PRODUCT MONOGRAPH

Pr Zmax SR

Azithromycin sustained-release granules for oral suspension

(as azithromycin dihydrate)

2 g azithromycin (on anhydrous basis)

Antibacterial Agent

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azithromycin sustained-release granules for oral suspension

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

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 *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae.*

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

Community acquired pneumonia of mild severity due to *Chlamydia pneumoniae, Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus 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 a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin and in those with a 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** section of the product monograph.

WARNINGS AND PRECAUTIONS

General

Serious allergic reactions, including angioedema, anaphylaxis and dermatological reactions including Stevens-Johnson syndrome, toxic epidermolysis, toxic epidermal necrolysis and Drug Reaction with Eosinophilia and Systemic symptoms (DRESS) 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** section of the product monograph.

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 (see **TOXICOLOGY**).

Cardiovascular

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and *torsade de pointes*, have been seen in treatment with macrolides including azithromycin (see **ADVERSE REACTIONS**). Prescribers should consider the risk of QT prolongation which can lead to fatal events when weighing the risks and benefits of azithromycin. Risk factors for *torsade de pointes* include patients:

- With a history of *torsade de pointes*
- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients may be more susceptible to drug-associated effects on the QT interval
- Exposed to higher plasma levels of azithromycin (e.g. receiving intravenous azithromycin, hepatobiliary impaired)

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 *torsade 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 *torsade de pointes*; a patient with previous history of arrhythmias who experienced *torsade 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 (see **ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology**).

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**).

***Clostridium difficile*-associated disease**

Clostridium 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 *Clostridium difficile*. *Clostridium 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 *Clostridium 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 *Clostridium 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. Azithromycin has not been studied in patients with severe 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**).

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

Musculoskeletal and connective tissue disorders
Myasthenia gravis
Exacerbations of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy. The use of azithromycin in patients with a known history of myasthenia gravis is not recommended.

Renal Impairment
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 (see **TOXICOLOGY**).

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. 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 Cmax of 2 ug/mL (see **TOXICOLOGY**).

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 any potential risk to the infant. Because azithromycin may accumulate in breast milk over time with Zmax SR single dose therapy, if the lactating mother is treated with **Zmax SR**, the breast milk should be expressed and discarded during treatment.

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

Monitoring and Laboratory Tests

Monitoring of QT/QTc intervals during treatment with Zmax SR may be considered by the physician as appropriate.

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. 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:

Table 2. 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
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

Table 3. Adverse Reactions Occuring in ≥1 Zmax SR treated 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. 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*, hearing decreased*
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
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

* 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. Abnormal Hematologic and Clinical Chemistry Findings occurring in ≥ 1% Zmax SR–treated Adult Patients in Pivotal Trials

Parameter	Criterion*	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

* 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. 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.

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

Table 7. Postmarket 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 & Precautions, Cardiovascular**).
Congenital, familial and genetic disorders	Pyloric stenosis
Ear and labyrinth disorders	Hearing impaired (including deafness and vertigo)[a], tinnitus
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. (see **Warnings and Precautions Hepatotoxicity**)
Immune system disorders	Anaphylactic reaction (with fatalities) (see **Warnings and Precautions**), serum sickness, angioedema,
Infections and infestations	Pseudomembranous colitis, vaginal infection
Metabolism and nutrition disorders	Dehydration, decreased appetite, hypoglycaemia
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia, myasthenia gravis
Nervous system disorders	Anosmia, convulsion, dizziness, hypoaesthesia, parosmia, paraesthesia, psychomotor hyperactivity, syncope
Psychiatric disorders	Aggression, agitation, anxiety, nervousness, delirium, hallucinations
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, Drug Reaction with Eosinophilia and Systemic symptoms (DRESS) (see **WARNINGS and PRECAUTIONS**).
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: 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.
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 Cmax 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 cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.
Indinavir	A single dose of 1200 mg azithromycin had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir three times daily. 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 Cmax 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 gram 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.

Table 9: 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 and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.
Disopyramide	Azithromycin may increase the pharmacologic effect of disopyramide.
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. (see **WARNINGS AND PRECAUTIONS**).
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** and **DETAILED PHARMACOLOGY, Human 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**).Elderly patients may be more susceptible to development of *torsade de pointes* arrhythmia than younger patients (see **WARNINGS AND PRECAUTIONS**).

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. Azithromycin has not been studied in patients with severe hepatic impairment. 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, Special Populations, 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 Impairment,** and **ACTION AND CLINICAL PHARMACOLOGY, 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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Azithromycin acts by binding to the 23S rRNA of the 50S ribosomal subunit of susceptible microorganisms. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Mechanism of Resistance

The erm gene encodes a 23S rRNA methyltransferase that adds methyl groups to the ribosomal RNA, and as a result disrupts the binding of azithromycin, which interferes with the antimicrobial efficacy of azithromycin. *Mef* encodes an efflux pump that decreases intracellular azithromycin.

The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

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).

Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial. A total of 119 health subjects were enrolled (mean age of 35.5 years; range 18-55 years), of which 116 subjects (97 males) completed the study and were included in the analysis. Subjects were randomized to one of 5 treatments and received orally once daily for 3 days: placebo, chloroquine 600 mg base only, or chloroquine 600 mg base in combination with azithromycin 500 mg, 1000 mg, and 1500 mg. On Day 3, the azithromycin mean (%CV) plasma Cmax values for the 500, 1000 and 1500 mg azithromycin dose regimens were 0.536 (33), 0.957 (31), and 1.54 (28) µg/mL, respectively. Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the day 3 maximum mean (90% 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.

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 ug/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 x 3 days azithromycin tablet regimen. Azithromycin uptake by leukocytes appears to be dose-proportional, suggesting linear kinetics (see **DETAILED PHARMACOLOGY, Human Pharmacology, Pharmacokinetics**).

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 (see **DETAILED PHARMACOLOGY, Human Pharmacology, Pharmacokinetics**).

Table 10. Mean (SD) Serum Pharmacokinetic Parameters for a Single 2 g Dose of Azithromycin Sustained Release

Cmax (μg/mL)	Tmax (hr)	AUC0-24h (μg/hr-mL)	AUC0-∞ (μg/hr-mL)	T1/2(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: 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)**	**$C_{t=120}$† (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: 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 (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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Zmax SR is supplied in 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.

Zmax SR contains the following inactive ingredients: artificial cherry flavour and artificial banana flavour, colloidal silicon dioxide, glyceryl behenate, hydroxypropylcellulose, magnesium hydroxide, poloxamers, sucrose, sodium phosphate tribasic anhydrous, titanium dioxide, 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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

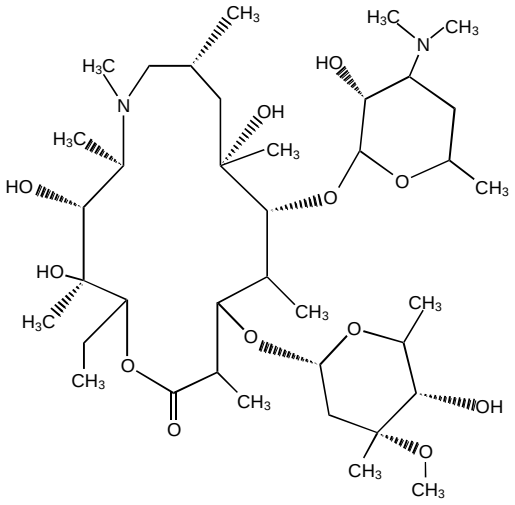
Drug Substance

Proper name: Azithromycin dihydrate

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 dihydrate

Molecular formula and molecular mass: $C_{38}H_{72}N_2O_{12,}$•2H2O, 785.0 (749.0 on anhydrous basis)

Structural formula:



Physicochemical properties: Azithromycin, as the dihydrate, is a white crystalline powder. The solubility of azithromycin decreases with increasing pH over the physiological range, from > 400 mg/mL at pH 2 to < 5 mg/mL at pH 7.5

CLINICAL TRIALS

Clinical efficacy for Zmax SR (azithromycin sustained-release granules for oral suspension) was assessed in 5 Phase 3 studies that enrolled over 2000 adult subjects. The results of the four studies in the three indicated infections are provided below, by indication.

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

Adults with a diagnosis of ABECB were evaluated in one clinical trial; the results are summarized in Tables 12 through 14.

Table 12: Acute Bacterial Exacerbation of Chronic Bronchitis: Baseline Demographics of the Study Population

Study Number	A0661102					
Study Design	Multi-centre[1], parallel group, double-blind, double-dummy, randomized					
	Zmax SR			Levofloxacin		
Dosing	2 g oral suspension, single-dose			500 mg oral once daily x 7 days		
	Male	Female	Total	Male	Female	Total
No. of subjects	177	91	268	196	78	274
Age [2] (years)						
Mean (SD)	63.3 (10.7)	60.5 (9.3)	62.3 (10.3)	62.9 (9.6)	58.7 (10)	61.7 (9.8)
Range	38-94	38-79	38-94	35-84	35-87	35-87
Race						
White	92	72	164	103	57	160
Black	26	6	32	19	9	28
Asian	45	1	46	53	0	53
Hispanic	11	11	22	19	9	28
Other	3	1	4	2	3	5
Weight (kg)						
Mean (SD)	72.4 (19.5)	70.8 (16.4)	71.8 (18.5)	71.5 (18.3)	68.7 (16.3)	70.7 (17.8)
Range	36.0-162.0	33.0-123.0	33.0-162.0	33.0-125.0	32.0-120.0	32.0-125.0

SD = standard deviation;

[1] Patients were enrolled in the following countries: Brazil, Canada, Costa Rica, Germany, India, Lithuania, Mexico, Netherlands, Russia, Spain, UK, Venezuela, US.

[2] Pursuant to Amendment 1 of the protocol, patients <50 years old were excluded from participation; 256/268 Zmax SR patients and 258/274 levofloxacin patients were ≥50 years old.

