ZITHROMAX*
Azithromycin dihydrate

TRADE NAME OF THE MEDICINAL PRODUCT

ZITHROMAX*

QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated Tablets 250 mg: Azithromycin dihydrate 262.05 mg equivalent to 250 mg azithromycin base.

Powder for Oral Suspension: Azithromycin dihydrate 209.64 mg/5 mL equivalent to 200 mg/5 mL of azithromycin base.

Powder for Intravenous Solution: Azithromycin dihydrate 524.1 mg equivalent to 500 mg azithromycin base.

(Not all presentations may be marketed.)

PHARMACEUTICAL FORM

Film-coated Tablets: Azithromycin film-coated tablets contain azithromycin dihydrate equivalent to 250 mg of azithromycin.

Powder for Oral Suspension: Azithromycin powder for oral suspension contains azithromycin dihydrate equivalent to 600 mg of azithromycin per bottle. After reconstitution, each bottle contains a suspension with azithromycin dihydrate equivalent to 600 mg per 15 mL (200 mg/5 mL) azithromycin.

Powder for Intravenous Solution: Azithromycin is supplied in lyophilized form under a vacuum in a glass vial equivalent to 500 mg azithromycin for intravenous (IV) administration. Upon reconstitution, azithromycin powder yields a solution containing the equivalent of 100 mg azithromycin per 1 mL.

INDICATIONS AND CLINICAL USE

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in skin and soft tissue infections, in acute otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx, however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present.)

In sexually transmitted diseases in men and women, azithromycin is indicated in the

treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated in the treatment of chancroid due to *Haemophilus ducreyi*, and uncomplicated genital infection due to non-multiresistant *Neisseria gonorrhoea*; concurrent infection with *Treponema pallidum* should be excluded.

Azithromycin is indicated, either alone or in combination with rifabutin, for prophylaxis against *Mycobacterium avium-intracellulare* complex (MAC) infection, an opportunistic infection prevalent in patients with advanced human immunodeficiency virus (HIV).

Azithromycin is indicated in combination with ethambutol for the treatment of disseminated MAC (DMAC) infection in patients with advanced HIV infection.

Azithromycin IV is indicated for the treatment of community acquired pneumonia (CAP) caused by susceptible organisms, including *Legionella pneumophila*, in patients who require initial intravenous therapy.

Azithromycin IV is indicated for the treatment of pelvic inflammatory diseases (PID) caused by susceptible organisms (*Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma hominis*), in patients who require initial intravenous therapy.

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

CONTRAINDICATIONS

ZITHROMAX (azithromycin dihydrate) 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 antibacterial agent, or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

General

Serious allergic reactions, including angioedema, anaphylaxis and dermatological reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Steven's Johnson syndrome (SJS), toxic epidermolysis, toxic epidermal necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic symptoms (DRESS) have been reported rarely (with rare reports of fatalities), in patients on ZITHROMAX (azithromycin dihydrate) therapy (see **CONTRAINDICATIONS**). Allergic reactions may occur during and soon after treatment with ZITHROMAX. 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 ZITHROMAX 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.

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

Caution in diabetic patients: 5 mL of reconstituted oral suspension contains 3.87 g of sucrose.

Due to the sucrose content (3.87 g/5 mL of reconstituted oral suspension), the oral suspension formulation is not indicated for persons with fructose intolerance (hereditary fructose intolerance), glucose-galactose malabsorption or saccharase-isomaltase deficiency.

Due to the lactose content in the tablet coating, patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption should not take the tablet formulation.

Intramuscular use of azithromycin is not recommended; extravasation of drug into the tissues may cause tissue injury.

Intravenous Administration
Azithromycin for injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. Do not administer as an intravenous bolus or an intramuscular injection (see **DOSAGE AND ADMINISTRATION** and **Special precautions for disposal and other handling**).

Local injection site reactions have been reported with the intravenous administration of ZITHROMAX. The incidence and severity of these reactions were the same when 500 mg azithromycin was given over 1 hour (2 mg/mL as 250 mL infusion) (see **ADVERSE REACTIONS**). All volunteers who received infusate concentrations

above 2.0 mg/mL experienced local IV site reactions, therefore, higher concentrations should be avoided.

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

Cardiovascular
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac 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 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.

***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 agents. 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**).

Hematologic
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 the relevant guidelines for treatment of patients with severe neutropenia. Efficacy and safety of azithromycin have not been studied in patients with severe neutropenia.

Hepatic/Biliary/Pancreatic
Since the liver is the principal route of elimination for azithromycin, the use of oral ZITHROMAX preparations should be undertaken with caution in patients with impaired hepatic function.

Azithromycin has not been studied in patients with severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**).

Due to the lack of data, ZITHROMAX for Injection should be used with caution in patients with hepatic impairment.

Hepatotoxicity
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Rare cases of acute hepatic necrosis requiring liver transplant or causing death have been reported in patients following treatment with oral azithromycin. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur (see **ADVERSE 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
The safety, efficacy and pharmacokinetics of ZITHROMAX 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 ZITHROMAX 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.

Due to limited data in subjects with GFR <10 mL/min, caution should be exercised when prescribing oral azithromycin in these patients (see **ACTIONS AND CLINICAL PHARMACOLOGY**).

Due to the lack of data, ZITHROMAX for Injection should be used with caution in patients with renal impairment (including patients on dialysis).

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.

Susceptibility/Resistance
Development of drug resistant bacteria
Prescribing ZITHROMAX 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.

