HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Zmax safely and effectively. See full prescribing information for Zmax.

Zmax® (azithromycin extended release) for oral suspension
Initial U.S. Approval: 1991

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**.**

----------RECENT MAJOR CHANGES----------

WARNINGS AND PRECAUTIONS, QT prolongation (5.5) 01/2013

----------INDICATIONS AND USAGE----------

Zmax is a macrolide antimicrobial indicated for mild to moderate infections caused by designated, susceptible bacteria:

- Acute bacterial sinusitis in adults (1)
- Community-acquired pneumonia in adults and children 6 months and older (1)

----------DOSAGE AND ADMINISTRATION----------

- Adults: 2 g as a single dose; consume contents of full bottle (2.1)
- Pediatric: 60 mg/kg (1 mL of suspension per pound body weight; equivalent to 27 mg/lb) as a single dose, up to a maximum of 2 g (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Bottle containing 2 g azithromycin for constitution with 60 mL of water (final concentration 27 mg/mL) (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to azithromycin, erythromycin, or any macrolide or ketolide antibiotic (4.1)
History of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin (4.2)

----------WARNINGS AND PRECAUTIONS----------

- Severe (including fatal) allergic and skin reactions: Discontinue Zmax if reaction occurs. (5.1)
- Hepatotoxicity: severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur. (5.2)
- *Clostridium difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.3)
- Exacerbation of myasthenia gravis (5.4)
- Prolongation of the QT interval and cases of torsades de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval. (5.5)
- Gastrointestinal Disturbances: higher incidence in patients with GFR<10 mL/min. (5.6)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥1%) are diarrhea/loose stools, nausea, abdominal pain, headache, and vomiting (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc at 1-800-438-1985 **or FDA at 1-800-FDA-1088 or** ***www.fda.gov/medwatch***

----------DRUG INTERACTIONS----------

Warfarin: Use with azithromycin may increase coagulation times; monitor prothrombin time (7)

----------USE IN SPECIFIC POPULATIONS----------

Pediatric use:

- Safety and efficacy in the treatment of patients under 6 months of age have not been established. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revision Date: 02/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Zmax is indicated for the treatment with mild to moderate infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below. *[See CLINICAL STUDIES (14)]*

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

Community-acquired pneumonia in adults and pediatric patients six months of age or older due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae,* in patients appropriate for oral therapy. Pediatric use in this indication is based on extrapolation of adult efficacy. *[See USE IN SPECIFIC POPULATIONS (8.4)]*

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. *[See Clinical Pharmacology (12.4)]* Therapy with Zmax may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

2 DOSAGE AND ADMINISTRATION

2.1 Adults

Zmax should be taken as a single 2 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).

2.2 Pediatric patients

For pediatric patients 6 months and older, Zmax should be taken as a single dose of 60 mg/kg (equivalent to 27 mg/lb) body weight. The Zmax dose in mL is equivalent to the child's weight in lb (1 mL/lb dose, see Table 1 below), for a body weight of less than 75 lb (34 kg). It is recommended that Zmax be taken on an empty stomach (at least 1 hour before or 2 hours following a meal).

Pediatric patients weighing 75 lb (34 kg) or more should receive the adult dose (2 g).

Table 1. Zmax Pediatric Dosage Guidelines: 1-dose regimen			
Dosing Calculated on 1 mL/lb, Dose 1 mL of Suspension for every 1 lb of Body Weight for Children <75 lb (34 kg)[a]			
Weight		**1 mL/lb Dose**	
Lb	**Kg**	**Dose (mg)**	**Volume (mL)**
10	5	270	10
15	7	405	15
20	9	540	20
25	11	675	25
30	14	810	30
35	16	945	35
40	18	1080	40
45	20	1215	45
50	23	1350	50
55	25	1485	55
60	27	1620	60
65	30	1755	65
70	32	1890	70
≥75	34	2000	Consume entire contents of bottle

[a] To ensure accurate dosing, a dosing spoon, medicine syringe, or cup is recommended.

2.3 Additional treatment after vomiting with 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. In patients with delayed gastric emptying, alternative therapy should be considered.

2.4 Instructions for the pharmacist

Constitute with 60 mL of water and replace cap. Shake bottle well before dispensing. Do not refrigerate. Constituted suspension should be consumed within 12 hours.