Table 13: Acute Bacterial Exacerbation of Chronic Bronchitis: Clinical Cure Rates in the Clinical Per Protocol Population at Test of Cure (TOC) Visit (Day 14 to 21)

Study A0661102	Zmax SR	levofloxacin	Difference in Cure Rates	95% CI for difference[1]
No. of Subjects at TOC	220	218	1.0%	(-3.4%, 5.5%)
Cure[2] (%)	206 (93.6%)	202 (92.7%)		
Failure (%)	14 (6.4%)	16 (7.3%)		

[1] 95% CI for the difference in cure rates was constructed using the normal approximation to the binomial distribution; Zmax SR was considered non-inferior to comparator if the lower boundary > -10%.
[2] A subject was considered a cure if signs and symptoms related to the acute infection returned to the subject's normal Baseline level, or if clinical improvement was such that no additional antibacterials were deemed necessary.

Table 14: Acute Bacterial Exacerbation of Chronic Bronchitis: Clinical Cure Rates by Pathogen

Study A0661102	Zmax SR		Levofloxacin	
Total Subjects	112		102	
Total Pathogens	123		124	
	n cured/N	%	n cured/N	%
Haemophilus influenzae	18/19	94.7	19/21	90.5
Moraxella catarrhalis	23/25	92.0	13/16	81.3
Streptococcus pneumoniae	19/20	95.0	26/26	100

N = no. of subjects evaluated; n = no. of subjects cured.

Acute Bacterial Sinusitis (ABS)

Adult subjects with a diagnosis of acute bacterial maxillary sinusitis were evaluated in one clinical trial; the results are summarized in Tables 15 through 17.

Table 15: Acute Bacterial Sinusitis: Baseline Demographics in Study Population

Study Number	A0661078					
Study Design	Multi-centre[1], parallel group, double-blind, double-dummy, randomized					
	Zmax SR			Levofloxacin		
Dosing	2 g oral suspension, single-dose			500 mg oral once daily x 10 days		
	Male	Female	Total	Male	Female	Total
No. of subjects	126	144	270	99	169	268
Age (years)						
Mean (SD)	36.2 (12.8)	40.3 (15.5)	38.4 (14.4)	37.5 (13.4)	40.6 (14.5)	39.4 (14.1)
Range	18-73	18-88	18-88	18-75	18-81	18-81
Race						
White	85	95	180	66	115	181
Black	2	7	9	1	4	5
Asian	24	13	37	16	21	37
Hispanic	15	29	44	16	27	43
Other	0	0	0	0	2	2
Weight (kg)						
Mean (SD)	79.9 (19.4)	67.4 (17.0)	73.2 (19.2)	79.9 (15.2)	70.3 (17.9)	73.9 (17.6)
Range	46.0-159.0	42.0-135.0	42.0-159.0	48.0-132.0	35.0-145.0	35.0-145.0

SD = standard deviation;
[1] Patients were enrolled in the following countries: Argentina, Chile, Costa Rica, Czech Republic, Estonia, Germany, India, Lithuania, Mexico, Poland, Russia, Slovakia, US

Table 16: Acute Bacterial Sinusitis: Clinical Cure Rates in the Clinical Per Protocol Population at Test of Cure (TOC) Visit (Day 17-24)

	Zmax SR	levofloxacin	Difference in Cure Rates	95% CI for difference[1]
No. of Subjects at TOC	256	251	1.7%	(-2.5%, 5.9%)
Cure[2] (%)	242 (94.5%)	233 (92.8%)		
Failure (%)	14 (5.5%)	18 (7.2%)		

[1] 95% CI for the difference in cure rates was constructed using the normal approximation to the binomial distribution; Zmax SR was considered non-inferior to comparator if the lower boundary > -10%.
[2] 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 antibacterials were deemed necessary.

Table 17: Acute Bacterial Sinusitis: Clinical Cure Rates by Pathogen

	Zmax SR		Levofloxacin	
Total Subjects	102		111	
Total Pathogens	114		129	
	n cured/N	%	n cured/N	%
Haemophilus influenzae	26/27	96.3	30/30	100.0
Moraxella catarrhalis	8/8	100.0	10/11	90.9
Streptococcus pneumoniae	36/37	97.3	36/39	92.3

N = no. of subjects evaluated; n = no. of subjects cured.

Community-Acquired Pneumonia (CAP)

Adult subjects with a diagnosis of mild community-acquired pneumonia were evaluated in 2 clinical trials; the results are summarized in Tables 18 through 20.

Table 18: Community-Acquired Pneumonia: Baseline Demographics in the Study Populations (2 trials)

Study Number	A0661075 [1]					
Study Design	Multi-centre[2], parallel group, double-blind, double-dummy, randomized					
	Zmax SR			clarithromycin ER		
Dosing	2 g oral suspension, single-dose			1 g oral tablet per day x 7 days		
	Male	Female	Total	Male	Female	Total
No. of subjects	112	135	247	134	118	252
Age (years)						
Mean (SD)	42.7 (14)	47.9 (17)	45.6 (15.9)	42.5 (15.2)	45 (15.4)	43.6 (15.3)
Range	17-70	17-81	17-81	16-77	16-76	16-77
Race						
White	78	112	190	98	93	191
Black	7	7	14	9	6	15
Asian	23	12	35	21	13	34
Hispanic	3	3	6	4	5	9
Other	1	1	2	2	1	3
Weight (kg)						
Mean (SD)	78.8 (20.6)	71.9 (20.3)	75 (20.7)	81.8 (21.8)	68.3 (18.4)	75.5 (21.3)
Range	35.0-136.0	40.0-159.0	35.0-159.0	37.0-141.0	32.0-142.6	32.0-142.6
Study Number	A0661103[1]					
Study Design	Multi-centre[3], parallel group, double-blind, double-dummy, randomized					
	Zmax SR			Levofloxacin		
Dosing	2 g oral suspension, single-dose			500 mg oral once daily x 7 days		
	Male	Female	Total	Male	Female	Total
No. of subjects	121	90	211	109	103	212
Age (years)						
Mean (SD)	44.9 (18.2)	52.6 (17)	48.2 (18.1)	50.3 (17.8)	47.7 (19.4)	49 (18.6)
Range	18-81	21-95	18-95	18-82	18-87	18-87
Race						
White	76	56	132	73	62	135
Black	3	2	5	1	2	3
Asian	31	16	47	26	22	48
Hispanic	1	1	2	2	0	2
Other	10	15	25	7	17	24
Weight (kg)						
Mean (SD)	74.3 (20.2)	69.5 (27.4)	72.2 (23.6)	76.3 (21.7)	65 (16.4)	70.8 (20.1)
Range	35.0-132.0	27.0-222.0	27.0-222.0	30.0-172.0	30.0-104.0	30.0-172.0

SD = standard deviation;

[1] Both studies enrolled FINE Class I and II CAP patients; study A0661103 also enrolled a small proportion of FINE Class III patients

[2] Patients were enrolled in the following countries: Argentina, Canada, Estonia, India, Lithuania, Netherlands, Russia, US

[3] Patients were enrolled in the following countries: Belgium, Brazil, Canada, Chile, India, Lithuania, Mexico, Peru, Russia, Venezuela, US.

Table 19: Community-Acquired Pneumonia: Clinical Cure Rates in the Clinical Per Protocol Populations at Test Of Cure (TOC) Visit (Day 14 to 21)

		Zmax SR	Comparator	Difference in Cure Rates	95% CI for difference[1]
Study A0661075	No. of Subjects at TOC	202	209	-2.2%	(-6.9%, 2.6%)
	Cure[2] (%)	187 (92.6%)	198 (94.7%)		
	Failure (%)	15 (7.4%)	11 (5.3%)		
Study A0661103	No. of Subjects at TOC	174	189	-4.0%	(-9.7%, 1.7%)
	Cure[2] (%)	156 (89.7%)	177 (93.7%)		
	Failure (%)	18 (10.3%)	12 (6.3%)		
Pooled	No. of Subjects at TOC	376	398	-3.0%	(-6.8%, 0.7%)
	Cure[2] (%)	343 (91.2%)	375 (94.2%)		
	Failure (%)	33 (8.8%)	23 (5.8%)		

[1] 95% CI for the difference in cure rates was constructed using the normal approximation to the binomial distribution; Zmax SR was considered non-inferior to comparator if the lower boundary > -10%.
[2] 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 antibacterials were deemed necessary; in addition a chest x-ray at TOC must have been improved or stable.

Table 20: Community-Acquired Pneumonia: Clinical Cure Rates by Pathogen (pooled results)

	Azithromycin SR		Comparator	
Total Subjects	191		231	
Total Pathogens	241		299	
	n cured/N	%	n cured/N	%
Haemophilus influenzae	28/30	93%	31/34	91%
Streptococcus pneumoniae	28/33	85%	35/39	90%
Chlamydia pneumoniae	37/40	93%	50/53	94%
Mycoplasma pneumoniae	30/33	91%	38/39	97%

N = no. of subjects evaluated; n = no. of subjects cured.

DETAILED PHARMACOLOGY

Animal Pharmacology

In vitro

Azithromycin was tested, in radioligand receptor binding assays in tissue isolated from the bovine brain, for binding affinity at various receptors at final drug concentrations up to 10 µM. At this concentration, azithromycin showed no significant binding (IC50 >10 µM) at the alpha1, alpha 2 and beta-adrenergic; 5HT1A and 5HT2 serotonergic; adenosine1, dopamine2, histamine1, GABA, muscarinic and mu-opioid receptors. Thus, azithromycin showed no interaction with a range of physiologically relevant receptors at a pharmacologically relevant concentration. Azithromycin showed no effects in the histamine-stimulated ileum and atrium, the norepinephrine-stimulated aorta isolated from the guinea pig, and the oxytocin-stimulated rat uterus at concentrations that ranged from 1 nM to 10 µM.

