Zmax SR™ P

azithromycin dihydrate

Antibacterial

Pfizer

Date of Preparation: July 31, 2009
Date of Revision: July 14, 2010

SUMMARY PRODUCT INFORMATION:

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Sustained-release granules for oral suspension 2 g azithromycin (on anhydrous basis)	Sucrose and sodium For a complete listing see Dosage Forms, Composition and Packaging.

INDICATIONS AND CLINICAL USE: Zmax SR (azithromycin sustained-release granules for oral suspension) is indicated for treatment of respiratory tract infections caused by susceptible strains of the designated microorganisms in the following diseases and specific conditions:

Acute bacterial exacerbations of chronic bronchitis due to *H. influenzae*, *M. catarrhalis* or *S. pneumoniae*.

Acute bacterial sinusitis due to *H. influenzae*, *M. catarrhalis* or *S. pneumoniae*.

Community acquired pneumonia of mild severity due to *C. pneumoniae*, *H. influenzae*, *M. pneumoniae* or *S. pneumoniae*.

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zmax SR and other antibacterial drugs, Zmax SR 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.

Because some strains are resistant to azithromycin, when applicable, appropriate specimens should be obtained before Zmax SR treatment, for initiation of culture, susceptibility and serology tests to determine the causative organism(s) and susceptibility to azithromycin. Therapy with Zmax SR may be initiated before results of these tests are known; once the results become available, antibacterial treatment should be modified accordingly.

Geriatrics (>65 years of age): In clinical trials of Zmax SR, 17% of patients were at least 65 years of age and 5% of patients were at least 75 years of age. In clinical trials, no overall differences in safety or effectiveness were observed between these patients and younger patients.

Pediatrics (<18 years of age): Zmax SR is not recommended in pediatric patients, i.e., patients below 18 years of age.

CONTRAINDICATIONS: Zmax SR (azithromycin sustained-release granules for oral suspension) is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic or to any ingredient in the formulation or component of the container. For a complete listing, see Dosage Forms, Composition and Packaging.

WARNINGS AND PRECAUTIONS: General: Serious allergic reactions, including angioedema, anaphylaxis and dermatological reactions including Stevens-Johnson syndrome and toxic epidermolysis have been reported rarely (with rare reports of fatalities) in patients on azithromycin therapy (see Contraindications). Allergic reactions may occur during and soon after treatment with azithromycin. 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. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

The use of azithromycin with other drugs may lead to drug-drug interactions. For established or potential drug interactions, see Drug Interactions.

In the absence of data on the metabolism and pharmacokinetics in patients with lysosomal lipid storage diseases (e.g., Tay-Sachs disease, Niemann-Pick disease) the use of Zmax SR (azithromycin sustained-release granules for oral suspension) in these patients is not recommended.

Azithromycin and ergot derivatives should not be co-administered due to the possibility that ergot toxicity may be precipitated by macrolide antibiotics. Acute ergot toxicity is characterized by severe peripheral vasospasm, including ischemia of the extremities, along with dysesthesia and possible central nervous system effects.

Severe Neutropenia (WBC <1000/mm^3) may adversely affect the distribution of azithromycin and its transport to the site of infection. Antibacterials with proven efficacy in this population should be used, as outlined by relevant guidelines for the treatment of patients with severe neutropaenia. No studies of Zmax SR have been conducted in patients with severe Neutropenia and the efficacy and safety of Zmax SR has not been established in this patient population.

Infantile hypertrophic pyloric stenosis (IHPS) has been reported in 2 premature siblings treated after birth with azithromycin; a causal relationship between azithromycin and IHPS could not be concluded from this report, but the theoretical possibility for such a relationship exists.

As with any antibacterial preparation, observation for signs of superinfection with nonsusceptible organisms, including fungi is recommended.

Zmax SR contains 19.36 g of sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine, due to the sucrose content. In addition, patients with diabetes mellitus should pay appropriate attention to the sugar content of Zmax SR.

Zmax SR contains 148 mg of sodium.

Carcinogenesis and Mutagenesis: Long term studies in animals have not been performed to evaluate carcinogenic potential. Azithromycin has shown no genotoxic or mutagenic potential in standard laboratory tests.

Cardiovascular: Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect has been reported with azithromycin and cannot be completely ruled out. There is information that "QT Related Adverse Events" may occur in some patients receiving azithromycin. There have been spontaneous reports from post marketing experience of prolonged QT interval and torsades de pointes (see Adverse Reactions, Post-Market Adverse Drug Reactions). These include but are not limited to: one AIDS patient dosed at 750 mg to 1 g daily experienced prolonged QT interval and torsades de pointes; a patient with previous history of arrythmias who experienced torsades de pointes and subsequent myocardial infarction following a course of azithromycin therapy; and a pediatric case report of prolonged QT interval experienced at a therapeutic dose of azithromycin which reversed to normal upon discontinuation. The effect of azithromycin on cardiac repolarization has not been formally investigated in a focused pharmacodynamic study of QTc effects.