For pediatric dosing in patients weighing less than 75 lb (34 kg), use of a dosing device is recommended. The pharmacist should inform the patient's caregiver that any suspension remaining after dosing MUST be discarded.

3 DOSAGE FORMS AND STRENGTHS

Each bottle of Zmax contains azithromycin dihydrate equivalent to 2 g of azithromycin. After constitution with 60 mL of water, each mL of suspension contains 27 mg of azithromycin. The suspension is a white or off-white color and has a cherry/banana flavor.

4 CONTRAINDICATIONS

4.1 Hypersensitivity reactions

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

4.2 Cholestatic jaundice/hepatic dysfunction

Zmax is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

5 WARNINGS AND PRECAUTIONS

5.1 Allergic and skin reactions

Serious allergic reactions, including angioedema, anaphylaxis, 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. 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.

5.2 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.

5.3 *Clostridium difficile*-associated diarrhea

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

5.4 Exacerbation of myasthenia gravis

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

5.5 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. Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure
- patients on drugs known to prolong 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.

5.6 Gastrointestinal Disturbances

A higher incidence of gastrointestinal adverse events (8 of 19 subjects) was observed when Zmax was administered to a limited number of subjects with GFR< 10 mL/min *[See USE IN SPECIFIC POPULATIONS (8.6)]*

5.7 Development of drug resistant bacteria

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.

6 ADVERSE REACTIONS

6.1 Clinical studies experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults:

The data described below reflect exposure to Zmax in 728 adult patients. All patients received a single 2 g oral dose of Zmax. The population studied had community-acquired pneumonia and acute bacterial sinusitis.

In controlled 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 patients receiving a single 2 g dose of Zmax were diarrhea/loose stools (12%), nausea (4%), abdominal pain (3%), headache (1%), and vomiting (1%). The incidence of treatment-related gastrointestinal adverse reactions was 17% for Zmax and 10% for pooled comparators.

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
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.

Pediatric Patients:
The data described below reflect exposure to Zmax in 907 pediatric patients. The population was 3 months to 12 years of age. All patients received a single 60 mg/kg oral dose of Zmax.

As in adults, the most common treatment-related adverse reactions in pediatric subjects were gastrointestinal in nature. The pediatric subjects all received a single 60 mg/kg dose (equivalent to 27 mg/lb) of Zmax.

In a study with 450 pediatric subjects (ages 3 months to 48 months), vomiting (11%), diarrhea (10%) loose stools (9%), and abdominal pain (2%) were the most frequently reported treatment-related gastrointestinal adverse reactions. Many treatment related gastrointestinal adverse reactions with an incidence greater than 1% began on the day of dosing in these subjects [43% (68/160)] and most [53% (84/160)] resolved within 48 hours of onset. Treatment-related adverse events that were not gastrointestinal, occurring with a frequency ≥ 1% were: rash (5%), anorexia (2%), fever (2%), and dermatitis (2%).

In a second study of 337 pediatric subjects, ages 2 years to 12 years, the most frequently reported treatment-related adverse reactions also included vomiting (14%), diarrhea (7%), loose stools (2%), nausea (4%) and abdominal pain (4%).

A third study investigated the tolerability of two different concentrations of azithromycin oral suspension in 120 pediatric subjects (ages 3 months to 48 months), all of whom were treated with azithromycin. The study evaluated the hypothesis that a more dilute, less viscous formulation (the recommended 27 mg/mL concentration of Zmax) is less likely to induce vomiting in young children than a more concentrated suspension used in other pediatric studies. The vomiting rate for subjects taking the dilute concentration azithromycin was 3% (2/61). The rate was numerically lower but not statistically different from the vomiting for the more concentrated suspension Across both treatment arms, the only treatment-related adverse events with a frequency of ≥ 1% were vomiting (6%, 7/120) and diarrhea (2%, 2/120).

Treatment-related adverse reactions with a frequency of < 1% following Zmax treatment in all 907 pediatric subjects in the Phase 3 studies were:

Body as a whole: chills, fever, flu syndrome, headache;
Digestive: abnormal stools, constipation, dyspepsia, flatulence, gastritis, gastrointestinal disorder, hepatitis;
*Hemic and Lymphatic***:** leukopenia;
*Nervous System***:** agitation, emotional liability, hostility, hyperkinesia, insomnia, irritability, parasthesia, somnolence;
Respiratory: asthma, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis;
Skin and Appendages: dermatitis, fungal dermatitis, maculopapular rash, pruritus, urticaria;
Special Senses: otitis media, taste perversion;
Urogenital: dysuria.