In vivo
At doses up to 80 mg/kg of azithromycin orally in rats, there were no biologically significant effects on, respiratory, urinary, and gastrointestinal systems. Mice given up to 1000 mg/kg of azithromycin orally showed no behavioral symptomatology.

During cardiovascular evaluation in conscious dogs given a single dose of 80 mg/kg *per os* (PO) of azithromycin, transient changes were observed in heart rate, arterial pressure, and myocardial contractility. There were initial increases in mean arterial pressure, heart rate, and Q-A interval (an index of contractility). These alterations occurred within approximately the first hour after compound administration and were accompanied by emesis. No alterations in the configuration of the Lead II electrocardiogram (ECG) were observed. Thus, the cardiovascular changes observed were considered of minimal physiological importance, as the events were short-lived compared to the long duration of activity of azithromycin in dogs.

Pharmacokinetics and 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). The efficacy of azithromycin as a single dose or simulated sustained release formulation compared to multiple day regimens was studied in animal infection models (murine acute infection (intraperitoneal) model challenged with *Streptococcus pneumoniae* and *Streptococcus pyogenes*, murine lung infection model challenged with *Streptococcus pneumoniae*, murine thigh infection model challenged with *Streptococcus pyogenes*). Results from these animal infection models indicate that a single dose is equally or more effective than the same dose divided over multiple days.

Human Pharmacology

Pharmacodynamics
The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with Zmax SR **(**see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).**

Pharmacokinetics
(See **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Comparison of the pharmacokinetics of Zmax SR sustained-release granules for oral suspension and azithromycin immediate-release oral formulations and regimens
The bioavailability of a single 2 g dose of Zmax SR relative to a single 2 g dose of azithromycin immediate-release (powder for oral suspension) was 83%; peak serum concentration was lower by 57% and was achieved approximately 2.5 hours later following Zmax SR administration. Thus, 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).

Serum pharmacokinetic parameters for a single 2 g Zmax SR dose, from a study in healthy adult subjects, are shown in Table 21 alongside data for 3- and 5-day azithromycin immediate-release tablet regimens from a separate clinical study in healthy adult subjects. The data from these two

studies suggest that higher peak serum concentration (C_{max}) and greater systemic exposure (AUC) of azithromycin are achieved on the day of dosing following a single 2 g dose of azithromycin sustained-release granules compared to dosing with conventional immediate-release formulations (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). Consequently, due to a different pharmacokinetic profile, Zmax SR is not bioequivalent to and is not interchangeable with azithromycin immediate-release tablet 3-day or 5-day dosing regimens.

Table 21: Mean (SD) Serum Pharmacokinetic Parameters for Azithromycin on Day 1 Following the Administration of a Single Dose of 2 g Zmax SR or 1.5 g of Azithromycin Immediate-release 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[1]	**Azithromycin Regimen**		
	Zmax SR [N=41][2]	**3-day[3] [N=12]**	**5-day[3] [N=12]**
C_{max} (µg/mL)	0.821 (0.281)	0.441 (0.223)	0.434 (0.202)
T_{max}[4] (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)
$AUC_{0-\infty}$[5] (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)

N = no. of subjects studied
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
[1] Zmax SR data and data for azithromycin immediate-release 3-day and 5-day regimens were obtained from two separate pharmacokinetic studies
[2] N = 21 for $AUC_{0-\infty}$ and $t_{1/2}$
[3] C_{max}, T_{max} and AUC_{0-24} values for Day 1 only
[4] Median (range)
[5] Total AUC for the 1-day, 3-day and 5-day regimens

MICROBIOLOGY

Mechanism of Action
Azithromycin acts by binding to the 23s rRNA of the 50S ribosomal subunit of susceptible microorganisms. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Mechanisms of Resistance
The erm gene encodes a 23S rRNA methyltransferase that adds methyl groups to the ribosomal RNA, and as a result disrupts the binding of azithromycin, which interferes with the antimicrobial efficacy of azithromycin. *Mef* encodes an efflux pump that decreases intracellular azithromycin.

The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

Cross-Resistance
Azithromycin demonstrates cross-resistance with erythromycin-resistant gram-positive strains. Most strains of methicillin-resistant staphylococci and penicillin-resistant *S. pneumoniae* are resistant to azithromycin. Beta-lactamase production has not been shown to produce an effect on the activity of azithromycin.

Development of Resistance
Resistant *S. pneumoniae* strains have been selected *in vitro* after between 25-50 passages in sub inhibitory concentrations of macrolides. The resistance that develops in vitro in *S. pneumoniae* strains after passage results from a mutation in 23S rRNA, specifically in nucleotides 2057-2059 or 2611 in domain V, or as a consequence of mutations in ribosomal proteins L4 or L22. The predictive value of these in vitro results to the development of resistant clinical isolates has not been established.

Interactions with Other Antimicrobials
In vitro interactions between azithromycin and other antimicrobials commonly used for the treatment of respiratory tract infections have not been studied.

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** section.

Aerobic and facultative Gram-positive microorganisms
Streptococcus pneumonia

NOTE: Erythromycin- and penicillin-resistant Gram-positive isolates may demonstrate crossresistance 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 pneumonia

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 notbeen 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 communityacquired 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[22,24] (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 following table.

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[23,24] 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 following table.

Table 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 following table. 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 Acceptable Quality Control Ranges for Azithromycin

QC Strain	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (zone diameters in mm)
Haemophilus influenza ATCC49247	1.0 – 4.0	13 – 21
Streptococcus pneumonia ATCC 49619	0.06 – 0.25	19 – 25

TOXICOLOGY

All nonclinical studies, except for a few exploratory studies, used an immediate release azithromycin formulation.

Table 26 Acute Toxicity: Mice and Rats

Oral and Intraperitoneal Toxicity Studies in Mice and Rats			
Route	**Species**	**Sex**	**LD_{50}** (mg of free base/kg)
Oral	Mice	M	3000
Oral	Mice	F	4000
Oral	Rats	M	>2000
Oral	Rats	F	>2000
Oral	Neonatal Rats	M	>1000
Oral	Neonatal Rats	F	>1000
I/P	Mice	M	>400 <600
I/P	Mice	F	NA
I/P	Rats	M	>500 <900
I/P	Rats	F	NA*

* NA = not available

Table 27: Acute Toxicity Studies in Dogs

Route/Dose	Species	Sex	LD_{50}/Observations
Oral 100, 300 mg/kg azithromycin in gelatin capsule	Dog Age 6 months	2M 2F	>300 mg/kg The single-dose toxicity of azithromycln was evaluated in 6-month old beagle dogs (1/sex/dose) given an oral dose of 100 or 300 mg/kg. The animals were observed daily for clinlcal signs and mortality during a 14-day observation period. Body weights were recorded weekly. Hematology and serum chemistry measurements were performed before dosing, at 6 and 24 hours postdose and on Day 15. No deaths occurred during the 14-day observation period. In all dogs, vomiting began to appear within 20 minutes postdose, and following this sign, loose and/or watery stool was observed sporadically in male and female dogs given 300 mg/kg and in the female dog given 100 mg/kg. All dogs seemed to be normal approximately 6 hours postdose. Body weights increased normally for all dogs. There were no drug-related changes in hematology or serum chemistry parameters.
Oral 100, 300 mg/kg azithromycin in gelatin capsule	Neonatal Dog Age 21 days	2M 2F	>300 mg/kg The single-dose toxicity of azithromycin was evaluated in 21-day old beagle dogs (1/sex/dose) given an oral dose of 100 or 300 mg/kg. All pups were separated from their dams and housed individually. The animals were observed daily for clinical signs and mortality during a 14-day observation period. Body weights were recorded weekly. Hematology and serum chemistry measurements were performed before dosing, at 6 and 24 hours postdose and on Day 15. No deaths occurred during the 14-day observation period. In all dogs, dry vomiting began to appear within 20 minutes postdose, and following this sign, loose to watery stool was observed sporadically. Most dogs seemed to be normal approximately 4 hours postdose. Body weights increased normally for all dogs. There were no drug-related changes in hematology or serum chemistry parameters. In conclusion, no serious toxicity was observed at 300 mg/kg. The single dose oral toxicity of azithromycin in neonatal dogs appeared to be very slight and generally similar to that in adult dogs.

Adult animals (Mice and Rats)
Most mortality occurred within 1 to 2 hours and generally within 48 hours of dosing. At higher doses in mice, symptomatology included clonic convulsive activity, loss of righting reflex, gasping, and blanching prior to death.

Gross necropsy of mice or rats which died following intraperitoneal doses revealed yellowish or clear fluid in the pleural and peritoneal cavities. At necropsy on Day 14 there were no gross pathological changes in either species aside from a few liver adhesions to the diaphragm.

Neonatal animals (Rats)
No deaths or remarkable clinical signs were observed in any animal during the 14-day observation period. All animals gained weight during the trial. At sacrifice on Day 15, no remarkable gross findings were observed in any surviving rat.

Subacute Toxicity
Phospholipidosis has been observed in animals administered high doses of azithromycin. This effect is reversible after cessation of azithromycin treatment in animals. Despite light- and electron-microscopic correlates of phospholipidosis (myeloid figures and intracytoplasmic vacuoles) in many organs, only in dogs receiving 100 mg/kg/day for at least 2 months have kidney, liver, and gallbladder toxicity been seen. This dose in dogs results in tissue levels greater than 5000 µg/g. Minimal increases in serum transaminase levels in rats and dogs at 20mg/kg/day and above have also been seen, but are consistent with findings previously reported for erythromycin. Special attention has been given to the effects of phospholipidosis in the retina, including studies of azithromycin, 30 and 100 mg/kg/day for 6 and 2 months, respectively, in dogs. No evidence was elicited of deleterious effects of azithromycin on vision, pupillary reflex or retinal vasculature. The detection of phospholipidosis in the choroid plexus and dorsal root ganglion was not associated with degenerative or functional changes.

Carcinogenicity
Long-term toxicology studies to assess the carcinogenicity potential have not been conducted.

