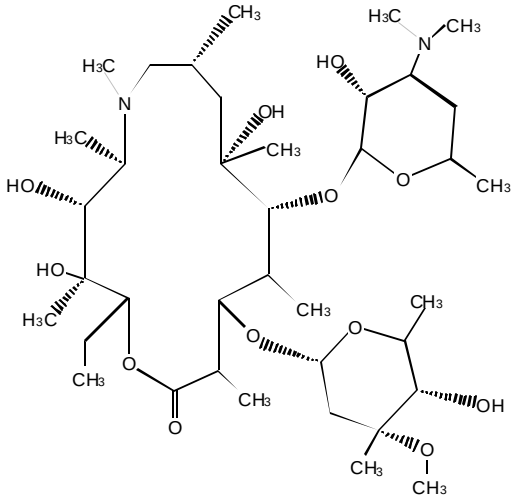
Zmax™

(azithromycin extended release) for oral suspension

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

DESCRIPTION

Zmax (azithromycin extended release) for oral suspension contains the active ingredient azithromycin (as azithromycin dihydrate), an azalide, a subclass of macrolide antibiotics. Azithromycin has the chemical name (*2R,3S,4R,5R,8R,10R,11R,12S,13S,14R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-*L*-*ribo*-hexopyranosyl) oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-*D*-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one. Azithromycin is derived from erythromycin; however, it differs chemically from erythromycin in that a methyl-substituted nitrogen atom is incorporated into the lactone ring. Its molecular formula is $C_{38}H_{72}N_2O_{12}$, and its molecular weight is 749.0. Azithromycin has the following structural formula:



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

Zmax is a single-dose, extended release formulation of microspheres for oral suspension containing azithromycin (as azithromycin dihydrate) and the following excipients: glyceryl behenate, poloxamer 407, sucrose, sodium phosphate tribasic anhydrous, magnesium hydroxide, hydroxypropyl cellulose, xanthan gum, colloidal silicon dioxide, titanium dioxide, artificial cherry flavor, and artificial banana flavor.

Each bottle contains azithromycin dihydrate equivalent to 2.0 g of azithromycin. It is constituted with 60 mL of water and the entire contents are administered orally as a single dose.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Zmax is an extended release microsphere formulation. Based on data obtained from studies evaluating the pharmacokinetics (PK) of azithromycin in healthy adult subjects a higher peak serum concentration (C_{max}) and greater systemic exposure (AUC_{0-24}) of azithromycin are achieved on the day of dosing following a single 2.0 g dose of Zmax versus 1.5 g of azithromycin tablets administered over 3 days (500 mg/day) or 5 days (500 mg on day 1, 250 mg/day on days 2-5) [Table 1]. Consequently, due to these different PK profiles, Zmax is not interchangeable with azithromycin tablet 3-day and 5-day dosing regimens.

Table 1. Mean (SD) Pharmacokinetic Parameters for Azithromycin on Day 1 Following the Administration of a Single Dose of 2.0 g Zmax or 1.5 g of Azithromycin Tablets Given over 3 Days (500 mg/day) or 5 Days (500 mg on Day 1 and 250 mg on Days 2-5) to Healthy Adult Subjects

Pharmacokinetic Parameter*	Azithromycin Regimen		
	Zmax [n=41]†	3-day ‡ [n=12]	5-day ‡ [n=12]
C_{max} (µg/mL)	0.821 (0.281)	0.441 (0.223)	0.434 (0.202)
T_{max} § (hr)	5.0 (2.0-8.0)	2.5 (1.0-4.0)	2.5 (1.0-6.0)
AUC_{0-24} (µg·hr/mL)	8.62 (2.34)	2.58 (0.84)	2.60 (0.71)
AUC_{0-8} ¶ (µg·hr/mL)	20.0 (6.66)	17.4 (6.2)	14.9 (3.1)
$t_{1/2}$ (hr)	58.8 (6.91)	71.8 (14.7)	68.9 (13.8)

* Zmax, 3-day and 5-day regimen parameters obtained from separate PK studies

† n = 21 for AUC_{0-8} and $t_{1/2}$

‡ C_{max}, T_{max} and AUC_{0-24} values for Day 1 only

§ Median (range)

¶ Total AUC for the 1-day, 3-day and 5-day regimens

SD = standard deviation

C_{max} = maximum serum concentration

T_{max} = time to C_{max}

AUC = area under concentration vs. time curve

$t_{1/2}$ = terminal serum half-life

Absorption
In a two-way crossover study, sixteen healthy adult subjects were administered single doses of 2.0 g Zmax and azithromycin powder for oral suspension (POS) (2×1.0 g sachets). The mean C_{max} and AUC_{0-t} of azithromycin were lower by 57% and 17%, respectively with Zmax compared to azithromycin POS. The bioavailability of Zmax relative to azithromycin POS was 83%. On average, peak serum concentrations were achieved approximately 2.5 hours later following Zmax administration compared to azithromycin POS. Thus, single 2.0 g doses of Zmax and azithromycin POS are not bioequivalent and are not interchangeable.