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

- with an incidence of greater than or equal to 1%: elevated eosinophils, BUN, and potassium; decreased lymphocytes; and alterations in neutrophils;
- with an incidence of less than 1%: elevated SGOT, SGPT and creatinine; decreased potassium; and alterations in sodium and glucose.

6.2 Postmarketing experience with other azithromycin products

Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Adverse events reported with azithromycin immediate release formulations during the postmarketing 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, pyloric stenosis, 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: Adverse reactions related to hepatic dysfunction have been reported in postmarketing experience with azithromycin. *[See WARNINGS AND PRECAUTIONS (5.2)]*
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/smell perversion and/or loss

7 DRUG INTERACTIONS

Warfarin
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.

8 USE IN SPECIFIC POPULATIONS

8.1 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 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.

8.3 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.

8.4 Pediatric Use
Safety and effectiveness in the treatment of pediatric patients under 6 months of age have not been established.

Community-Acquired Pneumonia: The safety and effectiveness of Zmax have been established in pediatric patients 6 months of age or older with community-acquired pneumonia due to *Chlamydophila pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae* or *Streptococcus pneumoniae.* Use of Zmax for these patients is supported by evidence from adequate and well-controlled studies of Zmax in adults with additional safety and pharmacokinetic data in pediatric patients. *[See DOSAGE AND ADMINISTRATION (2.2), ADVERSE REACTIONS (6), CLINICAL PHARMACOLOGY (12.3)*]

Acute bacterial sinusitis: Safety and effectiveness in the treatment of pediatric patients with acute bacterial sinusitis have not been established.

8.5 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, 17% of subjects were at least 65 years of age (214/1292) and 5% 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. Elderly patients may be more susceptible to development of torsades de pointes arrhythmia than younger patients. *[See WARNINGS AND PRECAUTIONS (5.5)]*.

8.6 Renal Impairment

No dosage adjustment is recommended for patients GFR >10 mL/min. Caution should be exercised when Zmax is administered to patients with GFR <10 mL/min, due to a higher incidence of gastrointestinal adverse events (8 of 19 subjects) observed in a limited number of subjects with GFR <10 mL/min. *[See CLINICAL PHARMACOLOGY (12)]*

8.7 Gender

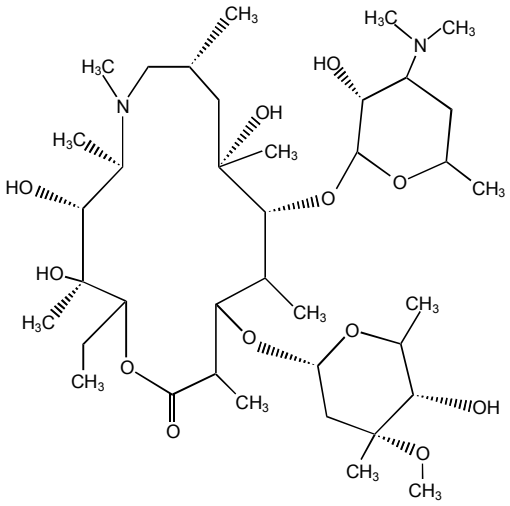
The impact of gender on the pharmacokinetics of azithromycin has not been evaluated for Zmax. However, previous studies have demonstrated no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment of Zmax is recommended based on gender.

10 OVERDOSAGE

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

11 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.

Note: Each bottle of Zmax 2 g for oral suspension contains approximately 148 mg of sodium and 19 g of sucrose. Constituted Zmax oral suspension contains approximately 2 mg/mL of sodium and 0.26 g/mL of sucrose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Azithromycin is an antimicrobial agent *[See Clinical Pharmacology (12.4)]*

12.2 Pharmacodynamics

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

12.3 Pharmacokinetics

Zmax is an extended release microsphere formulation. Based on data obtained from studies evaluating the pharmacokinetics 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 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 2]. Consequently, due to these different pharmacokinetic profiles, Zmax is not interchangeable with azithromycin tablet 3-day and 5-day dosing regimens.