Genetic Toxicology
Azithromycin was examined in several genetic toxicology assays for induction of gene mutations in microbial and mammalian cells and for chromosomal mutations *in vivo* and *in vitro*. No evidence of genotoxic activity was observed in any of the following assays:

Microbial Assay: Tests were conducted on strains TA 1535, TA 1537, TA 98 and TA 100 of *Salmonella typhimurium* at concentrations up to 2 µg/plate (higher concentrations cause bacterial growth inhibition) in the presence and absence of Aroclor-stimulated rat or mouse liver microsomal enzymes. Additional tests were performed using the same strains of *Salmonella* spp. and urine from mice treated orally with up to 200 mg/kg of azithromycin.

Mammalian Cell Gene Mutation Assay: The L5178Y Mouse Lymphoma Assay for gene mutations at the thymidine kinase locus was conducted at concentrations of 36-360 µg/mL to cytotoxicity in the presence and absence of rat liver microsomal enzymes.

***In Vitro* Cytogenetics Assay:** The clastogenic activity of azithromycin was evaluated in human lymphocytes *in vitro* exposed up to toxic concentrations of 40 μg/mL in the presence and 7.5 μg/mL in the absence of rat liver microsomal enzymes.

***In Vivo* Cytogenetics Assay:** Azithromycin was examined for clastogenic activity in the bone marrow cells of male and female CD-1 mice treated orally at 200 mg/kg, and sacrificed at 6, 24 or 48 hours post-treatment.

Antigenicity Studies

Azithromycin was tested for the induction of a systemic anaphylaxis reaction in guinea pigs and in rabbits. Azithromycin did not have antigenic potential under the conditions used in the studies.

Table 28: Summary of Subacute and Chronic Toxicity Studies

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
ORAL in Adult Animals					
Rat (Adult)	Oral (gavage)	50 100 200	10/sex	36 days + reversibility	Cecal enlargement was dose-related. Elevated serum hepatic enzyme (SGPT, SGOT, SDH, and 5'NT) levels were dose- and time-related at high and mid levels; marginal SGPT elevations only were observed in 2 rats at the low dose. Histological examination of tissues from 6/sex of mid- and high-dose and 10/sex of low-dose rats revealed evidence of phospholipidosis in bile ducts (8/20, 12/12, 12/12 low-, mid-, and high-dose rats, respectively) and hepatocytes (10/12 high dose only), fatty change (4/20, 10/12, 11/12 in low-, mid-, and high-doses, respectively), and necrosis of single hepatocytes (6/12 and 11/12, respectively, in mid- and high-dose only). Phospholipidosis also occurred in high-dose rats in the tubular cells of the renal medulla 12/12, spleen 2/12, thymus 2/12, and choroid plexus 10/12; 3/12 rats at 100 mg/kg and 10/12 at 200 mg/kg exhibited mesenteric sinusoidal lymph node phospholipidosis. Phospholipidosis is characterized by accumulation of drug-lipid complexes in lysosomes where they form ultramicroscopic lamellated structures typified at the microscopic level by vacuolated macrophage or tissue cells. The remaining animals (4/sex in control, mid- and high-dose groups) were sacrificed 20 days after termination of treatment. Phospholipidosis was still observable in the renal tubules of 7/8 high dose animals and in 1/8 mid-dose animals and in the bile duct of 1/8 high-dose animals. Fatty change was still detectable in livers of 5/8 and 6/8 mid- and high-dose. animals, respectively. Megaceca also regressed following drug withdrawal.

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Dog (Adult)	Oral (gavage)	25 50 100	3/sex	36 days	Transaminase levels (SGPT, SGOT) were elevated in a dose-related pattern at the 2 higher doses. ALP (alkaline phosphatase), gamma-GTP, and SDH elevations occurred only at the high dose. Histological examination of tissues revealed the presence of phospholipidosis in all treated animals. It occurred in six or more organs in all 100 mg/kg/day animals. These included kidney, liver, spleen, gallbladder, thymus, mesenteric lymph node, esophagus, uterus and cervix as well as lymphatic nodules of gastrointestinal tissues. At the low dose of 25 mg/kg phospholipidosis was confined to the spleen, gallbladder, thymus, mesenteric lymph node and the lymphatic nodules of the ileum and colon.
Rat (Adult)	Oral (gavage)	40 (10 days on 10 days off) 0 continuous 10 " 20 "	15/sex 25/sex	 190-193 days + reversibility	Sporadic mild elevations in SGOT and SGPT occurred in all dose groups during and after the treatment period. There was no evidence of phospholipidosis.
Dog (Adult)	Oral (gavage)	40 (10 days on 10 days off) 0 10 20	4/sex 4/sex + 2/sex + 2/sex	190 days + reversibility 1 month 2 months	Sporadic elevations in SGPT levels occurred at 20 and 40 mg/kg only. Phospholipidosis, was minimal to mild in the kidney, liver, gallbladder, spleen, mesenteric lymph node, esophagus and prostate of almost all 40 and 20 mg/kg dogs. In dogs dosed for 6 months at 20 mg/kg/day complete reversibility of phospholipidosis of the kidney, liver, and spleen with minimal phospholipidosis still present in the gallbladder and esophagus was demonstrated in the animals sacrificed 2 months after the end of treatment.

Dog (Adult)	Oral (gavage)	30, 100	6/sex	6 months 2 months + reversibility	Selected animals were sacrificed at end of treatment; sacrifices (1/sex/dose level) were also performed 1 month (100 mg/kg), 2 months (30 mg/kg) and 4 months (100 mg/kg) post-treatment. Necropsies of the remaining animals were performed 7 months (30 mg/kg) and 11 months (100 mg/kg) post treatment. Drug treatment of high dose dogs was terminated at 2 months (61 doses) due to intolerance. Serum chemistry changes including substantial increases in liver enzymes (SGPT, SGOT, ALP, SDH, gamma-GPT) and BUN as well as mild decreases in erythrocytic parameters (RBC, Hb, Hct) and the presence of atypical eosinophil and vacuolated lymphocytes returned to normal range within 2 months of withdrawal from treatment. The low dose was well tolerated. Dose-related effects on tapetum lucidum reflectivity ranged from trace (low dose) to moderate (high dose) decoloration, dulled reflectivity and loss of the tapetum-choroid junctional zone. Following cessation of treatment, most animals showed improvements in these ocular changes. Normal junctional tissue was evident in high dose animals 4 months after withdrawal. At no time was there ophthalmoscopic evidence of an effect on vision. Histological examination at the end of treatment showed phospholipidosis. In the eye it included the tapetum, neurons of the retinal ganglion cell, inner nuclear, inner and outer plexiform layers, and mural pericytes of the superficial retinal vasculature. The rod and cone segments and retinal pigmented epithelium were generally spared. Also affected were dorsal root ganglion, liver, gallbladder, kidneys, spleen and pancreas and, at the high dose only gastrointestinal tract, mesenteric lymph nodes, thymus, aorta, heart, salivary gland and lung. Dose-related degenerative changes were observed only in the liver (focal necrosis of hepatocytes and bile duct epithelium), gallbladder (hyperplasia) and kidneys

					(glomerulonephrosis). All of the above effects, with the exception of those on the retina, dorsal root ganglion and gallbladder which all abated in severity, were completely reversible on drug withdrawal from both low and high dose animals. In general, these changes were consistent with the relative drug/tissue concentrations attained and their decline following withdrawal. Biochemical measurements of spleen, liver, kidney and retinal phospholipids of animals treated with 30 mg/kg drug for 6 months showed a difference from control only for the spleen, the tissue with the highest drug concentration. This experiment demonstrates that drug-induced phospholipidosis, although dose-dependent in tissue distribution and intensity, does not represent a toxic end point per se but is responsible for the cumulative tissue deposition of azithromycin.
Dog (Adult)	Oral (gavage)	30 100	6/sex	6 months + reversibility	Intermittent dosing: (10 days on, 10 days off drug) for: 5 months (100 mg), 6 months (30 mg). This experiment demonstrates that intermittent administration (to mimic a hypothetical clinical dose regime) produced less phospholipidosis than azithromycin administered continuously.

ORAL in Neonatal Animals Oral Subacute/Neonatal RATS					
Rat (Neonatal 4 days)	Oral (gavage)	10 20 40	10/sex 10/sex	18 days (Day 4 to Day 21 postpartum) 10 days (Day 4 to Day 13 postpartum)	No treatment-related clinical signs were observed. Males given the dose of 20 mg/kg weighed significantly more than the vehicle controls on Day 7 and from Day 13 to sacrifice on Day 22 postpartum. A slight increase in the incidence and prominence of periportal vacuolization appeared treatment related. However, the vacuolization observed in the treated animals was qualitatively no different from that seen in the vehicle-treated controls. There was no histologic evidence of phospholipidosis.
Rat (Neonatal 4 days)	Oral (gavage)	40 60 80	10/sex	18 days (Day 4 to Day 21 postpartum)	The purpose of this study was to determine the dose at which there was evidence of phospholipidosis. There were no clinical signs of toxicity or effects on body weight. The administration of azithromycin to neonatal rats by gavage for 18 days produced clear evidence of phospholipidosis of bile duct epithelium in a dose related manner in males and females at all dose levels. Hepatocellular vacuolation, which may also be a manifestation of phospolipidosis, was apparent in most males given azithromycin but was not observed in the vehicle-treated males. However, in the female rats, hepatocellular vacuolation was seen in the azithromycin treated animals as well as in those given the vehicle, suggesting that it does not represent phospholipidosis in this study.
Rat (Neonatal 4 days)	Oral (gavage)	100 120 140	10/sex	18 days (Day 4 to Day 21 postpartum)	In the previous study, evidence of dose-related phospholipidosis was observed in only the bile duct epithelium of males and females at each dose. The purpose of the present study was to attempt to identify doses at which phospholipidosis is produced in more than one organ and/or tissue. There were no clinical signs of toxicity.