When a 2.0 g dose of Zmax was administered to 15 healthy adult subjects following a high-fat meal (150 kcal from proteins, 250 kcal from carbohydrates and 500-600 kcal from fats) the mean azithromycin C_{max} increased by 115% and the mean AUC_{0-t} increased by 23% as compared to administration in a fasted state. When a 2.0 g dose of Zmax was administered to 88 adult subjects following a standard meal (56 kcal from proteins, 316 kcal from carbohydrates, and 207 kcal from fats) the mean azithromycin C_{max} increased by 119% and the mean AUC_{0-72} increased 12% as compared to administration in the fasted state. (See **DOSAGE AND ADMINISTRATION**.)

In a two-way crossover study, 39 healthy adult subjects were administered 2.0 g dose of Zmax alone and with 20 mL of regular strength aluminum and magnesium hydroxide antacid. Following the administration of Zmax with an aluminum and magnesium hydroxide antacid, the rate and extent of azithromycin absorption were not altered.

Distribution
The serum protein binding of azithromycin is concentration dependent, decreasing from 51% at 0.02 μg/mL to 7% at 2.0 μg/mL. Following oral administration, azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg.

Higher azithromycin concentrations in tissues than in plasma or serum have been observed. The extensive distribution of drug to tissues may be relevant to clinical activity. The antimicrobial activity of azithromycin is pH related and appears to be reduced with decreasing pH. Hence, high tissue concentrations should not be interpreted as being quantitatively related to clinical efficacy. Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in Table 2.

Table 2. Azithromycin Concentrations Following a 500 mg Dose in Adults*

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

* 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). However, the clinical significance of these tissue concentration data is unclear as clinical data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites are not available.

Following a regimen of 500 mg of azithromycin tablets 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
Serum azithromycin concentrations following a single 2.0 g dose of Zmax declined in a polyphasic pattern with a terminal elimination half-life of 59 hours. The prolonged terminal half-life is thought to be due to a large apparent volume of distribution.

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 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). Based upon the pharmacokinetic data for azithromycin in subjects with renal impairment, no dose adjustment for Zmax is recommended in patients with GFR >10 mL/min. (See **DOSAGE AND ADMINISTRATION**.)

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

Gender
The impact of gender on the pharmacokinetics of azithromycin has not been evaluated for Zmax. However, previous studies have demonstrated no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment of Zmax is recommended based on gender.

Geriatric Patients
The pharmacokinetics of azithromycin following administration of Zmax has not been evaluated in geriatric patients.

Pediatric Patients
Zmax is not approved for pediatric patients.

Drug-Drug Interactions
Drug interaction studies were performed with azithromycin capsules and tablets (doses ranged from 500 to 1200 mg) and drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 3 and the effects of other drugs on the pharmacokinetics of azithromycin are shown in Table 4.

Co-administration of azithromycin capsules and tablets at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 3. Although the drug interaction studies were not conducted with Zmax , no potential drug interactions are expected since the total exposure to azithromycin is comparable for Zmax and the other azithromycin regimens. Therefore, no dosage adjustment of drugs listed in Table 3 is recommended when co-administered with Zmax. (See **PRECAUTIONS - Drug Interactions**.)

Co-administration of azithromycin tablets with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the C_{max} and AUC of azithromycin. Similar results are expected with Zmax . Although no dosage adjustment of Zmax is recommended when administered with drugs listed in Table 4, close monitoring for known side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted when co-administered with nelfinavir. (See **PRECAUTIONS - Drug Interactions** .)

Table 3. 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_{max}	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	‡	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, then 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

* Refers to azithromycin capsules and tablets unless specified

† 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 4. 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_{max}	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	‡	NA
Al and Mg hydroxide	20 mL regular strength, single dose	2.0 g Zmax, single dose	39	0.99 (0.93 to 1.06)	0.99 (0.92 to 1.08)

NA = not available
* Refers to azithromycin capsules and tablets unless specified
† 90% confidence interval not reported
‡ Mean azithromycin concentrations one day after the last dose were 53 ng/mL when co-administered with 300 mg daily rifabutin and 49 ng/mL when co-administered with placebo.