Gastrointestinal: A higher incidence of gastrointestinal adverse events (8 of 19 subjects) was observed when Azithromycin was administered to a limited number of subjects with GFR<10 mL/min (see Warning and Precautions, Renal).

***C. difficile*-associated disease:** *C. difficile*-associated disease (CDAD) has been reported with use of many antibacterial agents, including azithromycin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *C. difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *C. difficile*. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases (see Adverse Reactions).

Hepatic/Biliary/Pancreatic: The safety, efficacy and pharmacokinetics of Zmax SR in patients with hepatic impairment have not been established. Based on studies with immediate-release formulations, no dosage adjustment of Zmax SR is recommended for patients with mild to moderate hepatic impairment.

Since the liver is the principle route of elimination for azithromycin, the use of Zmax SR should be undertaken with caution in patients with impaired hepatic function (see Action and Clinical Pharmacology, Pharmacokinetics).

Cases of acute hepatic necrosis requiring liver transplant or causing death have been reported in patients following treatment with oral azithromycin (see Adverse Reactions, Post-Market Adverse Drug Reactions).

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

Renal: The safety, efficacy and pharmacokinetics of Zmax SR in patients with renal impairment have not been established. No dose adjustment is recommended for patients with GFR 10-80 mL/min. Caution should be exercised when Zmax SR is administered to patients with GFR <10 mL/min. This precaution is based on a clinical study of azithromycin immediate-release tablets, in which patients with GFR <10 mL/min showed a significant (61%) increase in mean C_{max} and a significant (35%) increase in systemic exposure to azithromycin, and experienced a high incidence of gastrointestinal adverse events (8 of 19 clinical study subjects). Patients with GFR 10-80 mL/min showed only slightly increased serum azithromycin levels compared to patients with normal renal function (see Action and Clinical Pharmacology, Pharmacokinetics, and Warnings and Precautions, Gastrointestinal).

Sensitivity/Resistance: Prescribing Zmax SR 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.

Sexual Function/Reproduction: There are no adequate and well-controlled studies in humans. In fertility studies conducted in the rat, reduced pregnancy rates were noted following administration of azithromycin. The predictive value of these data to the response in humans has not been established.

Special Populations: Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Zmax SR should not be used during pregnancy unless the expected benefit to the mother outweighs any potential risk to the fetus. Animal reproduction studies are not always predictive of human response. In animal reproduction studies in mice and rats, at azithromycin doses up to 200 mg/kg/day (moderately maternally toxic), effects were noted in the rat at 200 mg/kg/day, during the prenatal development period (delayed ossification) and during the postnatal development period (decreased viability, delayed developmental landmarks, differences in performance of learning task). The 200 mg/kg/day dose in mice and rats, is approximately 0.5-fold and 1-fold, respectively, the single adult oral dose of 2 g, based on mg/m^2 (body surface area). Pharmacokinetic data from the 200 mg/kg/day dose level in these studies showed that azithromycin crossed the placenta and distributed to fetal tissue at 5 to 9-fold the maternal plasma C_{max} of 2 µg/mL.

Nursing Women: Azithromycin has been reported to have been secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk. In addition, the safety of azithromycin has not been studied in infants less than 6 months of age. Therefore, Zmax SR should not be used in the treatment of nursing women unless the expected benefit to the mother outweighs the possibility of any potential risk to the infant. Azithromycin may accumulate in breast milk over time with Zmax SR single dose therapy.

Pediatrics (<18 years of age): Zmax SR is not recommended in pediatric patients, i.e., patients below 18 years of age.

ADVERSE REACTIONS: Adverse Drug Reaction Overview: During Phase III pivotal clinical studies, 23% of adult subjects receiving Zmax SR (azithromycin sustained-release granules for oral suspension) experienced treatment-related adverse reactions, as judged by the Investigator to be possibly, probably or definitely related to Zmax SR. The most common treatment-related adverse reactions in adult patients receiving a single 2 g dose of Zmax SR were diarrhea/loose stools, nausea, abdominal pain, headache and vomiting. Most gastrointestinal events were mild-to-moderate in severity, occurred on the day of dosing and resolved within 1-2 days. Discontinuations from study due to treatment-related adverse events were comparable between the pooled Zmax SR studies (0.2%, 3/1292) and comparator groups (0.5%, 6/1304).

Clinical Trial Adverse Drug Reactions: Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates seen in clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse drug reactions (adverse reactions) are new or worsening medical events that are judged by the Investigator to be possibly, probably or definitely related to the study drug. Adverse reactions that could occur with Zmax SR are derived from several sources: (i) adverse reactions observed in the pivotal clinical trials of Zmax SR; (ii) adverse reactions observed in other Zmax SR trials, including studies performed in other indications or in other target populations; and (iii) adverse reactions that are known to occur with immediate release azithromycin, but were not observed in clinical trials of Zmax SR (azithromycin sustained-release granules for oral suspension).