Table 2. Mean (SD) Pharmacokinetic Parameters for Azithromycin on Day 1 Following the Administration of a Single Dose of 2 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)
$AUC_{0-\infty}$¶ (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 pharmacokinetic studies
† N = 21 for $AUC_{0-\infty}$ 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
The bioavailability of Zmax relative to azithromycin immediate release (IR) (powder for oral suspension) was 83%. On average, peak serum concentrations were achieved approximately 2.5 hours later following Zmax administration and were lower by 57%, compared to 2 g azithromycin IR. Thus, single 2 g doses of Zmax and azithromycin IR are not bioequivalent and are not interchangeable.

Effect of food on absorption: A high-fat meal increased the rate and extent of absorption of a 2 g dose of Zmax (115% increase in $C_{max,}$ and 23% increase in AUC_{0-72}) compared to the fasted state. A standard meal also increased the rate of absorption (119% increase in C_{max}) and with less effect on the extent of absorption (12% increase in AUC_{0-72}) compared to administration of a 2 g Zmax dose in the fasted state.

Effect of antacids: 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 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.

Azithromycin concentrates in fibroblasts, epithelial cells, macrophages, and circulating neutrophils and monocytes. Higher azithromycin concentrations in tissues than in plasma or serum have been observed. White blood cell and lung exposure data in humans following a single 2 g dose of Zmax in adults are shown in Table 3. Following a 2 g single dose of Zmax, azithromycin achieved higher exposure (AUC_{0-120}) in mononuclear leukocytes (MNL) and polymorphonuclear leukocytes (PMNL) than in serum. The azithromycin exposure (AUC_{0-72}) in lung tissue and alveolar cells (AC) was approximately 100 times that in serum; and the exposure in epithelial lining fluid (ELF) was also higher (approximately 2-3 times) than in serum. The clinical significance of this distribution data is unknown.

Table 3. Azithromycin Exposure Data in White Blood Cells and Lung Following a 2 g Single Dose of Zmax in Adults

A single 2 g dose of Zmax				
WBC	C_{max} (μg/mL)	AUC_{0-24} (μg·hr/mL)	AUC_{0-120} (μg·hr/mL)	$C_{t=120}$† (μg/mL)
MNL‡	116 (40.2)	1790 (540)	4710 (1100)	16.2 (5.51)
PMNL‡	146 (66.0)	2080 (650)	10000 (2690)	81.7 (23.3)
LUNG	C_{max} (μg/mL)	AUC_{0-24} (μg·hr/mL)	AUC_{0-72} (μg·hr/mL)	
ALVEOLAR CELL¶	669	7028	20403	-
ELF¶	3.2	17.6	131	-
	C_{max} (μg/g)	AUC_{0-24} (μg·hr/g)	AUC_{0-72} (μg·hr/g)	
LUNG TISSUE¶	37.9	505	1693	-

Abbreviation: WBC: white blood cells; MNL: mononuclear leukocytes; PMNL: polymorphonuclear leukocytes; ELF: Epithelial lining fluid
† Azithromycin concentration at 120 hours after the start of dosing
‡ Data are presented as mean (standard deviation)
¶ C_{max} and AUC were calculated based on composite profile (n = 4 subjects/time point/formulation).

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.

Excretion
Serum azithromycin concentrations following a single 2 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 Impairment
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 1.0 g dose of azithromycin (4 × 250 mg capsules), the mean C_{max} and AUC_{0-120} were 5.1% and 4.2% higher, 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} were 61% and 35% higher, respectively in subjects with GFR <10 mL/min compared to subjects with normal renal function. (See Renal Impairment (8.6).)

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

Pediatric Patients
The pharmacokinetics of azithromycin were characterized following a single 60 mg/kg dose of Zmax in pediatric patients aged 3 months to 16 years. Although there was high inter-patient variability in systemic exposure (AUC and C_{max}) across the age groups studied, individual azithromycin AUC and C_{max} values in pediatric patients were comparable to or higher than those following administration of 2 g Zmax in adults (Table 4). (See Pediatric Use (8.4).)