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

Azithromycin concentrates in fibroblasts, epithelial cells, macrophages, and circulating neutrophils and monocytes. *In vitro* incubation techniques have shown that the ratio of intracellular to extracellular concentration was >30 after one hour incubation. *In vivo* studies suggest that concentration in macrophages and circulating white blood cells may contribute to drug distribution to inflamed tissues.

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

Aerobic and facultative Gram-positive microorganisms
Streptococcus pneumoniae

NOTE: Erythromycin- and penicillin-resistant Gram-positive isolates may demonstrate cross-resistance to azithromycin.

Aerobic and facultative Gram-negative microorganisms
Haemophilus influenzae
Moraxella catarrhalis

"Other" microorganisms
Chlamydophila pneumoniae
Mycoplasma pneumoniae

Beta-lactamase production should not affect azithromycin activity.

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

At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoints for azithromycin. However, the safety and effectiveness of azithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic and facultative Gram-positive microorganisms
Staphylococcus aureus
Streptococcus pyogenes
Streptococcus agalactiae
Streptococci (Groups C, F, G)
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms
Bordetella pertussis
Legionella pneumophila

Anaerobic microorganisms
Peptostreptococcus species
Prevotella bivia

"Other" microorganisms
Ureaplasma urealyticum

Susceptibility Testing Methods :
When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should 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[1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of azithromycin powder. The MIC values should be interpreted according to criteria provided in Table 5.

Diffusion techniques:
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15-µg azithromycin to test the susceptibility of microorganisms to azithromycin. The disk diffusion interpretive criteria are provided in Table 5.

Table 5. Susceptibility Test Result Interpretive Criteria for Azithromycin

	Minimum Inhibitory Concentrations (mg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R***	**S**	**I**	**R***
***Haemophilus* spp.**	≤ 4	--	--	≥ 12	--	--
Streptococci including *S. pneumoniae*	≤ 0.5	1	≥ 2	≥ 18	14-17	≤ 13

* The current absence of data on resistant strains precludes defining any category other than "susceptible." If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

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

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 quality control microorganisms to control the technical aspects of the test procedures. Standard azithromycin powder should provide the range of values noted in Table 6. Quality control microorganisms are specific strains of organisms with intrinsic biological properties. QC strains are very stable strains, which will give a standard and repeatable susceptibility pattern. The specific strains used for microbiological quality control are not clinically significant.

Table 6. Acceptable Quality Control Ranges for Azithromycin

QC Strain	Minimum Inhibitory Concentrations (mg/mL)	Disk Diffusion (zone diameters in mm)
Haemophilus influenzae ATCC 49247	1.0-4.0	13-21
Streptococcus pneumoniae ATCC 49619	0.06-0.25	19-25

INDICATIONS AND USAGE

Zmax is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific dosing recommendations.

Adults
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. (See **CLINICAL STUDIES**.)

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

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

CONTRAINDICATIONS

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

WARNINGS

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy using other formulations. 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 exposure to antigen has not been determined.

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

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

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

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

PRECAUTIONS

General
Because azithromycin is principally excreted 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**.)

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

Prescribing Zmax in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients
Patients should be instructed to take Zmax on an empty stomach (at least 1 hour before or 2 hours following a meal).

Patients should be instructed to immediately contact a physician if any signs of an allergic reaction occur.

Patients who vomit within the first hour should contact their health care provider about further treatment.

Keep bottle tightly closed. Store at room temperature. Use within 12 hours of constitution. Shake bottle well before use. The entire contents of the bottle should be consumed.

Patients should be advised that Zmax may be taken without regard to antacids containing magnesium hydroxide and/or aluminum hydroxide.

Patients should be counseled that antibacterial drugs including Zmax should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Not taking the complete prescribed dose 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 Zmax or other antibacterial drugs in the future.

Drug Interactions
Co-administration of nelfinavir at steady-state with a single dose of azithromycin (2 × 600 mg tablets) results 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**.)

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

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 co-administered 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.
Cyclosporine, hexobarbital and phenytoin concentrations.

Laboratory Test Interactions
There are no reported laboratory test interactions.

Repeat Treatment
Studies evaluating the use of repeated courses of Zmax have not been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay. No evidence of impaired fertility due to azithromycin was found in rats given daily doses up to 10 mg/kg (approximately 0.05 times the single 2.0 g oral adult human dose on a mg/m^2 basis).