The most common adverse drug reactions in the 5 Phase III double-blind controlled pivotal clinical trials of Zmax SR are shown in Table 1.

Table 1: Zmax SR

Adverse Reactions Occurring in ≥1% of Zmax SR-Treated Adult Patients in Pivotal Clinical Trials (Pooled Results of 5 Studies)

System Organ Class	Adverse Reaction	Zmax SR % (N=1292)	All Comparators[a] % (N=1304)
Patients with ≥1% Adverse Reaction		22.8	17.6
Gastrointestinal Disorders	Diarrhoea	10.9	4.8
	Nausea	3.9	2.1
	Abdominal pain	2.7	2.1
	Vomiting	1.1	0.7
Nervous System Disorders	Headache	1.3	0.6

[a] Comparators were levofloxacin, clarithromycin ER, and azithromycin 3-day.

Less Common Clinical Trial Adverse Drug Reactions (<1%): The following adverse reactions occurred in pivotal Zmax SR clinical trials with a frequency of <1% in adult patients treated with Zmax SR: See Table 2.

Table 2: Zmax SR

Adverse Reactions Occurring in <1% of Zmax SR-Treated Adult Patients in Pivotal Clinical Trials (Pooled Results of 5 Studies)

System Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	Leukopenia, eosinophilia
Cardiac Disorders	Palpitations
Ear and Labyrinth Disorders	Ear disorder, vertigo
Eye Disorders	Visual impairment
Gastrointestinal Disorders	Stools loose, flatulence, dyspepsia, gastritis, constipation, dry mouth, eructation, dysphagia, salivary hypersecretion, mouth ulceration, dysgeusia
General Disorders and Administration Site Conditions	Pain, chest pain, oedema peripheral, face oedema, malaise, oedema, pyrexia

(cont'd)

Table 2: Zmax SR *(cont'd)*

Adverse Reactions Occurring in <1% of Zmax SR-Treated Adult Patients in Pivotal Clinical Trials (Pooled Results of 5 Studies)

System Organ Class	Adverse Reaction
Infections and Infestations	Fungal infection, vaginal infection, oral candidiasis, pneumonia, rhinitis, bacterial infection, gastroenteritis, pharyngitis
Investigations	Aspartate aminotransferase increased, blood alkaline phosphatase increased
Metabolism and Nutrition Disorders	Decreased appetite
Musculoskeletal and Connective Tissue Disorders	Back pain, neck pain, myalgia, osteoarthritis
Nervous System Disorders	Paresthesia, dizziness
Psychiatric Disorders	Insomnia
Renal and Urinary Disorders	Dysuria, renal pain
Reproductive System and Breast Disorders	Metrorrhagia, testicular disorder
Respiratory, Thoracic and Mediastinal Disorders	Respiratory disorder, epistaxis, dyspnoea
Skin and Subcutaneous Tissue Disorders	Rash, pruritus, hyperhidrosis, dermatitis, dermatitis exfoliative, dry skin, urticaria
Vascular Disorders	Hot flush

Additional Adverse Drug Reactions from Non-Pivotal Zmax SR Trials: See Table 3.

Table 3: Zmax SR

Adverse Reactions Occuring in ≥1 Zmax SR-Ttreated Subjects in Non-Pivotal Trials Not Reported in the Pivotal Trials

System Organ Class	Adverse Reaction
Cardiac Disorders	Tachycardia, syncope
Eye Disorders	Conjunctivitis, cataract
Gastrointestinal Disorders	Abdominal distension, abnormal faeces, cheilitis, stomatitis, abdominal cramping, tooth disorder, colitis
General Disorders and Administration Site Conditions	Asthenia, chills, fatigue, irritability, thirst
Hepatobiliary Disorders	Hepatitis
Immune System Disorders	Hypersensitivity
Infections and Infestations	Fungal skin infection, influenza, bronchitis, herpes zoster, otitis media
Investigations	Alanine aminotransferase increased, gamma-glutamyltransferase increased
Metabolism and Nutrition Disorders	Increased appetite
Nervous System Disorders	Somnolence, hyperkinesia
Psychiatric Disorders	Agitation, affect lability, hostility, nervousness
Renal and Urinary Disorders	Urine abnormality
Respiratory, Thoracic and Mediastinal Disorders	Cough, oropharyngeal pain
Skin and Subcutaneous Tissue Disorders	Erythema multiforme
Vascular Disorders	Haemorrhage

Adverse Reactions Known to Occur with Azithromycin (Immediate-Release Formulations) Yet Not Seen in the Zmax SR Clinical Trial Program: Table 4 lists adverse reactions that have been reported in patients taking other formulations of azithromycin (immediate-release tablets, oral solution and intravenous solution) but have not been reported in the Zmax SR clinical trials (pivotal or non-pivotal).