Special Populations
Pregnant Women:
There are no adequate and well-controlled studies in pregnant women. ZITHROMAX 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 pre-natal development period (delayed ossification) and during the post-natal development period (decreased viability, delayed developmental landmarks, differences in performance of learning task). The 200 mg/kg/day dose in mice and rats, is approximately 0.5-fold and 1-fold, respectively, the single adult oral dose of 2 g, based on mg/m^2 (body surface area). Pharmacokinetic data from the 200 mg/kg/day dose level in these studies showed that azithromycin crossed the placenta and distributed to fetal tissue at 5- to 9-fold the maternal plasma C_{max} of 2 µg/mL.

Nursing Women:
Limited information available from published literature indicates that azithromycin

is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed. However, the safety of azithromycin has not been studied in infants less than 6 months of age. Therefore, ZITHROMAX should not be used in the treatment of nursing women unless the expected benefit to the mother outweighs any potential risk to the infant. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Because azithromycin may accumulate in breast milk over time with continued ZITHROMAX therapy, if the lactating mother is treated with ZITHROMAX, the breast milk should be expressed and discarded during treatment.

Pediatrics:
Acute Otitis Media: Safety and efficacy in the treatment of children with otitis media under 6 months of age have not been established.

Community-Acquired Pneumonia (CAP): Safety and efficacy in the treatment of children with CAP under 6 months of age have not been established.

Pharyngitis and Tonsillitis: Safety and efficacy in the treatment of children with pharyngitis and tonsillitis under 2 years of age have not been established.

Studies evaluating the use of repeated courses of therapy have not been conducted. Safety data with the use of ZITHROMAX at doses higher than proposed and for durations longer than recommended are limited to a small number of immunocompromised children who underwent chronic treatment.

Infantile Hypertrophic Pyloric Stenosis:
Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

The safety and effectiveness of ZITHROMAX for Injection in children or adolescents under 16 years have not been established.

Prevention of Disseminated Mycobacterium Avium Complex (MAC) Disease:
Safety and efficacy of ZITHROMAX for the prevention of MAC in children have not been established.

Limited safety data are available for 24 children 5 months to 14 years of age (mean 4.6 years) who received ZITHROMAX for treatment of opportunistic infections. The mean duration of therapy was 186.7 days (range 13-710 days) at doses of <5 to 20 mg/kg/day. Adverse events were similar to those observed in the adult population, most of which involved the gastrointestinal tract. While none of these children prematurely discontinued treatment due to a side effect, one child discontinued due to a laboratory abnormality (eosinophilia). Based on available pediatric pharmacokinetic data, a dose of 20 mg/kg in children would provide drug exposure similar to the 1,200 mg adult dose but with a higher C_{max}.

Geriatrics:
The pharmacokinetics in elderly volunteers (age 65 to 85) were similar to those in younger volunteers (age 18 to 40) for the 5-day oral therapeutic regimen. Dosage adjustment does not appear to be necessary for elderly patients with normal renal and hepatic function receiving treatment with this dosage regimen. Pharmacokinetic studies with intravenous azithromycin have not been performed in the elderly. Based on clinical trials, there appear to be no significant differences in safety or tolerance of intravenous azithromycin between elderly (age ≥65) and younger subjects (ages 16 to ≤64).

Monitoring and Laboratory Tests
Monitoring of QT/QTc intervals during treatment with ZITHROMAX may be considered by the physician as appropriate.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
The majority of side effects observed in controlled clinical trials involving patients (adults and children) treated with oral ZITHROMAX (azithromycin dihydrate) were of a mild and transient nature. Approximately 0.7% of both adult patients (n = 3,812) and children (n = 2,878) from the 5-day multiple dose clinical trials discontinued ZITHROMAX therapy because of drug related side effects. Among adults receiving ZITHROMAX intravenously, 1.2% of CAP, and 2% of PID patients discontinued treatment. Discontinuation rates were slightly higher for PID patients receiving concomitant metronidazole therapy (4%).

In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.4%. In clinical trials in children given 30 mg/kg, orally either as a single dose (n = 487) or over 3 days, (n = 1,729) discontinuation from therapy due to treatment-related side effects was approximately 1%.

Most of the side effects leading to discontinuation in patients on oral or intravenous therapy were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, along with abdominal pain, rashes and increases in aminotransferases and/or alkaline phosphatase levels in adult patients receiving intravenous ZITHROMAX. Potentially serious treatment-related side effects including angioedema and cholestatic jaundice occurred in less than 1% of patients.

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 in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Oral Regimen: Adults
Multiple-dose Regimens:
In adult patients, the most common treatment-related side effects in patients receiving the 3 or 5 day oral multiple-dose regimens of ZITHROMAX were related to the gastrointestinal system with diarrhea/loose stools (4%-5%), abdominal pain

(2%-3%), vomiting (1%) and nausea (3%-4%).

Treatment-related side effects that occurred with a frequency of 1% or less include:

Cardiovascular:	hypertension
Gastrointestinal:	dry mouth, esophagitis, gastroenteritis, rectal hemorrhage, cholestatic jaundice
Genitourinary:	menorrhagia, urinary frequency, vaginitis
Special senses:	conjunctivitis
Nervous system:	dizziness
Allergic:	pruritus

Single 1-gram Dose Regimen:
In adult patients (n = 904), side effects that occurred on the single one-gram dosing regimen of ZITHROMAX with a frequency greater than 1% included diarrhea (6.1%), nausea (4.9%), abdominal pain (4.9%), vomiting (1.7%), vaginitis (1.3%), loose stools (1.2%), and dyspepsia (1.1%).