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 daily doses in rats and mice, based on mg/m^2, are estimated to be approximately equivalent to one or one-half of, respectively, the single adult oral dose of 2.0 g. 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.

Geriatric Use
Data collected from the azithromycin capsule and tablet formulations indicate that a dosage adjustment does not appear to be necessary for older patients with normal renal function (for their age) and hepatic function receiving treatment with Zmax.

In clinical trials of Zmax, 16.6% of subjects were at least 65 years of age (214/1292) and 4.6% of subjects (59/1292) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

Zmax 2.0 g oral suspension contains 148 mg of sodium.

ADVERSE REACTIONS

In controlled Phase 3 clinical trials with Zmax, the majority of the reported treatment-related adverse reactions were gastrointestinal in nature and mild to moderate in severity.

Overall, the most common treatment-related adverse reactions in adult subjects receiving a single 2.0 g dose of Zmax were diarrhea/loose stools (11.6%), nausea (3.9%), abdominal pain (2.7%), headache (1.3%), and vomiting (1.1%). The incidence of treatment-related gastrointestinal adverse reactions was 17.2% for Zmax and 9.7% for pooled comparators.

No other treatment-related adverse events occurred in subjects on Zmax with a frequency of $\geq$1%.

Treatment-related adverse reactions following Zmax treatment that occurred with a frequency of <1% included the following:
Cardiovascular: palpitations, chest pain
Gastrointestinal: constipation, dyspepsia, flatulence, gastritis, oral moniliasis, loose stools
Genitourinary: vaginitis
Nervous System: dizziness, vertigo
General: asthenia
Allergic: rash, pruritus, urticaria
Special Senses: taste perversion

Laboratory Abnormalities
In subjects with normal baseline values, the following clinically significant laboratory abnormalities (irrespective of drug relationship) were reported in Zmax clinical trials:

- with an incidence of greater than or equal to 1%: reduced lymphocytes and increased eosinophils; reduced bicarbonate;
- with an incidence of less than 1%: leukopenia, neutropenia, elevated bilirubin, AST, ALT, BUN, creatinine, alterations in potassium.

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

Post-Marketing Experience with Azithromycin Immediate Release
Adverse events reported with azithromycin during the post-marketing period for which a causal relationship may not be established include:

Allergic: arthralgia, edema, urticaria and angioedema
Cardiovascular: palpitations and 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 and rare reports of tongue discoloration
General: asthenia, paresthesia, fatigue, malaise and anaphylaxis (rarely fatal)
Genitourinary: interstitial nephritis,acute renal failure, moniliasis and vaginitis
Hematopoietic: thrombocytopenia, mild neutropenia
Liver/Biliary: abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death
Nervous System: convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope
Psychiatric: aggressive reaction and anxiety
Skin/Appendages: pruritus, rash, photosensitivity, 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 rare reports of taste perversion

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

Zmax should be taken as a single 2.0 g dose. Zmax provides a full course of antibacterial therapy in a single oral dose. It is recommended that Zmax be taken on an empty stomach (at least 1 hour before or 2 hours following a meal).

In the Phase 3 program, no patient vomited within 5 minutes of dosing Zmax. In the event that a patient vomits within 5 minutes of administration, the health care provider should consider additional antibiotic treatment since there would be minimal absorption of azithromycin. Since insufficient data exist on absorption of azithromycin if a patient vomits between 5 and 60 minutes following administration, alternative therapy should be considered. Neither a second dose of Zmax nor alternative treatment is warranted if vomiting occurs ≥60 minutes following administration, in patients with normal gastric emptying.

Instructions for Pharmacist
Constitute with 60 mL of water and replace cap. Shake bottle well before dispensing.

Special Populations
Renal Insufficiency:
No dosage adjustment is recommended for patients with renal impairment (GFR 10-80 mL/min). Caution should be exercised when Zmax is administered to patients with end-stage renal disease (GFR <10 mL/min). (See **CLINICAL PHARMACOLOGY - Special Populations - Renal Insufficiency**.)

Hepatic Insufficiency:
The pharmacokinetics of azithromycin in patients 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**.)

HOW SUPPLIED

Zmax is supplied in bottles (NDC 0069-4170-21) containing 2.0 g of azithromycin and should be constituted with 60 mL of water.

See **DOSAGE AND ADMINISTRATION** for constitution instructions.

Storage
Before constitution, store dry powder at or below **30°C (86°F)**.