Table 4. Mean (SD) Pharmacokinetic Parameters for Azithromycin Following Administration of a Single Dose of Zmax (60 mg/kg, maximum dose of 2 g) to Pediatric Subjects Aged 3 Months to 16 Years

Treatment Group	Pharmacokinetic Parameters			
	C_{max} (µg/mL)	T_{max}* (hr)	$AUC_{(0-24)}$ (µg·hr/mL)	$AUC_{(0-\infty)}$ (µg·hr/mL)
Group 1 (N = 6) [3 to 18 months]	0.74 (0.20)	3 (3-3)	6.29 (1.17)	14.1 (2.16) (n = 3)
Group 2† (N = 6) [>18 to 36 months]	1.88† (0.50)	3 (3-3)	19.7† (5.35)	37.3 (12.9) (n = 5)

Group 3 (N = 6) [>36 to 48 months]	1.23 (0.42)	3 (3-6)	12.9 (3.79)	22.4 (5.96)
Group 4 (N = 6) [>48 months to 8 years]	1.13 (0.34)	3 (3-6)	13.0 (4.21)	22.2 (6.89)
Group 5 (N = 6) [>8 to 12 years]	1.65 (0.38)	3 (3-6)	16.0 (4.99)	30.1 (10.7)
Group 6 (N = 6) [>12 to 16 years]	0.98 (0.35)	3 (3-6)	11.0 (4.78)	21.3 (9.37)
Pooled 1-6 (N = 36) [On an empty stomach]	1.27 (0.53)	3 (3-6)	13.1 (5.78)	25.2 (10.7) (n = 32)
Group 7‡ (N = 7) [Fed; 18 months to 8 years]	1.41 (0.62)	3 (1.5-3.1)	7.43 (3.00)	18.9 (3.57) (n = 3)

Empty stomach = dosed with Zmax at least 1 hour before or 2 hours after a meal (Groups I-VI)
Fed = dosed with Zmax within 5 minutes of consuming an age-appropriate high-fat breakfast (Group VII)
* Median (range) presented only for T_{max}
† High mean values were driven by 2 subjects with high exposure
‡ One subject vomited immediately after dosing and discontinued from the study

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.

Pharmacokinetic Interaction Studies
A drug interaction study was performed with Zmax and antacids. All other drug interaction studies were performed with azithromycin immediate release (IR) formulations (capsules and tablets, doses ranging from 500 to 1200 mg) 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 5 and the effects of other drugs on the pharmacokinetics of azithromycin are shown in Table 6.

When used at therapeutic doses, azithromycin IR had a minimal effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, nelfinavir, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine (Table 5). Although the drug interaction studies were not conducted with Zmax, similar modest effect as observed with IR formulation are expected since the total exposure to azithromycin is comparable for Zmax and other azithromycin IR regimens. Therefore, no dosage adjustment of drugs listed in Table 5 is recommended when co-administered with Zmax.

Nelfinavir significantly increased the C_{max} and AUC of azithromycin following co-administration with azithromycin IR 1200 mg (Table 6). However, no dose adjustment of azithromycin is recommended when Zmax is co-administered with nelfinavir.

Pharmacokinetic and/or pharmacodynamic 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, pharmacokinetic and/or pharmacodynamic interactions with these drugs have been observed with other macrolide products. Until further data are developed, careful monitoring of patients is advised when azithromycin and these drugs are used concomitantly: digoxin, ergotamine or dihydroergotamine, cyclosporine, hexobarbital and phenytoin.

Table 5. Drug Interactions: Pharmacokinetic Parameters of 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)
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)

* Refers to azithromycin capsules and tablets unless specified
† 90% confidence interval not reported

Table 6. Drug Interactions: Pharmacokinetic Parameters of Azithromycin in the Presence of Co-administered Drugs

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)
Aluminum and Magnesium hydroxide	20 mL regular strength, single dose	2 g Zmax, single dose	39	0.99 (0.93 to 1.06)	0.99 (0.92 to 1.08)

* Refers to azithromycin capsules and tablets unless specified
† 90% confidence interval not reported

12.4 Microbiology

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

Spectrum of Activity
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

Beta-lactamase production should not affect azithromycin activity.

"Other" microorganisms
Chlamydophila pneumoniae
Mycoplasma pneumoniae

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 azithromycin susceptible breakpoints of <4 µg/mL. 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 agalactiae
Streptococcus pyogenes
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 7.

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 7.