Single 2-gram Dose Regimen:
Overall, the most common side effects in patients receiving a single 2-gram dose of ZITHROMAX were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of a 1% or greater included nausea (18.2%), diarrhea/loose stools (13.8%), vomiting (6.7%), abdominal pain (6.7%), vaginitis (2.2%), dyspepsia (1.1%), and dizziness (1.3%). The majority of these complaints were mild in nature.

Prevention of *Mycobacterium Avium* Complex (MAC) Disease:
Chronic therapy with ZITHROMAX 1,200 mg weekly regimen: The nature of side effects seen with the 1,200 mg weekly dosing regimen for the prevention of *Mycobacterium avium* complex infection in severely immunocompromised HIV-infected patients were similar to those seen with short-term dosing regimens.

Incidence[1)] (%) of Treatment Related* Adverse Events in HIV-infected Patients Receiving Prophylaxis for Disseminated MAC**

	Study 155		Study 174		
	Placebo (n = 91)	Azithromycin 1,200 mg weekly (n = 89)	Azithromycin 1,200 mg weekly (n = 233)	Rifabutin 300 mg daily (n = 236)	Azithromycin & Rifabutin (n = 224)
Mean Duration of Therapy (days)	303.8	402.9	315	296.1	344.4
Discontinuation of Therapy (%)	2.3	8.2	13.5	15.9	22.7
AUTONOMIC NERVOUS SYSTEM					
Mouth Dry	0	0	0	3.0	2.7
CENTRAL NERVOUS SYSTEM					
Dizziness	0	1.1	3.9	1.7	0.4
Headache	0	0	3.0	5.5	4.5
GASTROINTESTINAL					

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	Study 155		Study 174		
	Placebo (n = 91)	Azithromycin 1,200 mg weekly (n = 89)	Azithromycin 1,200 mg weekly (n = 233)	Rifabutin 300 mg daily (n = 236)	Azithromycin & Rifabutin (n = 224)
Diarrhea	15.4	52.8	50.2	19.1	50.9
Loose Stools	6.6	19.1	12.9	3.0	9.4
Abdominal Pain	6.6	27	32.2	12.3	31.7
Dyspepsia	1.1	9	4.7	1.7	1.8
Flatulence	4.4	9	10.7	5.1	5.8
Nausea	11	32.6	27.0	16.5	28.1
Vomiting	1.1	6.7	9.0	3.8	5.8
GENERAL					
Fever	1.1	0	2.1	4.2	4.9
Fatigue	0	2.2	3.9	2.1	3.1
Malaise	0	1.1	0.4	0	2.2
MUSCULOSKELETAL					
Arthralgia	0	0	3.0	4.2	7.1
PSYCHIATRIC					
Anorexia	1.1	0	2.1	2.1	3.1
SKIN & APPENDAGES					
Pruritus	3.3	0	3.9	3.4	7.6
Rash	3.2	3.4	8.1	9.4	11.1
Skin Discoloration	0	0	0	2.1	2.2
SPECIAL SENSES					
Tinnitus	4.4	3.4	0.9	1.3	0.9
Hearing Decreased	2.2	1.1	0.9	0.4	0
Taste Perversion	0	0	1.3	2.5	1.3

* Includes those events considered possibly or probably related to study drug.

** >2% adverse event rates for any group.

[1)] Reflects the occurrence of ≥1 event during the entire treatment period.

Side effects related to the gastrointestinal tract were seen more frequently in patients receiving azithromycin than in those receiving placebo or rifabutin. In one of the studies, 86% of diarrheal episodes were mild to moderate in nature with discontinuation of therapy for this reason occurring in only 9/233 (3.8%) of patients.

Intravenous/Oral Regimen: Adults

The most common side effects (greater than 1%) in adult patients who received sequential IV/oral ZITHROMAX in studies of CAP were related to the gastrointestinal system: diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%). Approximately 12% of patients experienced a side effect related to the intravenous infusion; most common were pain at the site and/or during the infusion (6.5%) and local inflammation (3.1%).

In adult women who received sequential IV/oral ZITHROMAX in studies of PID, the most common side effects (greater than 1%) were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most frequently reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus

(1.9%). When azithromycin was co-administered with metronidazole in these studies, a higher proportion of women experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%) and application site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).

Side effects that occurred with a frequency of 1% or less included:
Gastrointestinal: dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis
Nervous System: headache, somnolence
Allergic: bronchospasm
Special Senses: taste perversion

Oral Regimen: Children
Single and Multiple-dose regimens:
In children enrolled in controlled clinical trials in acute otitis media and *S. pyogenes* pharyngitis, the type of side effects were comparable to those seen in adults (see below).

Different side effect incidence rates for the dosage regimens recommended in children were observed.