					The administration of azithromycin to neonatal rats by gavage for 18 days produced clear evidence of phospholipidosis of bile duct epithelium in all males and females at each dose. The hepatocellular vacuolation apparent in some animals from each dose was above that seen in the vehicle-treated animals and also appeared to be a manifestation of phospholipidosis. In addition, myocardial phospholipidosis was evident in a majority of high and intermediate dose males and females and in a single low dose male.
Rat (Neonatal 4 days)	Oral (gavage)	30 70 140	20/sex 10/sex 10/sex 20/sex	18 days (Day 4 to Day 21 postpartum) and 30 Day Reversibility Period for 10/sex in groups treated by 0 and 140 mg/kg.	The purpose of this study was to determine whether phospholipidosis, previously diagnosed by light and electron microscopic examination in neonatal animals treated with azithromycin could be confirmed biochemically by measurement of tissue phospholipid levels. All low and intermediate dose animals, plus one half of the high dose and vehicle-treated control animals were sacrificed on Day 22 postpartum. The remaining rats were sacrificed on Day 52 postpartum after a 30-day reversibility period. Assays for drug in serum, liver and brain samples obtained from pups sacrificed 24 hours after the last dose revealed that the azithromycin concentrations increased with dose and were highest in the liver, lower in the brain and lowest in serum. The concentration of azithromycin in the serum, liver and brain had declined substantially when next measured 31 days after cessation of dosing of the high dose group. Azithromycin was still detectable in the liver and brain, but serum concentrations were generally below the limit of detection. Despite the high azithromycin concentrations detected in both the liver and brain at 24 hours after the last dose, the phospholipid levels in these tissues from rats given azithromycin were no greater than those of the vehicle-treated controls at both the end of the dosing period and after the one month reversibility period. The administration of azithromycin to neonatal Long-Evans rats for 18 days produced light

					microscopic evidence (vacuolation) of phospholipidosis in bile duct epithelium, hepatocyte cytoplasm, cardiac muscle, smooth muscle of the duodenum and uterus and in the choroid plexus. These changes, seen in the rats sacrificed on the day after the last dose (i.e., Day 22 postpartum), were evident primarily in high dose animals, and, except for the bile ducts, at a much reduced incidence in intermediate dose animals. The only histological evidence of phospholipidosis at the low dose was in the bile ducts of a single male. No light microscopic evidence of phospholipidosis was visible in the high dose animals examined following a 30 day reversibility period. It is concluded that, in spite of histological indications of phospholipidosis and high tissue concentrations of azithromycin, there was no biochemical evidence of phospholipid accumulation in affected organs (brain and liver).

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Oral Subacute/Neonatal DOGS					
Dog (Neonatal 3-5 days)	Oral (gavage)	10 30 60	3/sex	5 weeks	Pups were removed from their mothers 2 hrs prior to dosing and then returned to their litters immediately thereafter. They were observed daily for developmental landmarks (eye opening, upper canine tooth eruption, ear opening and when pup "leaves the pack"). Body weights were obtained daily. Blood samples for clinical pathology profiles were drawn pretest and prior to dosing on Days 14 and Days 28 or 30. Blood samples for serum drug level determinations were obtained on Days 2, 22 or 24. Ophthalmological examinations were conducted at termination of the treatment period. All dogs were anesthetized and exsanguinated on Days 35 or 37 for necropsy. Selected organs were weighed. Tissues were taken for assays of drug concentrations and for histopathological evaluation. With the exception of a possible lag in body weight gain of female pups, there were no treatment-related effects on developmental landmarks, hematology, clinical chemistry, ophthalmological findings nor upon organ weights. Mean blood concentrations of azithromycin, generally related to dose, especially at 10 and 30 mg/kg, were somewhat higher on Day 24 than on Day 2. Evidence of phospholipidosis, previously observed in other azithromycin animal studies, was detected microscopically as swollen vacuolated cells due to myelin figures, i.e., large lysosomes containing aggregates of undigested membranes. As in adult dogs, the dose related phospholipidosis was seen in selected tissues. The effects were minimal to mild at 10 mg/kg. Phospholipidosis was not observed in the brain or in liver. Other dose related lesions were swelling and vacuolation of cells of the tapetum lucidum of the eye due to tapetal rodlet swelling and dissolution, and degeneration and necrosis of epithelial cells lining the gallbladder. The latter occurred only in mid- and high dose animals. Twenty-four (24) hrs after the last dose, tissue levels of drug were much higher than in serum with mean concentrations in the order of serum=brain <eye <kidney <liver=spleen.
Dog	Oral	10	4/sex	11 days	Two/sex/group were necropsied at the end of the dosing period.

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
(Neonatal 3-5 days)	(gavage)	30 60			The remaining animals were maintained for an additional 1 month dose free period prior to being necropsied. There were no treatment-related effects on developmental landmarks, body weight, hematology, clinical chemistry or organ weights. Evidence of phospholipidosis (PL) was observed microscopically at the end of the treatment period in the spleen of dogs given 30 or 60 mg/kg/day and at all dose levels in the neurons of the retina and sympathetic ganglion. The incidence and severity was generally dose related. There was no evidence of PL in the liver or brain. At the end of the 1 month drug free period, the retina and sympathetic ganglion of animals given 10 mg/kg/day had no evidence of PL. PL was still evident, although at a reduced incidence and severity, at dose levels of 30 and 60 mg/kg/day. Following a 1 month drug free period, tissue concentrations of azithromycin in the liver, kidney and spleen were approximately 1.5% of those observed at the end of dosing, indicating elimination of azithromycin from these organs. The extent of elimination from the retina could not be accurately quantitated in this study. However, the reversibility of the PL in the retina would suggest that elimination was occurring.
Dog (Neonatal 3-5 days) and 25 days	Oral (gavage)	10 60	4/sex (3-5 days) 2/sex (25 days)	11 days and 30 Day Recovery Period	The purpose of this study was to further characterize the absorption and elimination of azithromycin from the choroid/retina of neonatal beagle dogs. At the end of the treatment period, 2/sex from the 3-5 day old dogs and all of the older dogs were necropsied. The remaining dogs were maintained for a 1 month dose free period to further document the elimination of azithromycin from the retina. There were no treatment-related effects on developmental landmarks, body weight, hematology or clinical chemistry. Mean whole blood concentrations of azithromycin were dose related and increased between Days 2 and 11. Liver and choroid/retina of all animals contained dose related concentrations of azithromycin. In general, these were higher in the dogs 3-5 days of age. Concentrations in the choroid/retina were less than those in the previous study (WEL 90-252) and were within historical predictions, while liver concentrations

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
					were similar to previous studies and within expectations. At the end of the one month treatment free period, the tissue concentrations of azithromycin had decreased and were within expected levels.
INTRAVENOUS In Adult Animals					
Rat (Adult)	IV	10 20 20 (every other day)	10/sex	14 days	No untoward effects.
Dog (Adult)	IV	10 20 10 (every other day)	3/sex	14 days	No untoward effects with 3 exceptions in the former two groups. Sporadic elevated serum liver enzyme levels in 2/3 females at the high-dose level; serum alkaline phosphatase levels gradually increased in one 10 mg/kg/day female; phospholipidosis by accumulation of vacuolated macrophages within the lamina propria of the gallbladder and germinal centers of the mesenteric lymph nodes of dogs receiving 20 mg/kg/day.
Rat (Adult)	IV	5 10 20	10/sex	1 month (36-39 days)	Minimal phospholipidosis in the epithelium of the large bile ducts was observed in all high dose and in 13/20 mid-dose animals and at the injection site in the tail of one high dose rat.
Dog (Adult)	IV	5 10 20	3/sex	1 month (36 days)	Slight SGPT elevations occurred in 4/6 high dose animals together with a slight increase in serum alkaline phosphatase activity. Slight SGPT elevations were also noted in 1 low dose and 1 control animal. Histological changes at the high dose were limited to the presence of phospholipidosis. One 10 mg/kg dog also showed minimal phospholipidosis in the large bile ducts. There was no evidence of phospholipidosis at 5 mg/kg/day.

SPECIAL EXPLORATORY TOXICOLOGY					
Rat	Oral (gavage)	10 0 40 200 chloroquine: 25	5/sex 10/sex 10/sex	5 days	Animals (5/sex/group) from the 40 and 200 mg/kg azithromycin and chloroquine groups were removed from treatment for 23 days to study the effect of reversibility. No elevations in tissue phospholipid levels or hepatic necrosis were seen at any dose. Myelin figures were seen in liver, bile ducts and retinal pigmented epithelium. One chloroquine animal had a few myelin figures in retinal ganglion cells.
Rat	Oral (gavage)	0 200	10/sex	42 days	Phospholipid levels were significantly elevated above control in liver, kidney, spleen and lymphocytes ($p<.05$).
Dog	Oral (gavage)	0 azithromycin: 10 40 200 chloroquine: 15	1/sex 2/sex 1/sex	5 days	The livers of the 200 mg/kg azithromycin animals showed the highest drug concentration (>4000 µg/g) of any tissues in the series of experiments. This was accompanied by a 38% elevation in hepatic phospholipids, multifocal hepatic necrosis and marked accumulation of myelin figures in both hepatocytes and bile duct epithelium. Myelin figures were also seen in the liver at 40 mg/kg azithromycin (drug concentration = 817 µg/g) and with chloroquine but not with 10 mg/kg azithromycin. Azithromycin caused the formation of myelin figures in retinal ganglion cells from equivocal at 10 mg/kg to moderate at 200 mg/kg. The effect was less severe than chloroquine, 15 mg/kg, which caused a marked degree of myelin figure formation in retinal ganglion cells.
Dog	Oral (gavage)	0 azithromycin: 30 erythromycin: 400	1/sex 2/sex 2/sex	5 days	Reversal periods of 22 and 36 days were included for those animals treated with azithromycin (1/sex/period). Tissue phospholipids were elevated in the livers of erythromycin animals only. Myelin figures or enlarged lysosomes were seen to a minimal extent in the retinal ganglion cells, liver and choroid plexus of azithromycin animals and in the liver of erythromycin dogs. The drug concentrations were markedly reduced at the end of the reversal periods and no myelin figures remained in the liver or choroid plexus.
Dog	Oral (gavage)	erythromycin: 400	2/sex	5 days	Dogs were necropsied immediately after the last dose. A few myelin figures were seen in the retinal ganglion cells of one animal.
Dogs Atapetal Tapetal	Oral	azithromycin: 0 100 0	 3 (2M,1F) 3 (2F, 1M) 3 (2M, 1F)	35-36 days	Ophthalmoscopic examinations revealed no changes in the atapetal dogs while tapetal decoloration, dulling of normal reflectivity and loss of color difference at the tapetal junctional zone was observed in the tapetal dogs. Light and/or electron microscopic examination of the retinas of both tapetal and atapetal dogs revealed signs of phospholipidosis in ganglion

