5th dose. These values are greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin. Biliary excretion is a major route of elimination for unchanged drug, following oral administration.

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

NDA 50-733/S-005

Page 7

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

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

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for ZITHROMAX® (azithromycin for injection).

**Aerobic gram-positive microorganisms**

*Staphylococcus aureus*

*Streptococcus pneumoniae*

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

**Aerobic gram-negative microorganisms**

*Haemophilus influenzae*

*Moraxella catarrhalis*

*Neisseria gonorrhoeae*

**“Other” microorganisms**

*Chlamydia pneumoniae*

*Chlamydia trachomatis*

*Legionella pneumophila*

*Mycoplasma hominis*

*Mycoplasma pneumoniae*

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

Azithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for ZITHROMAX® (azithromycin tablets) and ZITHROMAX® (azithromycin for oral suspension).

**Aerobic gram-positive microorganisms**

*Staphylococcus aureus*

*Streptococcus agalactiae*

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

NDA 50-733/S-005

Page 8

**Aerobic gram-negative microorganisms**

*Haemophilus ducreyi*

*Haemophilus influenzae*

*Moraxella catarrhalis*

*Neisseria gonorrhoeae*

**“Other” microorganisms**

*Chlamydia pneumoniae*

*Chlamydia trachomatis*

*Mycoplasma pneumoniae*

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

Azithromycin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 0.5 µg/mL or less against most (≥90%) strains of streptococci listed below and MIC's of 2.0 µg/mL or less against most (≥90%) strains of other listed microorganisms. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

NDA 50-733/S-005

Page 9

**Aerobic gram-positive microorganisms**

Streptococci (Groups C, F, G)

Viridans group streptococci

**Aerobic gram-negative microorganisms**

*Bordetella pertussis*

**Anaerobic microorganisms**

*Peptostreptococcus* species

*Prevotella bivia*

**“Other” microorganisms**

*Ureaplasma urealyticum*

**Susceptibility Tests**

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

**Dilution Techniques:**

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

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

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

For testing *Haemophilus* species:<sup>a</sup>

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤ 4	Susceptible (S)

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

The current absence of data on resistant strains precludes defining any categories other than

NDA 50-733/S-005

Page 10

“Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible” category should be submitted to a reference laboratory for further testing.

For testing streptococci including *S. pneumoniae*:<sup>b</sup>

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

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

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

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

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

<u>Microorganism</u>	<u>MIC (µg/mL)</u>
<i>Haemophilus influenzae</i> ATCC 49247 <sup>a</sup>	1.0-4.0
<i>Staphylococcus aureus</i> ATCC 29213	0.5-2.0
<i>Streptococcus pneumoniae</i> ATCC 49619 <sup>b</sup>	0.06-0.25

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

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

### **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

NDA 50-733/S-005

Page 11

procedure<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15- $\mu$ g azithromycin to test the susceptibility of microorganisms to azithromycin.

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

For testing aerobic microorganisms (including streptococci)<sup>a</sup> except *Haemophilus* species and *Neisseria gonorrhoeae*:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
$\geq 18$	Susceptible (S)
14-17	Intermediate (I)
$\leq 13$	Resistant (R)

<sup>a</sup> These zone diameter standards for streptococci apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO<sub>2</sub>.

For testing *Haemophilus* species:<sup>b</sup>

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
$\geq 12$	Susceptible (S)

<sup>b</sup> This zone diameter standard is applicable only to tests with *Haemophilus* species using *Haemophilus* Test Medium (HTM)<sup>2</sup>.

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

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

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

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

<u>Microorganism</u>	<u>Zone Diameter (mm)</u>
<i>Haemophilus influenzae</i> ATCC 49247 <sup>a</sup>	13-21
<i>Staphylococcus aureus</i> ATCC 25923	21-26
<i>Streptococcus pneumoniae</i> ATCC 49619 <sup>b</sup>	19-25



NDA 50-733/S-005

Page 12

- <sup>a</sup> These quality control limits are applicable only to tests conducted with *H. influenzae* ATCC 49247 using *Haemophilus* Test Medium (HTM)<sup>2</sup>.
- <sup>b</sup> These quality control limits are applicable only to tests conducted with *S. pneumoniae* ATCC 49619 using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub><sup>2</sup>.

## INDICATIONS AND USAGE

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

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

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

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

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

## CONTRAINDICATIONS

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

## WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy. Although rare, fatalities have been reported. (See **CONTRAINDICATIONS**.) Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon**

NDA 50-733/S-005

Page 13

**thereafter in some patients without further azithromycin exposure.** These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

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

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

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

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

NDA 50-733/S-005

Page 14

## PRECAUTIONS

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

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

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

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

### Information for Patients:

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

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

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

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

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

NDA 50-733/S-005

Page 15

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

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

Digoxin - elevated digoxin levels.

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

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

Drugs metabolized by the cytochrome P<sup>450</sup> system - elevations of serum carbamazepine, terfenadine, cyclosporine, hexobarbital, and phenytoin levels.

**Laboratory Test Interactions:** There are no reported laboratory test interactions.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found.