Table 4: Zmax SR

Adverse Reactions Occurring in Pivotal Clinical Trials with Azithromycin Immediate-Release Formulations and Not Listed for Zmax SR

System Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	Anaemia
Ear and Labyrinth Disorders	Tinnitus[a], hearing decreased[a]
Gastrointestinal Disorders	Enteritis, esophagitis, loose stools, mucositis, rectal hemorrhage
General Disorders and Administration Site Conditions	Infusion site local inflammation, infusion site pain
Hepatobiliary Disorders	Abnormal liver function, jaundice, jaundice cholestatic
Immune System Disorders	Angioedema
Infections and Infestations	Fungal infection

(cont'd)

Table 4: Zmax SR *(cont'd)*

Adverse Reactions Occurring in Pivotal Clinical Trials with Azithromycin Immediate-Release Formulations and Not Listed for Zmax SR

System Organ Class	Adverse Reaction
Investigations	Liver function test abnormal, aminotransferase increase
Renal and Urinary Disorders	Nephritis, urinary frequency
Reproductive System and Breast Disorders	Menorrhagia
Respiratory, Thoracic and Mediastinal Disorders	Bronchospasm, pleural effusion
Skin and Subcutaneous Tissue Disorders	Eczema, photosensitivity, skin discolouration
Vascular Disorders	Hypertension

[a] Hearing impairment has been associated with prolonged use of high doses of azithromycin immediate-release in clinical studies; in those cases where follow-up information was available the majority of these events were reversible.

Abnormal Hematologic and Clinical Chemistry Findings: Table 5 shows the incidence of abnormal (out of range) laboratory findings for routinely administered hematology and clinical chemistry tests in patients treated with Zmax SR in the Zmax SR pivotal studies, with normal baseline values.

Table 5: Zmax SR

Abnormal Hematologic and Clinical Chemistry Findings Occurring in ≥1% Zmax SR-treated Adult Patients in Pivotal Trials

Parameter	Criterion[a]	N tested	%
Basophil count increased	>1.2 ULN	623	3.9
Blood bicarbonate decreased	<0.9 LLN	522	1.1
Eosinophil count increased	>1.2 ULN	644	3.6
Lymphocyte count decreased	<0.8 LLN	401	4.7
Lymphocyte count increased	>1.2 ULN	401	1.2
Monocyte count increased	>1.2 ULN	617	1.5
Neutrophil count decreased	<0.8 LLN	445	1.1

[a] Out of range criteria in terms of upper and lower limits of normal (ULN, LLN, respectively).

Table 6 shows clinically significant abnormalities as defined by Grade 3 or 4 toxicity (Common Toxicity Criteria), occurring in adult patients treated with Zmax SR in the Zmax SR pivotal studies, with normal baseline values.

Table 6: Zmax SR

Clinically Significant Abnormal Hematologic and Clinical Chemistry Findings in Zmax SR-treated Adult Patients in Pivotal Clinical Trials

Test
Alanine aminotransferase (increase)
Aspartate aminotransferase (increase)
Haemoglobin (decrease)
Hyperglycaemia
Hypochloraemia
Hyponatraemia
Lymphocyte count (decrease)
Neutrophil count (decrease)
White blood cell count (decrease)

Post-Market Adverse Drug Reactions: The following adverse experiences have been reported in patients receiving azithromycin under conditions (e.g., open trials, marketing experience) where a causal relationship is uncertain or in patients treated with significantly higher than the recommended doses for prolonged periods. See Table 7.

In addition, because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency is not always possible.

Table 7: Zmax SR

Post-Market Adverse Reaction Reported in Patients Receiving Azithromycin

System Organ Class	Adverse Reaction
Blood and the Lymphatic System Disorders	Agranulocytosis, haemolytic anaemia, thrombocytopenia
Cardiac Disorders	Arrhythmia (including ventricular tachycardia), palpitations. There have been reports of electrocardiogram QT prolonged and torsade de pointes in patients receiving therapeutic doses of azithromycin, including a pediatric case report of QT interval prolongation which reversed to normal upon discontinuation (see Warning and Precautions, Cardiovascular).
Congenital, Familial and Genetic Disorders	Pyloric stenosis
Ear and Labyrinth Disorders	Hearing impaired (including deafness and vertigo)[a], tinnitus

(cont'd)