Acute Otitis Media: For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects (≥1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea and rash. The incidence, based on dosing regimen, is described in the table below:

Regimen	Subjects	Overall ADR Incidence	Diarrhea	Abdominal pain	Vomiting	Nausea	Rash
1-Day	487	14%	4%	1%	5%	1%	1%
3-Day	1395	7%	3%	2%	1%	<1%	<1%
5-Day	1888	6%	2%	1%	1%	1%	<1%

Community-Acquired Pneumonia: For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects attributed to treatment were diarrhea/loose stools, abdominal pain, vomiting/nausea and rash. The incidence is described in the table below:

Dosage Regimen	Subjects	Overall ADR Incidence	Diarrhea/ Loose stools	Abdominal Pain	Vomiting	Nausea	Rash
5-Day	323	12%	5.8%	1.9%	1.9%	1.9%	1.6%

Pharyngitis/Tonsillitis: For the recommended total dosage regimen of 60 mg/kg, the most frequent side effects attributed to treatment were diarrhea, vomiting, abdominal pain, nausea and headache. The incidence is described in the table below:

Regimen	Subjects	Overall ADR Incidence	Diarrhea	Abdominal pain	Vomiting	Nausea	Rash	Headache
5-Day	447	17%	5%	3%	6%	2%	<1%	1%

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

Cardiovascular:	Palpitations, chest pain;
Gastrointestinal:	Dyspepsia, flatulence, melena, constipation, anorexia, enteritis, loose stools, oral moniliasis and gastritis;
Genitourinary:	Moniliasis, vaginitis and nephritis;
Hematologic and Lymphatic:	Anemia, leukopenia
Nervous System:	Dizziness, vertigo, somnolence, agitation, nervousness, insomnia and hyperkinesia;
General:	Fatigue, face edema, fever, fungal infection, pain and malaise;
Respiratory:	Cough increased, pharyngitis, pleural effusion and rhinitis;
Skin and Appendages:	Eczema, fungal dermatitis, sweating and vesiculobullous rash
Allergic:	Allergic reaction, photosensitivity, angioedema, erythema multiforme, pruritus and urticaria.
Liver/Biliary:	Liver function test abnormal, jaundice and cholestatic jaundice.

Abnormal Hematologic and Clinical Chemistry Findings
Oral Therapy:
Adults:
Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials in patients were reported as follows:

With an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, monocytes, albumin and blood glucose, elevated serum creatine phosphokinase, potassium, ALT (SGPT), GGT and AST (SGOT), BUN, creatinine, blood glucose, platelet count, eosinophils and monocytes.

With an incidence of less than 1%: leukopenia, neutropenia, decreased platelet count, elevated serum alkaline phosphatase, bilirubin, LDH and phosphate.

The majority of subjects with elevated serum creatine also had abnormal values at baseline.

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

In multiple-dose clinical trials involving more than 4,500 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities, one for treatment-related elevated transaminases and triglycerides and one because of a renal function abnormality.

Prevention of Mycobacterium Avium Complex (MAC) Disease:
In these immunocompromised patients with advanced HIV infection, it was sometimes necessary to assess laboratory abnormalities developing on study with additional criteria if baseline values were outside the normal range.

Prophylaxis Against Disseminated MAC Abnormal Laboratory Values

Criteria[a]	Study 155		Study 174		
	Placebo (n = 88)	Azithromycin 1200 mg weekly (n = 89)	Azithromycin 1200 mg weekly (n = 208)	Rifabutin 300 mg daily (n = 205)	Azithromycin & Rifabutin (n = 199)
Hemoglobin					
<0.8 x LLN[b]	31%	30%	19%	26%	21%
Platelet Count					
<0.75 x LLN	19%	16%	11%	10%	16%
WBC Count					
<0.75 x LLN	48%	49%	60%	53%	60%
Neutrophils					
<0.5 x LLN	16%	28%	23%	20%	29%
<500/mm^3	6%	13%	5%	6%	8%
AST (SGOT)					
>2.0 x ULN[c]	28%	39%	33%	18%	30%
>200 U/L	10%	8%	8%	3%	6%
ALT (SGPT)					
>2.0 x ULN	24%	34%	31%	15%	27%
>250 U/L	2%	6%	8%	2%	6%

[a] Secondary criteria also applied if baseline abnormal, as follows: Hemoglobin, 10% decrease; Platelet, 20% decrease; WBC count, 25% decrease; Neutrophils, 50% decrease; AST (SGOT), 50% increase; ALT (SGPT), 50% increase.

[b] Lower limit of normal.

[c] Upper limit of normal.

In a phase I drug interaction study performed in normal volunteers, 1 of 6 subjects given the combination of azithromycin and rifabutin, 1 of 7 given rifabutin alone and 0 of 6 given azithromycin alone developed a clinically significant neutropenia (<500 cells/mm^3).

Children:

One-, Three- and Five-Day Regimens

Laboratory data collected from 64 subjects receiving azithromycin in comparative clinical trials employing the 1-day regimen (30 mg/kg as a single dose), 1198 and 169 subjects receiving azithromycin respectively employing the two 3-day regimens (30 mg/kg or 60 mg/kg in divided doses over 3 days) were similar for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1%-5%.

Similar results were obtained in subjects receiving the two 5-day regimens. Overall, 1,948 and 421 patients were exposed to 30 mg/kg or 60 mg/kg, respectively in divided doses over 5 days. The data collected in the subset of azithromycin patients assessed for laboratory abnormalities were similar to those in all comparators combined with most clinically significant laboratory abnormalities occurring at incidences of 1%-5%.

In a single center clinical trial, a decrease in absolute neutrophils was observed in the range of 21%-29% for azithromycin regimens of 30 mg/kg given either as a single dose or over 3 days, as well as the comparator. No patients had significant neutropenia defined as an absolute neutrophil count <500 cells/mm^3.

In clinical trials involving approximately 4,700 pediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

Intravenous Therapy

Adults:

With an incidence of 4%-6%, elevated ALT, AST, and creatinine.
With an incidence of 1%-3%, elevated LDH and bilirubin.
With an incidence of less than 1%, leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase.