Table 7. Susceptibility Test Result Interpretive Criteria for Azithromycin

	Minimum Inhibitory Concentrations (μg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R***	**S**	**I**	**R***
Haemophilus influenzae	≤ 4	--	--	≥ 12	--	--
Streptococcus 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 determine if the test was performed correctly. Standard azithromycin powder should provide the range of values noted in Table 8. Quality control (QC) 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 8. Acceptable Quality Control Ranges for Azithromycin

QC Strain	Minimum Inhibitory Concentrations (μg/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

13 NONCLINICAL TOXICOLOGY

13. 1 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 g oral adult human dose on a mg/m^2 basis).

13. 2 Animal Toxicology and/or Pharmacology

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 g.) Similarly, it has been shown in the dog (10 mg/kg/day dose) at the observed maximal serum concentration of 1 μg/mL (1.2 times the observed C_{max} of 0.821 μg/mL at the adult dose of 2 g).

Phospholipidosis was also observed in neonatal rats dosed for 18 days at 30 mg/kg/day, which is less than the pediatric dose of 60 mg/kg on a mg/m^2 basis, but was not observed in neonatal rats treated for 10 days at 40 mg/kg/day with mean maximal serum concentrations of 1.86 μg/ml, approximately 1.5 times the C_{max} of 1.27 μg/ml at the pediatric dose. Phospholipidosis has been observed in neonatal dogs (10 mg/kg/day) at maximum mean whole blood concentrations of 3.54 μg/ml, approximately 3 times the pediatric dose C_{max}.

The significance of the finding for animals and for humans is unknown.

14 CLINICAL STUDIES

Acute Bacterial Maxillary Sinusitis

Adult subjects with a diagnosis of acute bacterial maxillary sinusitis were evaluated in a randomized, double-blind, multicenter 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 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%)

Community-Acquired Pneumonia

Adult 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 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	N=202	N=209
CURE	187 (92.6%)	198 (94.7%)
FAILURE	15 (7.4%)	11 (5.3%)
ZMAX VS. LEVOFLOXACIN	N=174	N=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%)

15 REFERENCES

1. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Seventh Edition.* 2006. CLSI Document M7-A7 [ISBN 1-56238-587-9]. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006.

2. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – Ninth Edition.* CLSI Document M2-A9 (ISBN 1-56238-586-0). CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006.

3. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; Eighteenth Informational Supplement.* 2008. CLSI Document M100-S18 [ISBN

1-56238-653-0]. CLSI, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2008.

16 HOW SUPPLIED/STORAGE AND HANDLING

NDC 0069-4170-34 for combined adult and pediatric use is supplied in bottles containing 2 g of azithromycin and should be constituted with 60 mL of water.

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. For adult patients, the entire bottle should be consumed. For pediatric patients, any suspension remaining after dosing **MUST** be discarded.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 General Patient Counseling

- Patients should be instructed to take Zmax on an empty stomach (at least 1 hour before or 2 hours following a meal).
- To ensure accurate dosing for children, use of a dosing spoon, medicine syringe, or cup is recommended.
- Patients should be told that Zmax needs time to work, so the patient may not feel better right away. If the patient's symptoms do not improve in a few days, the patient or their guardian should call their doctor.
- Patients should be instructed to immediately contact a physician if any signs of an allergic reaction occur.
- 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.
- 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. Adult patients should consume the entire contents of the bottle; pediatric patients should take the recommended dose and MUST discard any unused portion.
- 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.

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FDA-approved patient labeling
Read the Patient Information that comes with Zmax ® carefully before you or your child take it. This leaflet does not take the place of talking with your doctor about you or your child's medical condition or treatment. Only your doctor can decide if Zmax is right for you or your child.

What is Zmax?
Zmax is an antibiotic that kills certain bacteria. Zmax is dosed differently from other antibiotics.
You take **just one dose, one time**.
- Day 1: Take Zmax in one dose. Zmax starts working.
- Days 2 – 3: As with most antibiotics, you may not feel better right away.
- After Day 3: Zmax continues to work over time. If your symptoms are not better, call your doctor.

Zmax is used in adults and in children over the age of 6 months against bacteria to treat certain kinds of pneumonia (lung infections)

Zmax is used in adults against bacteria to treat sinus infections.
Zmax only works against bacteria. It does not work against viruses, like the common cold or flu.