Table 7: Zmax SR *(cont'd)*

Post-Market Adverse Reaction Reported in Patients Receiving Azithromycin

System Organ Class	Adverse Reaction
Eye Disorders	Visual impairment
Gastrointestinal Disorders	Constipation, diarrhoea, pancreatitis, tongue discolouration, vomiting, ageusia, dysgeusia
General Disorders and Administration Site Conditions	Asthenia, fatigue, oedema
Hepato-biliary Disorders	Hepatitis fulminant, hepatitis, hepatic function abnormal, jaundice cholestatic. There have also been cases of hepatic necrosis and hepatic failure, which have resulted in death
Immune System Disorders	Anaphylactic reaction (with fatalities), serum sickness, angioedema
Infections and Infestations	Pseudomembranous colitis, vaginal infection
Metabolism and Nutrition Disorders	Dehydration, decreased appetite, hypoglycaemia
Musculoskeletal, Connective Tissue and Bone Disorders	Arthralgia, myalgia
Nervous System Disorders	Anosmia, convulsion, dizziness, hypoaesthesia, parosmia, paraesthesia, psychomotor hyperactivity, syncope
Psychiatric Disorders	Aggression, agitation, anxiety, nervousness
Renal and Urinary Disorders	Nephrotic syndrome, renal failure acute, tubulointerstitial nephritis
Skin and Subcutaneous Tissue Disorders	Dermatitis exfoliative, erythema multiforme, photosensitivity reaction, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria
Vascular Disorders	hypotension, vasculitis

[a] Hearing impairment (including hearing loss, deafness and/or tinnitus) has been reported in some patients receiving azithromycin. Many of these have been associated with prolonged use of high doses in investigational studies. In those cases where follow up information was available the majority of these events were reversible.

DRUG INTERACTIONS: Overview: Caution is warranted when azithromycin is administered to a patient with a history of a significant cardiac repolarization disorder or who is taking other medicinal products that cause a prolonged QT interval (see Warnings and Precautions, Cardiovascular and Adverse Reactions, Post-Market Adverse Drug Reactions).

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the cytochrome P450-related drug interactions seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inhibition via cytochrome metabolite complex does not occur with azithromycin.

Concomitant administration of azithromycin with P-glycoprotein substrates may result in increased serum levels of P-glycoprotein substrates. Concomitant administration of P-glycoprotein inhibitors with azithromycin sustained-release form had minimal effect on the pharmacokinetics of azithromycin.

Drug-Drug Interactions: A drug interaction study was performed with Zmax SR (azithromycin sustained-release granules for oral suspension) and antacids. All other drug interaction studies for azithromycin were performed with immediate-release formulations providing comparable total azithromycin exposure (capsules and tablets, dosing regimes ranging from 500 mg to 1200 mg).

Table 8: Zmax SR

Drug-Drug Interactions with Azithromycin

Co-Administered Medication	Pharmacologic Effect When Co-Administered with Azithromycin
Antacids	Co-administration of azithromycin sustained-release granules with a single 20 mL dose of aluminum hydroxide/magnesium hydroxide (MAALOX regular strength) did not affect the rate and extent of azithromycin absorption.
Carbamazepine	In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin immediate-release.
Cetirizine	In healthy male volunteers, co-administration of a 5-day regimen of azithromycin immediate-release with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.
Cimetidine	In a pharmacokinetic study investigating the effects of a single dose of cimetidine on the pharmacokinetics of azithromycin immediate-release, no alteration of azithromycin pharmacokinetics was seen when cimetidine was given 2 hours before azithromycin.
Coumarin-Type Oral Anticoagulants	Although, in a pharmacokinetic interaction study of 22 healthy men, a 5-day course of azithromycin did not affect the prothrombin time from a subsequently administered single 15 mg 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 concomitantly-administered oral anticoagulants.
Cyclosporin	In a pharmacokinetic study of healthy volunteers that were administered a 500 mg/day oral dose of azithromycin immediate-release for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and its dose adjusted accordingly.
Didanosine	Daily doses of 1200 mg azithromycin immediate-release had no effect on the pharmacokinetics of didanosine.
Efavirenz	Efavirenz, when administered at a dose of 400 mg for 7 days, produced a 22% increase in the C_{max} of azithromycin administered as a 600 mg single dose. AUC was not affected. Administration of a single 600 mg dose of azithromycin immediate-release had no effect on the pharmacokinetics of efavirenz given at 400 mg doses for 7 days.