		100	3 (2F, 1M)		cells, the inner nuclear layer and inner and outer plexiform layers. Other changes observed in both tapetal and atapetal dogs are comparable to those observed in previous studies at the same dose.
SPECIAL TOXICOLOGY					
Rabbit	IM	0 200 400 (single dose)	3/sex	3 days and 7 days (observation)	Signs indicative of considerable pain upon injection were produced by both volumes of the azithromycin test solution. These changes subsided within 2 to 4 days of dosing. At sacrifice 3 or 7 days post dose, substantial changes were observed in the subcutaneous tissue and the muscle. At 7 days, these changes were much smaller at 1 mL than they were at 2 mL dose.
Rabbit	IV	0 10 (single dose)	3/sex	1 and 2 days (observation)	There were no obvious signs of pain or discomfort upon injection of normal saline with or without azithromycin in the marginal ear vein of six albino rabbits. The gross and microscopic tissue changes indicated that this solution was only minimally irritating.

Table 29: Reproductive Studies

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
FERTILITY AND REPRODUCTIVE PERFORMANCE					
Rat	Oral (gavage)	0 10 20	15M/dose 30F/dose	64-66 days	In females the drug given for 14 days prior to and during cohabitation (1M:2F) and to all females throughout gestation, parturition, and lactation until Day 21 postpartum resulted in a lower pregnancy rate of 63% for the high-dose group compared to 83% and 87% for the low-dose and control groups, respectively.
Rat	Oral (gavage)	30	15M/dose 15F/dose	64-66 days	In females the drug was given 15 days prior to mating and continuously throughout the 3 weeks of mating. A lower pregnancy rate for the drug-treated group (67% compared to 100% in the concurrent control group) was also found here.
FERTILITY EFFECT ON MALES OR FEMALES					
Rat	Oral	0 30	40M/dose 80F/dose (Fertile animals only)	64 days (males) See text (females)	In females the drug was given 15 days prior to mating and continuously throughout the 3 weeks of mating. Groups were mated as follows: Group 1: Drug treated males mated with drug treated females. Group 2: Drug treated males mated with control females. Group 3: Control males mated with drug treated females. Group 4: Control males mated with control females. Pregnancy rates were: Group 1, 84%; Group 2, 89%; Group 3, 90%; and Group 4, 96%. The pregnancy rate was statistically significantly lower than control when the males and females were both treated with azithromycin (Group 1). The pregnancy rate of 84% in that group was, however, higher than in the two previous studies and well within our historical control range. The nearly identical pregnancy rates in Groups 2 and 3 (89% and 90%, respectively) do not indicate an effect on either sex alone as being the cause for the apparently reduced pregnancy rate.

Table 30: Fetotoxicity Teratology

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Mice	Oral (gavage)	0 10 20 40	20	Days 6-13 Of gestation	Azithromycin was not toxic to the dams or their fetuses nor was there evidence of teratogenicity.
Mice	Oral (gavage)	0 50 100 200	20	Days 6-13 Of gestation	Azithromycin was not toxic to the dams or their fetuses nor was there evidence of teratogenicity. Azithromycin was assayed in maternal plasma, amniotic fluid and fetal homogenates on day 13 of gestation in mice after 8 consecutive daily doses of 200 mg/kg. Azithromycin concentrations in fetal homogenate from 3 dams sampled at 6 hours postdose were approximately 9 fold higher (mean 18.4 ± 3.1 µg/g wet weight) than those in maternal plasma at 1 hour postdose (mean 2.13 ± 0.81 µg/mL). Concentrations in amniotic fluid measured at 6 hours postdose (mean 1.64 ± 0.23 µg/mL) were lower than those measured in maternal plasma at 1 hours postdose. At 6 hours postdose the mean concentration in plasma was 1.18 ± 0.18 µg/mL.
Rat	Oral (gavage)	0 10 20 40	20	Days 6-15 Of gestation	Azithromycin was not toxic to the dams or to their fetuses nor was there evidence of teratogenicity.
Rat	Oral (gavage)	0 50 100 200	20	Days 6-15 Of gestation	Azithromycin was not toxic to the dams or fetuses. Dose levels of 100 and 200 mg/kg induced slight delays in maternal body weight gain and in ossification process of fetuses. The compound was neither embryotoxic nor teratogenic at the three dose levels. Azithromycin was assayed in maternal plasma, amniotic fluid and fetal homogenates on day 15 of gestation in rats after 10 consecutive daily doses of 200 mg/kg. Azithromycin concentrations in fetal homogenate from 5 dams sampled at 6 hours postdose were approximately 5 fold higher (mean 10.4 ± 1.8 µg/g wet weight) than those in maternal plasma at 3 hours postdose (mean 1.87 ± 0.71 µg/mL). Concentrations in amniotic fluid at 6 hours postdose (mean 1.14 ± 0.32 µg/mL) were lower than those in maternal plasma at 6 hours post dose (mean 1.43 ± 0.18 µg/mL). The 50 mg/kg dose can be considered as the no-observable-effect-level.

PERI/POSTNATAL					
Rat	Oral (gavage)	10 20 40	15	See text	Azithromycin administered from day 15 p.i. through end of gestation and for the whole period of lactation was not toxic to the dams. The pre- and post-natal development of pups was not affected.
Rat	Oral (gavage)	0 50 100 200	20	See text	Azithromycin administered from day 15 p.i. through end of gestation and for the whole period of lactation was not toxic to the dams. A slight reduction in weight gain of pups and their post-natal development was related to the litter size and not to drug administration. No drug-related external or visceral anomalies were observed.

Table 31: Neonatal Studies

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Rat	Oral	0 10 20 40	10/sex	18 days (4-21 days postpartum) 10 days (4-13 days postpartum)	There was no evidence of toxicity and no observation of phospholipidosis.
Rat	Oral (gavage)	0 40 60 80	5/sex	18 days (4-21 days postpartum)	Azithromycin induced dose-related microscopic evidence of phospholipidosis only in the bile duct epithelium of both males and females.
Rat	Oral (gavage)	0 100 120 140	5/sex	18 days (4-21 days postpartum)	Azithromycin in addition to affecting the gallbladder epithelium of all animals, induced microscopic evidence of myocardial phospholipidosis in a majority of high and intermediate dose pups as well as in a single low dose male. Hepatocellular vacuolation, apparent in some animals at each dose level, more pronounced than that of vehicle treated rats, appeared to be a manifestation of drug-induced phospholipidosis.
Rat	Oral (gavage)	30700140	10/sex 20/sex	18 days (4-21 days postpartum) + reversibility	Animals (treated and controls) exhibited normal growth and development. All animals at each dose were systemically exposed to azithromycin, as evidenced by the concentration of the compound in the rats' serum, liver and brain at 24 hours after the last dose. At this time point, the concentration of azithromycin in brain and especially liver greatly exceeded that in serum. At 31 days after the last dose, azithromycin is still detectable in the liver and brain of all rats in the high dose (140 mg/kg/day) reversibility group, but the serum concentrations were generally below the limit of detection (<0.01 µg/mL) and the concentration of azithromycin in the liver, brain, and serum was substantially lower than that found one day after the last dose. In spite of the high azithromycin concentrations detected in both the liver and brain at 24 hours after the last dose, the phospholipid levels in these tissues from rats given azithromycin were generally no greater than those of the vehicle-treated controls at both the end of the dosing period and after the one-month reversibility period. In the animals sacrificed the day after the last dose, i.e. on Day 22 postpartum, light microscopic evidence of phospholipidosis was apparent in bile duct epithelium, hepatocyte cytoplasm, cardiac muscle, smooth muscle of the duodenum and uterus, and in the choroid plexus. The only evidence of phospholipidosis at the low dose was in the bile ducts of a single male. No light microscopic evidence of phospholipidosis remained in high dose animals examined after a 30-day reversibility period.