**Pregnancy:** Teratogenic Effects. Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose levels (i.e., 200 mg/kg/day by the oral route). These doses, based on a mg/m<sup>2</sup> basis, are estimated to be 4 and 2 times, respectively, the human daily dose of 500 mg by the oral route. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

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

**Pediatric Use:** Safety and effectiveness of azithromycin for injection in children or adolescents under 16 years have not been established. In controlled clinical studies, azithromycin has been administered to pediatric patients (age 6 months to 16 years) by the oral route. For information regarding the use of ZITHROMAX<sup>®</sup> (azithromycin for oral suspension) in the treatment of pediatric patients, refer to the **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections of the prescribing information for ZITHROMAX<sup>®</sup> (azithromycin for oral suspension) 100

NDA 50-733/S-005

Page 16

mg/5 mL and 200 mg/5 mL bottles.

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

## ADVERSE REACTIONS

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

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

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

### **Clinical:**

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

The most common side effects associated with treatment in adult women who received I.V./P.O. ZITHROMAX<sup>®</sup> in studies of pelvic inflammatory disease were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most commonly reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was co-administered with metronidazole in these studies, a higher proportion of women experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), application site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).

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

NDA 50-733/S-005

Page 17

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

**Gastrointestinal:** dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis

**Nervous System:** headache, somnolence

**Allergic:** bronchospasm

**Special Senses:** taste perversion

### **Post-Marketing Experience:**

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

**Allergic:** arthralgia, edema, urticaria, angioedema

**Cardiovascular:** arrhythmias, including ventricular tachycardia

**Gastrointestinal:** anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea rarely resulting in dehydration, pseudomembranous colitis and rare reports of tongue discoloration

**General:** asthenia, paresthesia and anaphylaxis (rarely fatal)

**Genitourinary:** interstitial nephritis and acute renal failure, moniliasis, vaginitis

**Hematopoietic:** thrombocytopenia

**Liver/Biliary:** abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, which have rarely resulted in death

**Nervous System:** convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, and agitation

**Psychiatric:** aggressive reaction and anxiety

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

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

### **Laboratory Abnormalities:**

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

with an incidence of 4-6%, elevated ALT (SGPT), AST (SGOT), creatinine

with an incidence of 1-3%, elevated LDH, bilirubin

with an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase

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

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

NDA 50-733/S-005

Page 18

## **DOSAGE AND ADMINISTRATION**

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

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

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

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

### **Preparation of the solution for intravenous administration is as follows:**

#### **Reconstitution**

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

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

### **Dilute this solution further prior to administration as instructed below.**

#### **Dilution**

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

Normal Saline (0.9% sodium chloride)



NDA 50-733/S-005

Page 19

1/2 Normal Saline (0.45% sodium chloride)

5% Dextrose in Water

Lactated Ringer's Solution

5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride) with 20 mEq KCl

5% Dextrose in Lactated Ringer's Solution

5% Dextrose in 1/3 Normal Saline (0.3% sodium chloride)

5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride)

Normosol®-M in 5% Dextrose

Normosol®-R in 5% Dextrose

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

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

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

Other intravenous substances, additives, or medications should not be added to ZITHROMAX® (azithromycin for injection), or infused simultaneously through the same intravenous line.

### **Storage**

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

### **HOW SUPPLIED**

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

These are packaged as follows:

10 vials of 500 mg

NDC 0069-3150-83

### **CLINICAL STUDIES**

#### **Community-Acquired Pneumonia**



NDA 50-733/S-005

Page 20

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

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

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

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

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

#### Combined Bacteriological Eradication Rates for Azithromycin:

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

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

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

NDA 50-733/S-005

Page 21

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

### ANIMAL TOXICOLOGY

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and pancreas) in dogs treated with azithromycin at doses which, expressed on a mg/kg basis, are only 2 times greater than the recommended adult human dose and in rats at doses comparable to the recommended adult human dose. This effect has been reversible after cessation of azithromycin treatment. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs given daily doses of azithromycin ranging from 10 days to 30 days. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (30 mg/kg dose) at observed  $C_{max}$  value of 1.3  $\mu\text{g/mL}$  (6 times greater than the observed  $C_{max}$  of 0.216  $\mu\text{g/mL}$  at the pediatric dose of 10 mg/kg). Similarly, it has been shown in the dog (10 mg/kg dose) at observed  $C_{max}$  value of 1.5  $\mu\text{g/mL}$  (7 times greater than the observed same  $C_{max}$  and drug dose in the studied pediatric population). On  $\text{mg/m}^2$  basis, 30 mg/kg dose in the rat (135  $\text{mg/m}^2$ ) and 10 mg/kg dose in the dog (79  $\text{mg/m}^2$ ) are approximately 0.4 and 0.6 times, respectively, the recommended dose in the pediatric patients with an average body weight of 25 kg. This effect, similar to that seen in the adult animals, is reversible after cessation of azithromycin treatment. The significance of these findings for animals and for humans is unknown.

### REFERENCES:

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Third Edition. Approved Standard NCCLS Document M7-A3, Vol. 13, No. 25, NCCLS, Villanova, PA, December, 1993.
2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Fifth Edition. Approved Standard NCCLS Document M2-A5, Vol. 13, No. 24, NCCLS, Villanova, PA, December, 1993.

**Rx only**

NDA 50-733/S-005  
Page 22

Licensed from Pliva

©2000 PFIZER INC



**Pfizer Labs**

Division of Pfizer Inc  
NY, NY 10017

70-5191-00-4

Printed in U.S.A  
Revised July 2000