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Table 8: Zmax SR *(cont'd)*

Drug-Drug Interactions with Azithromycin

Co-Administered Medication	Pharmacologic Effect When Co-Administered with Azithromycin
Fluconazole	A single dose of 1200 mg azithromycin immediate-release did not alter the pharmacokinetics of a single 800 mg oral dose of fluconazole. Total exposure and half-life of 1200 mg azithromycin were unchanged and C_{max} had a clinically insignificant decrease (18%) by coadministration with 800 mg fluconazole.
HMG-CoA Reductase Inhibitors	In healthy volunteers, co-administration of atorvastatin (10 mg daily) and azithromycin immediate-release (500 mg daily) did not alter plasma concentrations of atorvastatin (based on HMG-CoA reductase inhibition assay). However, post-marketing case reports are suggestive of a potential drug interaction between statins and azithromycin leading to an increased incidence of rhabdomyolysis.
Indinavir	A single dose of 1200 mg azithromycin had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir t.i.d. for 5 days).
Midazolam	In healthy volunteers (N=12), co-administration of azithromycin immediate-release 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.
Nelfinavir	Co-administration of azithromycin immediate-release (single dose of 1200 mg) and nelfinavir steady-state (750 mg three times daily) produced an approximately 16% decrease in mean AUC_{0-8} of nelfinavir and its M8 metabolite. C_{max} was not affected. Co-administration of azithromycin immediate-release (single dose of 1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased mean AUC of azithromycin by 113% and mean C_{max} by 136%. Dose adjustment of Zmax SR is not recommended. However, close monitoring for known side effects of azithromycin, when administered in conjunction with nelfinavir, is warranted.
P-Glycoprotein Inhibitors	Co-administration of P-glycoprotein inhibitors (Vitamin E, Poloxamer 407, or Poloxamer 124) with azithromycin sustained release form (1 g dose) had minimal effect on the pharmacokinetics of azithromycin.
Rifabutin	Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment with azithromycin and rifabutin. Neutropenia has been associated with the use of rifabutin, but it has not been established if concomitantly-administered azithromycin potentiates that effect (see Adverse Reactions).
Sildenafil	In normal healthy male volunteers, there was no evidence of a statistically significant effect of azithromycin immediate-release (500 mg daily for 3 days) on the AUC, C_{max}, T_{max}, elimination rate constant, or subsequent half-life of sildenafil or its principal circulating metabolite.
Theophylline	Concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. Azithromycin did not affect the pharmacokinetics of theophylline administered either as a single intravenous infusion or multiple oral doses at a recommended dose of 300 mg every 12 hours. There is one post-marketing report of supraventricular tachycardia associated with an elevated theophylline serum level that developed soon after initiation of treatment with azithromycin. Until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving azithromycin and theophylline concomitantly.
Trimethoprim/Sulfamethoxazole	Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin immediate-release 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.
Zidovudine	Single 1 g doses and multiple 1200 mg or 600 mg doses of azithromycin immediate-release did not affect the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells.

Concomitant Therapy: The following drug interactions have not been reported in clinical trials with azithromycin and no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. Nonetheless, they have been observed with macrolide products, and there have been spontaneously reported cases with azithromycin and some of these drugs, in postmarketing experience. Until further data are developed regarding drug interactions, when Zmax SR and these drugs are used concomitantly, careful monitoring of patients is advised both during and for a short period following therapy. See Table 9.

Table 9: Zmax SR

Concomitant Medications

Concomitant Medication	Reported Effect When Administered Concomitantly with Azithromycin
Antihistamines	Prolongation of QT intervals, palpitations or cardiac arrhythmias have been reported with concomitant administration of azithromycin and astemizole or terfenadine.
Cisapride, hexobarbital, phenytoin	Increased serum levels of hexobarbital, cisapride or phenytoin have been reported.
Digoxin/P-Glycoprotein Substrates	Concomitant administration of some macrolide antibiotics with P-glycoprotein substrates, including digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered.
Disopyramide	Azithromycin may increase the pharmacologic effect of disopyramide.

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Table 9: Zmax SR *(cont'd)*

Concomitant Medications

Concomitant Medication	Reported Effect When Administered Concomitantly with Azithromycin
Ergot (ergotamine or dihydroergotamine)	Azithromycin and ergot derivatives should not be co-administered due to the possibility that ergot toxicity may be precipitated by some macrolide antibiotics. Acute ergot toxicity is characterized by severe peripheral vasospasm, including ischemia of the extremities, along with dysesthesia and possible central nervous system effects.
Gentamicin	No data are available on the concomitant clinical use of azithromycin and gentamicin or other amphiphilic drugs which have been reported to alter intracellular lipid metabolism.
Triazolam	Azithromycin may decrease clearance of triazolam and increase the pharmacologic effect of triazolam.

Drug-Food Interactions: When a 2 g dose Zmax SR (azithromycin sustained-release granules for oral suspension) was administered to healthy subjects following a high-fat meal, peak serum concentration and systemic exposure increased (115% and 23% respectively). Following a standard meal in healthy subjects, peak serum concentration was increased by 119% but systemic exposure was not affected.

DOSAGE AND ADMINISTRATION:

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

A single 2 g dose of Zmax SR is not bioequivalent and is not interchangeable with a single 2 g dose of azithromycin immediate-release (tablets or powder for oral suspension).

A single 2 g dose of Zmax SR is not bioequivalent and is not interchangeable with any regimens employing azithromycin immediate-release oral formulations (tablets or oral suspension) due to a different pharmacokinetic profile (see Action and Clinical Pharmacology, Pharmacokinetics).