In multiple dose clinical trials involving more than 750 patients treated with sequential IV/oral ZITHROMAX less than 2% of patients discontinued therapy because of treatment-related liver enzyme abnormalities.

When follow-up was provided, changes in laboratory tests appeared to be reversible for both oral and IV dosing.

Post-market Adverse Drug Reactions

The following adverse experiences have been reported in patients 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.

Allergic:	Arthralgia, edema, anaphylaxis (with rare reports of fatalities) (see **WARNINGS AND PRECAUTIONS**), serum sickness, urticaria, vasculitis, angioedema, pruritus;
Blood and the lymphatic system disorders:	Agranulocytosis, haemolytic anaemia, thrombocytopenia
Cardiovascular:	Cardiac arrhythmias (including ventricular tachycardia), palpitations, hypotension. There have been rare reports of QT prolongation 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 **WARNINGS AND PRECAUTIONS**).
Gastrointestinal:	Anorexia, constipation, hypoglycaemia, dehydration, vomiting/diarrhea rarely resulting in dehydration, pancreatitis, pseudomembranous colitis, rare reports of tongue discoloration, pyloric stenosis/infantile hypertrophic pyloric stenosis (IHPS);
General:	Asthenia, paresthesia, fatigue, muscle pain;
Genitourinary:	Interstitial nephritis, acute renal failure, nephrotic syndrome, vaginitis;

Liver/Biliary:	Hepatitis fulminant. Abnormal liver function including drug-induced hepatitis and cholestatic jaundice have been reported. There have also been rare cases of hepatic necrosis and hepatic failure, which have resulted in death (see **WARNINGS AND PRECAUTIONS**).
Musculoskeletal and connective tissue disorders:	Myasthenia gravis
Nervous System:	Dizziness, hyperactivity, hypoaesthesia, seizure, convulsions, and syncope
Psychiatric Disorders:	Aggressive reaction, anxiety, nervousness, agitation, delirium, hallucinations
Skin/Appendages:	Serious skin reactions including erythema multiforme, exfoliative dermatitis, Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) (see **WARNINGS AND PRECAUTIONS**).
Special Senses:	Hearing disturbances including hearing loss, hearing impaired, deafness and/or tinnitus, vertigo, taste/smell perversion and/or loss, abnormal vision.

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

Established or Potential Drug-drug Interactions

Proper name	Ref	Effect	Clinical comment
Antacids Aluminum and magnesium containing antacids (Maalox®):	CT	Reduce the peak serum levels but not the extent of azithromycin absorption.	ZITHROMAX and these drugs should not be taken simultaneously.
Carbamazepine:	CT	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 ZITHROMAX.	
Cetirizine:	CT	In healthy male volunteers, co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.	
Cimetidine:	CT	Administration of a single-dose of cimetidine (800 mg) 2 hours prior to ZITHROMAX had no effect on azithromycin absorption or on azithromycin pharmacokinetics.	
Coumarin-Type Oral Anticoagulants:	CT	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.
Cyclosporine:	CT	In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporine, the resulting cyclosporine C_{max} and AUC_{0-5} were found to be significantly elevated.	Caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporine levels should be monitored and the dose adjusted accordingly.
Didanosine:	CT	Daily doses of 1,200 mg ZITHROMAX had no effect on the pharmacokinetics of didanosine.	

Proper name	Ref	Effect	Clinical comment
Efavirenz:	CT	Efavirenz, when administered at a dose of 400 mg for seven 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 seven days.	
Fluconazole:	CT	A single dose of 1,200 mg azithromycin immediate-release did not alter the pharmacokinetics of a single 800 mg oral dose of fluconazole. Total exposure and half-life of 1,200 mg azithromycin were unchanged and C_{max} had a clinically insignificant decrease (18%) by co-administration with 800 mg fluconazole.	
HMG-CoA Reductase Inhibitors:	CT	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:	CT	A single dose of 1,200 mg azithromycin immediate-release had no significant effect on the pharmacokinetics of indinavir (800 mg indinavir three times daily for 5 days).	
Midazolam:	CT	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:	CT	Co-administration of a single dose of 1,200 mg azithromycin immediate-release with steady-state nelfinavir (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 nelfinavir (750 mg three times daily) at steady-state with a single dose of 1,200 mg azithromycin immediate-release increased the mean $AUC_{0-\infty}$ of azithromycin by 113% and mean C_{max} by 136%.	Dose adjustment of ZITHROMAX is not recommended. However, close monitoring for known side effects of azithromycin, when administered in conjunction with nelfinavir, is warranted.

Proper name	Ref	Effect	Clinical comment
P-glycoprotein inhibitors:	CT	Co-administration of P-glycoprotein inhibitors (Vitamin E, Poloxamer 407, or Poloxamer 124) with azithromycin sustained release form (1 g dose) had minimal effect on the pharmacokinetics of azithromycin.	
Rifabutin:	CT	Co-administration of ZITHROMAX 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:	CT	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:	CT	Concurrent use of macrolides and theophylline has been associated with increases in the serum concentrations of theophylline. ZITHROMAX 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 ZITHROMAX.	Until further data are available, prudent medical practice dictates careful monitoring of plasma theophylline levels in patients receiving ZITHROMAX and theophylline concomitantly.
Trimethoprim/ Sulfamethoxazole:	CT	Co-administration of trimethoprim/ sulfamethoxazole (160 mg/800 mg) for 7 days with azithromycin immediate-release 1,200 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.	