Table 32: Additional Studies

SPECIES	ROUTE	DOSE mg/kg/day	ANIMALS PER DOSE LEVEL	DURATION	FINDINGS
Dog (Neonatal 3-5 days)	Oral (gavage)	0 10 30 60	3/sex	5 weeks	Pups were removed from their mothers 2 hrs prior to dosing and then returned to their litters immediately thereafter. They were observed daily for developmental landmarks (eye opening, upper canine tooth eruption, ear opening and when pup "leaves the pack"). Body weights were obtained daily. Blood samples for clinical pathology profiles were drawn pretest and prior to dosing on Days 14 and Days 28 or 30. Blood samples for serum drug level determinations were obtained on Days 2, 22 or 24. Ophthalmological examinations were conducted at termination of the treatment period. All dogs were anesthetized and exsanguinated on Days 35 or 37 for necropsy. Selected organs were weighed. Tissues were taken for assays of drug concentrations and for histopathological evaluation. With the exception of a possible lag in body weight gain of female pups, there were no treatment-related effects on developmental landmarks, hematology, clinical chemistry, ophthalmological findings nor upon organ weights. Mean blood concentrations of azithromycin, generally related to dose, especially at 10 and 30 mg/kg, were somewhat higher on Day 24 than on Day 2. Phospholipidosis (PL) was diagnosed in the kidneys, gallbladder, lymphoid system (spleen, lymph nodes), smooth muscle of the gastrointestinal tract and choroid plexus at 60 mg/kg; gallbladder, lymphoid system, smooth muscle and choroid plexus at 30 mg/kg; and spleen at 10 mg/kg. The diagnosis of PL was based on the presence of swollen, markedly vacuolated cells that have been shown in previous studies to contain myelin figures (large lysosomes containing aggregates of undigested membranes) when examined with the electron microscope. The PL was generally mild to moderate at 60 mg/kg and had a decreased severity at lower doses. In the retina, PL was seen most prominently in ganglion cells and occasional cells along the outer margin of the inner nuclear layer. Cells of the inner plexiform, inner nuclear and outer nuclear layers were less affected, and the rods and cones were spared. The neurons in sympathetic ganglia had moderate PL similar to that seen in the retina. In both the retina and sympathetic ganglion, PL was seen at all doses at a severity generally ranging from moderate to marked at 60 mg/kg to minimal to mild at 10 mg/kg. Other dose related lesions were swelling and vacuolation of cells of the tapetum lucidum of the eye, interpreted based on previous studies as being due to tapetal rodlet swelling and dissolution, and degeneration and necrosis of epithelial cells lining the gallbladder. The latter occurred only in mid- and high dose animals. Twenty-four (24) hours after the last dose, tissue levels of drug (µg/g tissue) were much higher than in serum (µg/mL) with mean concentrations in animals in the 60 mg/kg/day group in the order of liver (3625 ± 190), spleen (2825 ± 818), kidney (1074 ± 257), eye (657 ± 160), brain (11.3 ± 3.7) and serum (8.17 ± 1.24).

Dog (Neonatal 3-5 days)	Oral (gavage)	0 10 30 60	4/sex	11 days	Two/sex/group were necropsied at the end of the dosing period. The remaining animals were maintained for an additional 1 month dose free period prior to being necropsied. There were no treatment-related effects on developmental landmarks, body weight, hematology, clinical chemistry or organ weights. Evidence of phospholipidosis (PL) was observed microscopically at the end of the treatment period in the spleen of dogs given 30 or 60 mg/kg/day and at all dose levels in the neurons of the retina and sympathetic ganglion. The incidence and severity was generally dose related. There was no evidence of PL in the liver or brain. At the end of the 1 month drug free period, the retina and sympathetic ganglion of animals given 10 mg/kg/day had no evidence of PL. PL was still evident, although at a reduced incidence and severity, at dose levels of 30 and 60 mg/kg/day. The mean concentration of azithromycin measured in blood 24 hours after the last dose of 60 mg/kg/day was 12.11 ± 2.37 µg/mL. At the same timepoint in the 60 mg/kg/day animals, mean concentrations in liver, spleen, kidney, eye and brain were 1255 (range 1027 – 1510), 639 (range 458 - 765), 385 (range 317 - 440, 1032 (range 461 – 1608) and 3.3 (range 2.8 – 4.0) µg/g tissue, respectively. Following a 1 month drug free period, tissue concentrations of azithromycin in the liver, kidney and spleen were approximately 1.5% of those observed at the end of dosing, indicating elimination of azithromycin from these organs. In animals in the 60 mg/kg/day group mean concentrations in liver, spleen, kidney, eye and brain were 2.7 (range 2.2 – 3.4), 8.2 (range 3.3 – 13.7), 1.9 (range 1.2 – 2.2), >40 (all) and 0.73 (range 0.2 – 1.4) µg/g tissue, respectively. The extent of elimination from the retina could not be accurately quantitated in this study. However, the reversibility of the PL in the retina would suggest that elimination was occurring.

Dog (Neonatal 3-5 days) and 25 days	Oral (gavage)	0 10 60	4/sex (3-5 days) 2/sex (25 days)	11 days and 30 Day Recovery Period	The purpose of this study was to further characterize the absorption and elimination of azithromycin from the choroid/retina of neonatal beagle dogs. At the end of the treatment period, 2/sex from the 3-5 day old dogs and all of the older dogs were necropsied. The remaining dogs were maintained for a 1 month dose free period to further document the elimination of azithromycin from the retina. There were no treatment-related effects on developmental landmarks, body weight, hematology or clinical chemistry. Mean whole blood concentrations of azithromycin were dose related and increased between Days 2 and 11. Mean concentrations in blood 24 hours after the last dose of 60 mg/kg/day were 11.0 ± 2.3 and 7.9 ± 2.6 µg/mL in younger (3-5 days) and older (23-25 days) dogs, respectively. Liver and choroid/retina of all animals contained dose related concentrations of azithromycin. In general, these were higher in the dogs 3-5 days of age. Mean concentrations in liver 24 hours after the last dose of 60 mg/kg/day were 1231 (range 835 – 1415) and 1138 (range 549 – 1583) µg/g tissue in younger and older dogs, respectively. Mean concentrations in retina 24 hours after the last dose of 60 mg/kg/day were 481 (range 277 – 582) and 446 (range 256 – 530) µg/g tissue in younger and older dogs, respectively. At the end of the one month treatment free period, the tissue concentrations of azithromycin had decreased. Concentrations in liver and retina of the younger dogs dosed at 60 mg/kg/day were 1.3 ± 0.9 and 49 ± 12 µg/g, respectively.
Rat	Oral (gavage)	0 50 200	22/24 pregnant 23/24 pregnant 23/24 pregnant	GD 6 to LD 21	Azithromycin was administered orally to 2 groups of 24 timed pregnant rats from Gestation Day 6 (GD 6) through Lactation Day 21 (LD 21). All F0 rats were allowed to litter and raise their F1 offspring until lactation day 21. The F1 offspring were examined for the appearance of postnatal deleopmental indices and reflexes. A functional observation battery (FOB) and tests of motor activity and learning were conducted on the F1 rats. These rats were assessed for reproductive success and the F2 offspring were evaluated for body weight and viability through Postnatal Day 21. One dam receiving 200 mg/kg/day was found dead during parturition on Gestational Day 22. Surviving dams in the 200 mg/kg/day dose group showed slight decreases in body weight gain and food consumption. There were no significant differences in the length of gestation or the number of resorptions between the control and treated groups and no drug-related findings were apparent at necropsy of the F0 dams. F1 offspring from the 200 mg/kg/day group showed significantly lower body weight from Postnatal Day 1 to the end of the study. There was also slightly decreased viability, delays in post natal development (eye opening, air righting, preputial separation and vaginal opening) and slight differences in performance on the water maze learning task. No adverse effects on fertility or reproductive parameters were found in any F1 animal. In the F2 pups, no drug-related effects were noted on the number of pups born alive, viability index or body weight gain. NOAEL for F0 dams = 50 mg/kg/day NOAEL for F1 pups = 50 mg/kg/day NOAEL for F2 offspring = 200 mg/kg/day

Rat	Oral IM	0 50 100 400 Kanamycin	5F 10F 10F 5F	28 days	The ototoxicity of azithromycin was evaluated by the differential frequency pinna reflex test and the histopathological examination of the cochlea. Kanamycin was used as positive control and animals were examined in the same manner. No functional or histopathologic evidence of ototoxicity was found in any rat dosed with azithromycin or in the negative control group animals. All rats given the positive control, kanamycin, showed extensive loss of outer hair cells of the cochlea. In addition, one rat in the positive control group lost the pinna reflex at 20000 Hz.

REFERENCES

1. Chandra R, et al., *Clinical Pharmacokinetics and Gastrointestinal Tolerability of a Novel Extended-Release Microsphere Formulation of Azithromycin*, Clin Pharmacokinet. 2007;46:247-259.

2. Cooper MA, Nye K, Andrews JM, Wise R. The pharmacokinetics and inflammatory fluid penetration of orally administered azithromycin. J Antimicrob Chemother 1990;26(4):533-8.

3. Den Hollander JG, Knudsen JD, Mouton JW, Fuursted K, Frimodt-Moller N, Verbrugh HA,et. al. Comparison of pharmacodynamics of azithromycin and erythromycin in vitro and in vivo. Antimicrobial Agents & Chemotherapy 1998;42(2):377-82. *[M5V48P897]*

4. D'Ignazio J, et al., *Novel, Single-Dose Microsphere Formulation of Azithromycin versus 7-day Levofloxacin Therapy for the Treatment of Mild to Moderate Community-Acquired Pneumonia in Adults*, Antimicrobial Agents and Chemotherapy. 2005; Vol. 49, No. 10, 4035-4041

5. Drehobl M, et al., *Single-Dose Azithromycin Microspheres vs Clarithromycin Extended Release for the Treatment of Mild-to-Moderate Community-Acquired Pneumonia in Adults*, CHEST 2005; 128, 2230-2237

6. Dunkin KT, Jones S, Howard AJ. The in-vitro activity of CP-62,993 against Haemophilus influenzae, Branhamella catarrhalis, staphylococci and streptococci. J Antimicrob Chemother 1988;21(4):405-11.

7. Foulds G, Shepard RM, Johnson RB. The pharmacokinetics of azithromycin in human serum and tissues. J Antimicrob Chemother 1990;25(Suppl A):73-82.

8. Girard AE, Girard D, English AR, Gootz TD, Cimochowski CR, Faiella JA, Haskell SL, Retsema JA. Pharmacokinetic and *in vivo* studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. Antimicrob Agents Chemother 1987;31(12):1948-54.

9. Girard AE, Girard D, Retsema JA. Correlation of the extravascular pharmacokinetics of azithromycin with in-vivo efficacy in models of localized infection. J Antimicrob Chemother 1990;25(Suppl A):61-71.

10. Gladue RP, Bright GM, Isaacson RE, Newborg MF. *In vitro* and *in vivo* uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. Antimicrob Agents Chemother 1989;33(3):277-82.

11. Gladue RP, Snider ME. Intracellular accumulation of azithromycin by cultured human fibroblasts. Antimicrob Agents Chemother 1990;34(6):1056-60.