Recommended Dose and Dosage Adjustment: The recommended dose for adults is a single 2 g dose of Zmax SR (azithromycin sustained-release granules for oral suspension) given as a suspension.

Zmax SR provides a full course of antibacterial therapy in a single oral dose.

It is recommended that Zmax SR be taken on an empty stomach (at least 1 hour before or 2 hours following a meal).

Geriatrics: No dose adjustment is necessary in elderly patients requiring Zmax SR therapy (see Action and Clinical Pharmacology, Pharmacokinetics, Special Populations and Conditions).

Pediatrics (<18 years of age): Zmax SR is not recommended in pediatric patients, i.e., patients below 18 years of age.

Hepatic Impairment: No dosage adjustment for Zmax SR is recommended for patients with mild to moderate hepatic impairment, based on studies with immediate-release formulations. Nonetheless, since the liver is the principal route of elimination for azithromycin, the use of Zmax SR should be undertaken with caution in patients with impaired hepatic function (see Action and Clinical Pharmacology, Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency).

Renal Impairment: No dosage adjustment for Zmax SR is recommended for patients with GFR 10-80 mL/min. Zmax SR should be used cautiously in patients with GFR<10 mL/min. These recommendations are based on a clinical study with azithromycin immediate-release tablets, in which patients with GFR <10 mL/min had increased serum azithromycin levels and a higher incidence of gastrointestinal adverse events; and, patients with GFR 10-80 mL/min showed only slightly increased serum azithromycin levels compared to patients with normal renal function. No studies have been conducted in patients requiring hemodialysis (see Warnings and Precautions, Renal, and Action and Clinical Pharmacology, Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency).

Vomiting After Dosing: In the event that a patient vomits within 5 minutes of administration of Zmax SR, the health care provider should consider additional antibacterial treatment since there would be minimal absorption of azithromycin. Since insufficient data exist on absorption of Zmax SR if a patient vomits between 5 and 60 minutes following administration, alternative therapy should be considered. Neither a second dose of Zmax SR 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.

Administration: Instructions for Pharmacist: To reconstitute, add 60 mL water and replace cap. Shake bottle well before dispensing. Do not refrigerate. Reconstituted suspension should be consumed in a single dose and within 12 hours of reconstitution.

Patients are advised to drink the entire content of the suspension of Zmax SR as a single dose on an empty stomach (at least 1 hour before or 2 hours following a meal) (see Drug Interactions, Drug-Food Interactions).

OVERDOSAGE:

Ototoxicity and gastrointestinal adverse events may occur with an overdose of azithromycin SR.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre. See the *CPS* Directory section for a list of Poison Control Centres.

ACTION AND CLINICAL PHARMACOLOGY: Mechanism of Action: Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms, thus interfering with microbial protein synthesis.

Mechanism of Resistance : There are 2 predominant azithromycin resistance determinants in clinical isolates of *S. pneumoniae*: mef and erm. Mef encodes an efflux pump that mediates resistance to 14- and 15-membered macrolides only. The erm gene encodes a 23S-rRNA methyltransferase that adds methyl groups to the 23S rRNA at a site that has been found to also interact with lincosamides and streptogramin B, resulting in a resistant phenotype known as MLS_B. Azithromycin resistance in *S. pneumoniae* clinical isolates, gathered between 1999 and 2003 from North American sites, ranged approximately 15 to 40%.

Pharmacodynamics: Based on animal models of infection, the antimicrobial activity of azithromycin appears to correlate with the ratio of area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for certain pathogens (*S. pneumoniae* and *S. aureus*). The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with Zmax SR (azithromycin sustained-release granules for oral suspension).

Pharmacokinetics: Zmax SR (azithromycin sustained-release granules for oral suspension) is a modified release formulation which provides a full course of antibacterial therapy in a single oral dose. Zmax SR is formulated to release azithromycin in the small intestine, not in the stomach. The steady state azithromycin concentration in polymorphonuclear leukocytes (80 µg/mL) is achieved approximately 8 hours after dosing with Zmax SR single dose, compared to 48 hours after the first dose of the 500 mg per day × 3 days azithromycin tablet regimen. Azithromycin uptake by leukocytes appears to be dose-proportional, suggesting linear kinetics.

A single 2 g dose of Zmax SR is not bioequivalent and is not interchangeable with regimens employing azithromycin immediate-release oral formulations (tablets or oral suspension) due to a different pharmacokinetic profile.

Table 10: Zmax SR

Mean (SD) Serum Pharmacokinetic Parameters for a Single 2 g Dose of Azithromycin Sustained Release

C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0\text{-}24}$h (µg/hr-mL)	$AUC_{0\text{-}\infty}$ (µg/hr-mL)	$T_{1/2}$ (hr)
0.821 (0.281)	5.0 (2.0–8.0)	8.62 (2.34)	20.0 (6.7)	58.8 (6.9)

Absorption: The Zmax SR microspheres encapsulate the active drug and prevent dissolution and absorption of azithromycin in the low pH of the stomach; in the higher pH of the small intestine the microspheres dissolve and the drug is absorbed in the small intestine.