Proper name	Ref	Effect	Clinical comment
Zidovudine:	CT	Single 1,000 mg doses and multiple 1,200 mg or 600 mg doses of ZITHROMAX did not affect the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of ZITHROMAX increased the concentrations of phosphorylated zidovudine, the clinically active metabolite in peripheral blood mononuclear cells.	

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical; UNK=Unknown.

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 rare spontaneously reported cases with azithromycin and some of these drugs, in post-marketing experience. Until further data are developed regarding drug interactions, when ZITHROMAX and these drugs are used concomitantly, careful monitoring of patients is advised both during and for a short period following therapy:

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 and colchicine/P-glycoprotein substrates

Concomitant administration of some macrolide antibiotics with P-glycoprotein substrates including digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin 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.

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 the clearance of triazolam and increase the pharmacologic effect of triazolam.

Drug-food Interactions
Azithromycin tablets and powder for oral suspension can be taken with or without food.

Drug-herb Interactions
Interactions with herbal products have not been established.

Drug-laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Oral azithromycin should be administered as a single daily dose. The period of dosing with regard to infection is given below.

Azithromycin tablets, powder for oral suspension can be taken with or without food.

In Adults:
For the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis*, *Haemophilus ducreyi* or susceptible *Neisseria gonorrhoea*, the dose is 1,000 mg as a single oral dose.

For prophylaxis against MAC infections in patients infected with the HIV, the dose is 1,200 mg once per week.

For the treatment of DMAC infections in patients with advanced HIV infection, the recommended dose is 600 mg once a day, Azithromycin should be administered in combination with other antimycobacterial agents that have shown *in vitro* activity against MAC, such as ethambutol at the approved dose.

ZITHROMAX IV:
For the treatment of adult patients with CAP due to the indicated organisms, the recommended dose of intravenous azithromycin is 500 mg as a single daily dose by the IV route for at least two days. Intravenous therapy should be followed by oral azithromycin at a single daily dose of 500 mg to complete a 7 to 10 day course of therapy. The timing of the conversion to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

For the treatment of adult patients with PID due to the indicated organisms, the recommended dose of intravenous azithromycin is 500 mg as a single dose by the IV route for one or two days. Intravenous therapy should be followed by azithromycin by the oral route at a single daily dose of 250 mg to complete a 7-day

course of therapy. The timing of the conversion to oral therapy should be done at the discretion of the physician and in accordance with clinical response. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial anaerobic agent with anaerobic activity may be administered in combination with azithromycin.

For all other indications in which the oral formulation is administered, the total dosage of 1,500 mg should be given as 500 mg daily for 3 days. As an alternative, the same total dose can be given over 5 days with 500 mg given on Day 1, then 250 mg daily on Days 2 to 5.

Intravenous Administration: After reconstitution and dilution, the recommended route of administration for intravenous azithromycin is by IV infusion only. **Do not administer as an intravenous bolus or an intramuscular injection** (see **WARNINGS AND PRECAUTIONS** and **Special precautions for disposal and other handling**).

The infusate concentration and rate of infusion for azithromycin IV should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour. An intravenous dose of 500 mg azithromycin should be infused for a minimum duration of 1 hour.

In Children:
The maximum recommended total dose for any treatment is 1500 mg for children.

In general, the total dose in children is 30 mg/kg. Treatment for pediatric streptococcal pharyngitis should be dosed at a different regimen (see below).

The total dose of 30 mg/kg should be given as a single daily dose of 10 mg/kg daily for 3 days, or given over 5 days with a single daily dose of 10 mg/kg on Day 1, then 5 mg/kg on Days 2-5.

As an alternative to the above dosing, treatment for children with acute otitis media can be given as a single dose of 30 mg/kg.

For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective; however, a daily dose of 500 mg must not be exceeded. In clinical trials comparing these two dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg per day dose. However, penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including prophylaxis of rheumatic fever.

For children weighing less than 15 kg, azithromycin suspension should be measured as closely as possible. For children weighing 15 kg or more, azithromycin suspension should be administered according to the guide provided below:

AZITHROMYCIN SUSPENSION 30 mg/kg Total Treatment Dose			
Weight (kg)	**3-Day Regimen**	**5-Day Regimen**	**Bottle Size (mg)**
<15	10 mg/kg once daily on Days 1-3	10 mg/kg on Day 1, then 5 mg/kg once daily on Days 2-5	600

15-25	200 mg (5 mL) once daily on Days 1-3	200 mg (5 mL) on Day 1, then 100 mg (2.5 mL) once daily on Days 2-5	600
26-35	300 mg (7.5 mL) once daily on Days 1-3	300 mg (7.5 mL) on Day 1, then 150 mg (3.75 mL) once daily on Days 2-5	900
36-45	400 mg (10 mL) once daily on Days 1-3	400 mg (10 mL) on Day 1, then 200 mg (5 mL) once daily on Days 2-5	1,200
>45	Dose as per adults	Dose as per adults	1,500

Azithromycin tablets should only be administered to children weighing more than 45 kg.

The safety and efficacy of intravenous azithromycin for the treatment of infections in children has not been established.

Safety and efficacy for the prevention or treatment of MAC in children have not been established. Based on pediatric pharmacokinetic data, a dose of 20 mg/kg would be similar to the adult dose of 1,200 mg but with a higher C_{max}.

In the Elderly: The same dosage as in adult patients is used in the elderly.

In Patients with Renal Impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 - 80 mL/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR <10 mL/min) (see **WARNINGS AND PRECAUTIONS** and **Pharmacokinetics**).

In Patients with Hepatic Impairment: The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE

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.