12. Jones RN, Croco MA, Kugler KC, Pfaller MA, Beach ML. Respiratory tract pathogens isolated from patients hospitalized with suspected pneumonia: frequency of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997). Diagn Microbiol Infect Dis 2000;37(2):115-25.

13. Jorgensen JH, Hindler J, Citron DM, Cockerill FR, Fritsche TR, Funke G, Patel JB, et al. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline. CLSI 2006; 26 Suppl 19:M45-A.

14. Liu P, Allaudeen H, Chandra R, et al. Comparative pharmacokinetics of azithromycin in serum and white blood cells of healthy subjects receiving a single-dose extended-release regimen versus a 3-day immediate-release regimen. Antimicrob Agents Chemother 2007;1(Jan):103-9

15. Murray J, et al., *Efficacy and Safety of a Novel, Single-dose Azithromycin Microsphere Formulation versus 10 Days of Levofloxacin for the Treatment of Acute Bacterial Sinusitis in Adults,* Otolaryngology-Head and Neck Surgery 2005; Volume 133, Number 2, 194-201

16. Plouffe J, Schwartz DB, Kolokathis A, et al. Clinical efficacy of intravenous followed by oral azithromycin monotherapy in hospitalized patients with community-acquired pneumonia. Antimicrob Agents Chemother 2000;44(7):1796-1802.

17. Retsema JA, Girard AE, Girard D, Milisen WB. Relationship of high tissue concentrations of azithromycin to bactericidal activity and efficacy *in vivo.* J Antimicrob Chemother 1990;25(Suppl A):83-9.

18. Shepard RM, Falkner FC. Pharmacokinetics of azithromycin in rats and dogs. J Antimicrob Chemother 1990;25(Suppl A):49-60.

19. Wikler MA, Cockerill FR, Bush K, Dudley MN, Eliopoulos GM, Hardy DJ, et al. Performance Standards for Antimicrobial Susceptibility Testing; Nineteenth Informational Supplement. CLSI 2009:29 Suppl 19:M100.

20. Wildfeuer A, Laufen H, Muller-Wening D, Haferkamp O. Interaction of azithromycin and human phagocytic cells. Uptake of the antibiotic and the effect on the survival of ingested bacteria in phagocytes. Arzneimittelforschung 1989;39(7):755-8.

21. Zervos M, et al, *Novel, Single-Dose Microsphere Formulation of Azithromycin versus Levofloxacin for the Treatment of Acute Exacerbation of Chronic Bronchitis*, Infectious Diseases in Clinical Practice, Vol 13, No 3, May 2005, 115-121

22. Clinical and Laboratory Standards Institute. *Methods for dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standrard – 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.

23. 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.

24. 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.

PART III: CONSUMER INFORMATION

[Pr] Zmax SR
Azithromycin sustained-release granules for oral suspension
(as azithromycin dihydrate)

This leaflet is part III of a three-part "Product Monograph" published when Zmax SR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Zmax SR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Zmax SR is an antibiotic for the treatment of the following mild to moderate infections by certain microorganisms:

- Exacerbations of chronic bronchitis
- Sinusitis
- Community acquired pneumonia

This medication is indicated for adult patients (including elderly > 65 years of age).Your doctor will decide on whether Zmax SR is the most appropriate antibacterial for you.

What it does:
Zmax SR belongs to a group of antibacterials known as macrolides. These medicinal products are used for the treatment of a large range of bacterial infections. Zmax SR stops the growth of the bacteria, which cause the infection. Zmax SR only works against bacteria. It does not work against viruses, like the common cold or flu.

Not all respiratory infections require the use of antibacterials. Unnecessary use of antibacterials induces the emergence of resistant bacteria in the community. In case of a respiratory infection, always consult your doctor regarding the need for an antibacterial.

When it should not be used:

- If you have a history of cholestatic jaundice/hepatis (liver problems) associated with prior use of azithromycin.
- if you are hypersensitive (allergic) to azithromycin, or any macrolide or ketolide antibiotic (including erythromycin) or any other ingredient of Zmax SR (see What the nonmedicinal ingredients are).

What the medicinal ingredient is:
Azithromycin sustained release granules for oral suspension (as azithromycin dihydrate).

What the nonmedicinal ingredients are:
Zmax SR sustained-release granules for oral suspension contains: Artificial cherry flavour and artificial banana flavour, colloidal silicon dioxide, glyceryl behenate, hydroxypropylcellulose, magnesium hydroxide, poloxamer, sucrose, sodium phosphate tribasic anhydrous, titanium dioxide, xanthan gum.

What dosage forms it comes in:
- Sustained-release granules for oral suspension, 2g azithromycin/bottle (as azithromycin dihydrate).

WARNINGS AND PRECAUTIONS

BEFORE you use Zmax SR talk to your doctor or pharmacist if:

- you have a known prolonged heart cycle (interval) (QT prolongation)
- you are currently taking medication known to prolong QT interval (prolong your heart cycle) such as antiarrhythmics (drugs to regulate your heart beat such as class IA: quinidine, procainamide and class III; dofetilide, amiodarone, sotalol); antipsychotic agents; antidepressants; and fluoroquinolones (a class of antibiotics)
- you have a history of life-threatening irregular heart beat
- you have constantly low levels of potassium or magnesium
- you have a history for heart problems such as bradycardia (slow heart rate), cardiac arrhythmia (irregular heart beat) or cardiac insufficiency (your heart has a hard time pumping blood to your body)
- you have liver problems
- you have kidney problems;
- you are pregnant, or might be pregnant. It is not known if Zmax SR could harm your baby
- you have any other medical problems
- you have myasthenia gravis (a chronic autoimmune neuromuscular disease which cause muscle weakness)
- you are immunocompromised
- you are taking any other medications including those obtained without a prescription, including natural/herbal remedies or antacids
- you have diabetes, or rare hereditary problems of fructose intolerance, glucose/galactose malabsorption or sucrase-isomaltase insufficiency, as this product contains sucrose.
- you are breastfeeding or planning to breastfeed. Azithromycin has been reported to be excreted in human breast milk. It is not known if Zmax could affect your baby. Discuss with your doctor.

Zmax SR is not recommended for use in children below the age of 18

If you develop diarrhea during or after your treatment, tell your doctor at once. Do not take any medicine to treat your diarrhea without first checking with your doctor.

This antibacterial fights certain bacteria, but it does not work for all bacteria or for infections caused by fungi (funguses).

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

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Zmax SR include:
- Warfarin (or other anticoagulant medicine);
- Cyclosporin (used in suppressing of the immune system to prevent and treat the rejection in organs or bone marrow transplants);
- Digoxin (used for treatment of cardiac impairment);
- Nelfinavir (used for treatment of HIV infections);
- Ergotamine and ergot derivatives (used for migraine treatment). Ergotamine and ergot derivatives should not be used with Zmax.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

PROPER USE OF THIS MEDICATION

Usual adult dose:

Always take Zmax SR exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Zmax SR allows you to complete treatment with a single dose, therefore this medicine should be taken once as a single dose. Zmax SR should be taken on an empty stomach (at least 1 hour before or 2 hours after a meal).

Use the prepared suspension within 12 hours after reconstitution. Drink the entire contents of the bottle as a single dose.

Overdose:

In case of drug overdosage, contact a healthcare professional (e.g. doctor), hospital emergency department or regional poison control centre, even if there are no symptoms.

Vomiting after Dosing

If you vomit (throw up) within 30 minutes of taking Zmax SR, call your health care professional (doctor, pharmacist or nurse) right away to see if more medicine is needed.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

As with most drugs, Zmax SR can cause some side effects.

The most common side effects are diarrhea/loose stools, stomach pain, nausea, headache, and vomiting.

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have Clostridium difficile colitis (bowel inflammation). If this occurs, stop taking Zmax SR and contact your healthcare professional immediately. Diarrhea can occur as late as two months after you take an antibacterial such as Zmax SR.

Allergic reactions to Zmax SR are rare, but these reactions can be very serious if not treated right away by a doctor. Symptoms of a severe allergic reaction may include trouble breathing; swelling of the face, mouth, throat, neck; or severe skin rash or blisters. If you think you might be having an allergic reaction to Zmax SR, call your doctor right away. If you cannot reach your doctor, go to the nearest hospital emergency room. These symptoms could go away and then come back.

If you develop symptoms of hepatitis (liver inflammation) such as abdominal pain, nausea, vomiting, yellowing of skin and eyes, dark urine etc., stop taking the medicine immediately and call the doctor or nurse.

If you develop symptoms of myasthenia gravis or the symptoms of your existing myasthenia gravis worsen, contact your doctor. These symptoms could include muscle weakness that gets worse with activity and gets better with rest, drooping eyelid, blurred or double vision, difficulty chewing and swallowing, or trouble breathing.

Please tell your doctor right away if you feel your heart beating in your chest or have an abnormal heart beat, or get dizzy or faint when taking Zmax SR.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Common	Diarrhea/loose stools Nausea Stomach pain Headache Vomiting	✓ ✓ ✓ ✓ ✓		
Uncommon	Abnormal heart rhythm			✓
	Severe allergic reaction with symptoms such as trouble breathing, swelling of the face, mouth, thoat, neck, severe skin rash or blisters)			✓
	Liver disorder (symptoms include abdominal pain, nausea, vomiting, yellowing of skin and eyes, dark urine)			✓
Uncommon	Myasthenia gravis (muscle weakness, drooping eyelid, vision changes, difficulty chewing and swallowing, trouble breathing)		✓	

This is not a complete list of side effects. For any unexpected effects while taking* Zmax SR*, contact your doctor or pharmacist.

HOW TO STORE IT

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.

Drink the entire contents of the bottle as a single dose.

Do not take Zmax SR after the expiry date shown on the package.

Always keep Zmax SR out of reach and sight of children.

The Zmax SR suspension is white or off-white, do not use Zmax SR if you notice discoloration of the suspension.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa, ON K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: *Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:
http://www.pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001.

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