The absolute bioavailability of Zmax SR has not been directly determined; indirect calculation from separate studies suggests that the absolute bioavailability is approximately 28% to 36%.

Administration of Zmax SR with food may increase absorption of azithromycin compared to the recommended mode of administration (empty stomach). Co-administration of an antacid with Zmax SR does not affect absorption.

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 a steady-state apparent volume of distribution of 31.1 L/kg.

Azithromycin concentrates in fibroblasts, epithelial cells, macrophages, and circulating neutrophils and monocytes. Azithromycin concentrations are higher in tissues than in plasma and serum. 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.

White blood cell and lung exposure data in humans following a single 2 gram dose of Zmax SR in adults are shown in Table 11. Following a 2 gram single dose of Zmax SR, 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 11: Zmax SR

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

A Single 2 g Dose of Zmax SR				
WBC	**C_{max} (µg/mL)**	**AUC_{0-24} (µg·hr/mL)**	**AUC_{0-120} (µg·hr/mL)**	**$C_{t=120}$[a] (µg/mL)**
MNL[b]	116 (40.2)	1790 (540)	4710 (1100)	16.2 (5.51)
PMNL[b]	146 (66.0)	2080 (650)	10 000 (2690)	81.7 (23.3)
Lung	**C_{max} (µg/mL)**	**AUC_{0-24} (µg·hr/mL)**	**AUC_{0-72} (µg·hr/mL)**	
Alveolar Cell[c]	669	7028	20 403	—
ELF[c]	3.2	17.6	131	—
	C_{max} (µg/g)	**AUC_{0-24} (µg·hr/g)**	**AUC_{0-72} (µg·hr/g)**	
Lung Tissue[c]	37.9	505	1693	—

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

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: Metabolism of azithromycin following administration of Zmax SR has not been studied. Based on studies with immediate-release formulations, the majority of systemically available azithromycin is excreted unchanged in the bile. Metabolites of azithromycin were identified in bile but have not been studied further.

Excretion: Serum azithromycin concentrations following a single 2 g dose of azithromycin sustained-release granules for oral suspension 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 an enlarged 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 and Conditions: Pediatrics (<18 years of age): Zmax SR is not recommended in pediatric patients, i.e., patients below 18 years of age.

Geriatrics: Elderly volunteers (>65 years) had slightly higher AUC values than in young volunteers (<40 years) after a 5-day regimen of azithromycin immediate-release, but these are not considered clinically significant, and hence no dose adjustment is recommended. No pharmacokinetic studies with Zmax SR were conducted in geriatric patients (see Dosage and Administration).

Gender: The impact of gender on the pharmacokinetics of azithromycin has not been evaluated for Zmax SR. However, previous studies with azithromycin immediate-release have demonstrated no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment of Zmax SR is recommended based on gender (see Dosage and Administration).

Hepatic Insufficiency: Based on studies with immediate-release formulations, in patients with mild (Child Pugh Class A) to moderate (Child Pugh Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. The urinary clearance of azithromycin is increased. No pharmacokinetic studies with Zmax SR were conducted in patients with hepatic impairment (see Dosage and Administration).

Renal Insufficiency: Azithromycin pharmacokinetics were investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1.0 g dose of azithromycin (4×250 mg capsules; immediate-release formulation), 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. No pharmacokinetic studies with Zmax SR were conducted in patients with renal impairment (see Dosage and Administration).

STORAGE AND STABILITY: Before reconstitution, store Zmax SR at 15-30°C. Keep container tightly closed. After reconstitution, store suspension at 25°C; excursions permitted to 15-30°C. Do not refrigerate or freeze. Reconstituted suspension should be consumed in a single dose and within 12 hours of reconstitution.

INFORMATION FOR THE PATIENT: Published in e-CPS, available by subscription at www.e-cps.ca.

DOSAGE FORMS, COMPOSITION AND PACKAGING: Bottles containing 2.05 g azithromycin dihydrate, corresponding to 2 g azithromycin on anhydrous basis, as sustained-release granules for oral suspension, and is reconstituted with 60 mL of water. After reconstitution 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. Nonmedicinal ingredients: artificial cherry flavour and artificial banana flavour, colloidal silicon dioxide, glyceryl behenate, hydroxypropylcellulose, magnesium hydroxide, poloxamers, sucrose, sodium phosphate tribasic anhydrous, titanium dioxide and xanthan gum. Each bottle of Zmax SR contains approximately 148 mg of sodium and 19 g of sucrose. Reconstituted Zmax SR oral suspension contains approximately 2 mg/mL of sodium and 0.26 g/mL of sucrose.