After constitution, store suspension at **25°C (77°F)**; excursions permitted to **15-30°C (59-86°F)** [see USP Controlled Room Temperature]. Do not refrigerate or freeze.

Constituted suspension should be consumed within 12 hours.

CLINICAL STUDIES
(See **INDICATIONS AND USAGE**)

Community-Acquired Pneumonia

Subjects with a diagnosis of mild-to-moderate community-acquired pneumonia were evaluated in two, randomized, double-blind, multicenter studies. In both studies, clinical and microbiologic evaluations were conducted for all subjects at the Test of Cure (TOC) visit, 7 to 14 days post-treatment. In the first study, 247 subjects were treated with a single 2.0 g oral dose of Zmax and 252 subjects were treated with clarithromycin extended release, 1 g orally QD for 7 days. In the second study, 211 subjects were treated with a single 2.0 g oral dose of Zmax and 212 subjects were treated with levofloxacin, 500 mg orally QD for 7 days. A patient was considered a cure if signs and symptoms related to the acute infection had resolved, or if clinical improvement was such that no additional antibiotics were deemed necessary; in addition, the chest x-ray performed at the TOC visit was to be either improved or stable. The clinical response at TOC for the primary population, Clinical Per Protocol Subjects, is presented in the table below.

	Zmax	Comparator
Zmax vs. Clarithromycin extended release	**202**	**209**
Cure	**187 (92.6%)**	**198 (94.7%)**
Failure	**15 (7.4%)**	**11 (5.3%)**
Zmax vs. Levofloxacin	**174**	**189**
Cure	**156 (89.7%)**	**177 (93.7%)**
Failure	**18 (10.3%)**	**12 (6.3%)**

Clinical response by pathogen in the Bacteriologic Per Protocol population, across both studies, is presented below:

Pathogen	**Zmax**		**Comparators**	
	N	Cure	N	Cure
S. pneumoniae	33	28 (84.8%)	39	35 (89.7%)
H. influenzae	30	28 (93.3%)	34	31 (91.2%)
C. pneumoniae	40	37 (92.5%)	53	50 (94.3%)
M. pneumoniae	33	30 (90.9%)	39	38 (97.4%)

Acute Bacterial Maxillary Sinusitis

Adult subjects with a diagnosis of acute bacterial maxillary sinusitis were evaluated in a randomized, double-blind, mulitcenter study; a maxillary sinus tap was performed on all subjects at baseline. Clinical evaluations were conducted for all subjects at the TOC visit, 7 to 14 days post-treatment. Two hundred seventy (270) subjects were treated with a single 2.0 g oral dose of Zmax and 268 subjects were treated with levofloxacin, 500 mg orally QD for 10 days. A subject was considered a cure if signs and symptoms related to the acute infection had resolved, or if clinical improvement was such that no additional antibiotics were deemed necessary. The clinical response for the primary population, Clinical Per Protocol Subjects, is presented below.

	Zmax	Levofloxacin
Response at TOC	**N = 255**	**N = 254**
Cure	**241 (94.5%)**	**236 (92.9%)**
Failure	**14 (5.5%)**	**18 (7.1%)**

Clinical response by pathogen in the Bacteriologic Per Protocol population is presented below.

	Zmax		**Levofloxacin**	
Pathogen	N	Cure	N	Cure
S. pneumoniae	37	36 (97.3%)	39	36 (92.3%)
H. influenzae	27	26 (96.3%)	30	30 (100.0%)
M. catarrhalis	8	8 (100.0%)	11	10 (90.9%)

ANIMAL TOXICOLOGY

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) in dogs treated with azithromycin at doses which, expressed on the basis of mg/m^2, are approximately one-sixth the recommended adult dose, and in rats treated at doses approximately one-fourth the recommended adult dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (50 mg/kg/day dose) at the observed maximal plasma concentration of 1.3 μg/mL (1.6 times the observed C_{max} of 0.821 μg/mL at the adult dose of 2.0 g.) Similarly, it has been shown in the dog (10 mg/kg/day dose) at the observed maximal serum concentration of 1.0 μg/mL (1.2 times the observed C_{max} of 0.821 μg/mL at the adult dose of 2.0 g. The significance of the finding 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* - Sixth Edition. Approved Standard NCCLS Document M7-A6 [ISBN 1-56238-486-4]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2003.

2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests* - Eighth Edition. Approved Standard NCCLS Document M2-A8 (ISBN 1-56238-485-6). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2003.

3. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing* - Fourteenth Informational Supplement. NCCLS Document M100-S14 [ISBN1-56238-516-X]. NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2004.

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