Up to 15 g cumulative dose of ZITHROMAX (azithromycin dihydrate) over 10 days has been administered in clinical trials without apparent adverse effect.

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ZITHROMAX (azithromycin dihydrate), a macrolide antibiotic of the azalide

subclass, exerts its antibacterial action by binding to the 23S rRNA of the 50S ribosomal subunits of susceptible bacteria. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Pharmacodynamics

Cardiac Electrophysiology:

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial. A total of 119 healthy 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 1,500 mg. On Day 3, the azithromycin mean (%CV) plasma C_{max} values for the 500, 1000 and 1,500 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 1,500 mg azithromycin, respectively.

Pharmacokinetics

No data exist in humans in regard to the extent of accumulation, duration of exposure, metabolism or excretory mechanisms of azithromycin in neural tissue, such as the retina and the cochlea.

Adult Pharmacokinetics:

Plasma concentrations of azithromycin decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. The prolonged half-life is likely due to extensive uptake and subsequent release of drug from tissues. Over the dose range of 250 to 1,000 mg orally, the serum concentrations are related to dose.

In adults, the following pharmacokinetic data have been reported:

DOSE/DOSAGE FORM	Subjects	C_{max} (µg/mL)	T_{max} (hr)	AUC (µg·hr/mL)	$T_{½}$ (hr)
500 mg/250 mg tablet	12; fasted	0.34	2.1	2.49[a]	-
500 mg/250 mg tablet	12; fed	0.41	2.3	2.40[a]	-
1,200 mg/600 mg tablet	12; fasted	0.66	2.5	6.8[b]	40

[a] 0-48 hr

[b] 0-last.

Intravenous Administration:

In patients hospitalized with CAP receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the median maximum concentration (C_{max}) achieved was 3.00 µg/mL (range: 1.70-6.00 µg/mL) while the 24-hour trough level was 0.18 µg/mL (range: 0.07-0.60 µg/mL) and the AUC_{24} was 8.50 µg·h/mL (range: 5.10-19.60 µg·h/mL).

The median C_{max}, 24-hour trough and AUC_{24} values were 1.20 µg/mL (range: 0.89-1.36 µg/mL), 0.18 µg/mL (range: 0.15-0.21 µg/mL) and 7.98 µg·h/mL (range: 6.45-

9.80 µg·h/mL), respectively, in normal volunteers receiving a 3-hour intravenous infusion of 500 mg azithromycin at a concentration of 1 mg/mL. Similar pharmacokinetic values were obtained in patients hospitalized with CAP that received the same 3-hour dosage regimen for 2-5 days.

Plasma concentrations (µg/mL) after the last daily intravenous infusion of 500 mg azithromycin [median (range)]									
Conc. + Duration	Time after starting infusion (hr)								
	0.5	1	2	3	4	6	8	12	24
2 mg/mL, 1 hr[a]	2.42 (1.71-5.12)	2.65 (1.94-6.03)	0.63 (0.21-1.07)	0.34 (0.18-0.87)	0.32 (0.16-0.69)	0.19 (0.12-0.58)	0.22 (0.10-0.61)	0.16 (0.09-0.46)	0.18 (0.07-0.60)
1 mg/mL, 3 hr[b]	0.87 (0.76-1.16)	1.03 (0.83-1.19)	1.16 (0.87-1.36)	1.17 (0.86-1.35)	0.32 (0.26-0.47)	0.29 (0.23-0.35)	0.27 (0.23-0.34)	0.22 (0.17-0.26)	0.18 (0.15-0.21)

[a] 500 mg (2 mg/mL) for 2-5 days in CAP patients.
[b] 500 mg (1 mg/mL) for 5 days in healthy subjects.

The average Cl_t and Vd values were 10.18 mL/min/kg and 33.3 L/kg, respectively, in 18 normal volunteers receiving 1,000 to 4,000 mg doses given as 1 mg/mL over 2 hours.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg intravenous azithromycin shows only an 8% increase in C_{max} but a 61% increase in AUC_{24} reflecting the 3-fold rise in C_{24} trough levels.

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

Absorption

Following oral administration, azithromycin is rapidly absorbed (T_{max} = 2-3 hours) and distributed widely throughout the body.

The absolute bioavailability is approximately 37%.

When azithromycin suspension was administered with food to 28 adult healthy male subjects, the rate of absorption (C_{max}) was increased by 56% while the extent of absorption (AUC) was unchanged. Food does not affect the absorption of azithromycin in the tablet dosage form. Azithromycin tablets and powder for oral suspension can be taken with or without food.

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.

Rapid movement of azithromycin from blood into tissue results in significantly higher azithromycin concentrations in tissue than in plasma (up to 50 times the maximum observed concentration in plasma).

The long tissue half-life and large volume of distribution result from intracytoplasmic uptake and storage in lysosomal phospholipid complexes.

Metabolism

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

Biliary excretion of azithromycin, predominantly as unchanged drug, is a main route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in the urine.

Special Populations and Conditions

Pediatric Pharmacokinetics

Pharmacokinetics in children receiving a total dose of 30 mg/kg:

The table below shows mean pharmacokinetic parameters on Day 5 in children 1 to 5 years and 5 to 15 years of age when azithromycin oral suspension was dosed in the absence of food at a total dose of 30 mg/kg delivered as 10 mg/kg on Day 1 and 5 mg/kg on Days 2-5.

Pharmacokinetics in children given a total dose of 30 mg/kg delivered as a single dose have not been studied.