Zmax has not been studied in children under 6 months of age.

Who should not take Zmax?
- You or your child should not take Zmax if allergic to:
    - anything in Zmax. See the end of this leaflet for a complete list of ingredients in Zmax.
    - antibiotics like erythromycin or telithromycin (Ketek®).

Talk with your doctor or pharmacist if you have questions about your medicine allergies.

Before you start Zmax…
Tell your doctor about all your or your child's medical problems including if you or your child :
- have liver problems.
- have kidney problems.
- have myasthenia gravis.
- are pregnant, or might be pregnant. It is not known if Zmax could harm your baby.
- are breast-feeding.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements. Especially tell your doctor if you or your child are taking warfarin (Coumadin®, Jantoven)

Know the medicines you take. Keep a list of your medicines and show it to your doctor or pharmacist when you get a new prescription.

Do I need to prepare Zmax?
- If you get Zmax in **liquid form, it is ready to take.**
- If you get Zmax as **dry powder, you must add water to the bottle before you take it.** To prepare Zmax:
    1. Open the bottle: To open the bottle, press down on the cap and twist.
    2. Use a measuring cup to add 60 mL (1/4 cup) water to the Zmax bottle.
    3. Tightly close the bottle and shake to mix it.

How do I take Zmax?

- Keep Zmax at room temperature between 59ºF to 86ºF (15º to 30ºC).
- Shake the bottle well before using.
- Take Zmax or give it to your child within 12 hours after it has been prepared by the pharmacy or you add water to the powder.
- Take Zmax or give it to your child exactly how your doctor prescribes it. This will help to treat you or your child's infection and decrease the chance that Zmax or other antibiotics will not work to treat infections in the future.
  - Adults: take all the medicine in the bottle.
  - Children: give your child the amount of Zmax prescribed by your doctor and throw away the rest of the medicine.
  - To be sure that you give your child the right dose of Zmax, use a dosing spoon, medicine syringe, or cup.
- Take Zmax on an empty stomach (at least 1 hour before eating or 2 hours after eating).
- You can take antacids with Zmax.
- If you or your child throws up (vomits) within one hour of taking Zmax, call your doctor right away to see if more medicine is needed. Do not give your child more Zmax unless your doctor tells you to.
- If your child takes too much Zmax, call your doctor right away or go to the nearest hospital emergency room.

How will I know Zmax is working?

Zmax needs time to work, so you or your child may not feel better right away. If you or your child's symptoms do not get better in a few days, call your doctor.

What are possible side effects of Zmax?

Zmax may cause serious side effects. These happened in a small number of patients. Call your doctor right away or get emergency treatment if you or your child have any of the following:

- **Serious allergic reaction or serious skin reaction:** Get emergency help right away if you or your child has:
  - Hives, skin rash, sores in your mouth, or your skin blisters and peels
  - Trouble swallowing,
  - Swelling of your face, eyes, lips, tongue or throat
  - Wheezing or trouble breathing

These symptoms could go away and then come back.

- **Diarrhea:** Call your doctor right away if you have diarrhea that does not go away, is severe, watery, or has blood in it. Diarrhea can occur as late as two or more months after you take an antibiotic such as Zmax.
- **Abnormal heart rhythm.** Tell your doctor right away if you or your child feel your heart beating in your chest or an abnormal heart beat, get dizzy or faint. This has been seen with other antibiotics like Zmax.

The most common side effects in **adults** are:

- Diarrhea/loose stools
- Nausea
- Stomach pain
- Headache
- Vomiting

The most common side effects in **children** are:

- Vomiting
- Diarrhea/loose stools
- Nausea
- Stomach pain

Tell your doctor if you have any side effects that bother your or your child, or that does not go away. These are not all of the possible side effects with Zmax. For a list of all reported side effects, ask your doctor or pharmacist.

General information about Zmax

Doctors sometimes prescribe medicines for conditions that are not in the patient leaflets. Do not use Zmax for anything other than what your doctor prescribed. Do not give it to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet is a summary of the most important information about Zmax. For more information, talk with your doctor. You can ask your doctor or pharmacist for information about Zmax that is written for healthcare professionals. For more information, go to our website at www.zmaxinfo.com or call 1-800-438-1985.

What is in Zmax?

Active ingredient: azithromycin dihydrate
Inactive ingredients: 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

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