Pharmacokinetic parameters on Day 5 at dosage 10 mg/kg (Day 1) and 5 mg/kg (Days 2-5)					
Age 1-5			Age 5-15		
C_{max} (µg/mL)	T_{max} (hrs)	AUC_{0-24} (µg·hr/mL)	C_{max} (µg/mL)	T_{max} (hrs)	AUC_{0-24} (µg·hr/mL)
0.216	1.9	1.822	0.383	2.4	3.109

Pharmacokinetics in children receiving a 60 mg/kg total dose:

Two clinical studies enrolled 35 and 33 children respectively aged 3-16 years with pharyngitis/tonsillitis to determine the pharmacokinetics and safety of azithromycin for oral suspension in children when given 60 mg/kg in divided doses delivered as 20 mg/kg/day over 3 days or 12 mg/kg/day over 5 days with a maximum daily dose of 500 mg.

The following table shows pharmacokinetic data in the subset of children who received a total dose of 60 mg/kg. In both studies azithromycin concentrations were determined over a 24 hour period following the last daily dose.

Similarity of overall exposure ($AUC_{0-\infty}$) between the 3 and 5 day regimen is unknown.

	3-Day Regimen (20 mg/kg x 3 days)	5-Day Regimen (12 mg/kg x 5 days)
N	11[b]	17[b]
C_{max} (µg/mL)	1.05 ± .44[a]	0.534 ± 0.361[a]
T_{max} (hr)	3 ± 2.0[a]	2.2 ± 0.8[a]
AUC_{0-24} (µg ×hr/mL)	7.92 ± 2.87[a]	3.94 ± 1.90[a]

[a] Arithmetic means.
[b] maximum weight for 3 day regimen was ≤25 kg and for 5 day regimen was ≤41.7 kg.

Geriatrics
When studied in healthy elderly subjects from age 65 to 85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults; however, in elderly women, although higher peak concentrations (increased by 30% to 50%) were observed, no significant accumulation occurred.

Gender
There are no significant differences in the disposition of immediate-release azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

Hepatic Insufficiency
In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of oral ZITHROMAX compared to those with normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase. Hence, no dose adjustment is recommended for patients with mild to moderate hepatic impairment. Azithromycin has not been studied in patients with severe hepatic impairment.

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 1,000 mg dose of azithromycin, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min).

MICROBIOLOGY

Mechanism of Resistance:
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.

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**.

Gram-positive bacteria
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae

Streptococcus pyogenes

Gram-negative bacteria
Haemophilus ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

"Other" bacteria
Chlamydophila pneumoniae
Chlamydia trachomatis
Mycoplasma pneumoniae

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

At least 90% of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the azithromycin susceptible breakpoint of ≤4 mcg/mL. However, safety and effectiveness of azithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

Gram-positive bacteria
Beta-hemolytic streptococci (Groups C, F, G)
Viridans group streptococci

Gram-negative bacteria
Bordetella pertussis

Anaerobic bacteria
Peptostreptococcus species
Prevotella bivia

"Other" bacteria
Ureaplasma urealyticum
Legionella pneumophila
Mycoplasma hominis

Activity of Azithromycin against *Mycobacterium avium* complex (MAC)
In vitro azithromycin has demonstrated activity against *Mycobacterium avium* complex (MAC) bacteria. Azithromycin has also been shown to be active against phagocytized MAC bacteria in mouse and human macrophage cell cultures.

Susceptibility Testing Methods:
When available, the results of *in vitro* susceptibility test results for antimicrobial drugs used in resident hospitals should be provided to the physician as periodic reports which describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports may differ from susceptibility data obtained from outpatient use, but could 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 (broth or agar) or equivalent with standardized inoculum concentration and standardized concentration of azithromycin powder. The MIC values should be interpreted according to criteria provided in Table 1.

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 requires the use of standardized inoculum concentration. This procedure uses paper disks impregnated with 15-mcg azithromycin to test the susceptibility of bacteria to azithromycin. The disk diffusion interpretive criteria are provided in Table 1.

Table 1. Susceptibility Interpretive Criteria for Azithromycin Susceptibility Test Result Interpretive Criteria

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Haemophilus influenzae[a]	≤4	--	--	≥12	--	--
Staphylococcus aureus	≤2	4	≥8	≥18	14 – 17	≤13
Streptococci including *S. pneumoniae*	≤0.5	1	≥2	≥18	14 – 17	≤13

Susceptibility to azithromycin must be tested in ambient air.
[a]Insufficient information is available to determine Intermediate or Resistant interpretive criteria. The ability to correlate MIC values and plasma drug levels is difficult as azithromycin concentrates in macrophages and tissues.

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 laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individual performing the test. Standard azithromycin powder should provide the following range of MIC values noted in Table 2. For the diffusion technique using the azithromycin 15 mcg disk, the criteria in Table 2 should be achieved.

Table 2. Acceptable Quality Control Ranges for Azithromycin

QC Strain	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion (zone diameters in mm)
Haemophilus influenza ATCC* 49247	1.0 – 4.0	13 – 21
Staphylococcus aureus ATCC 29213	0.5 – 2.0	---
Staphylococcus aureus ATCC 25923	---	21 – 26
Streptococcus pneumonia ATCC 49619	0.06 – 0.25	19 – 25

Susceptibility to azithromycin must be tested in ambient air.
*ATCC = American Type Culture Collection

PHARMACEUTICAL PARTICULARS

Incompatibilities
Intravenous: Other intravenous substances, additives or medications should not be added to intravenous azithromycin, or infused simultaneously through the same intravenous line.

Shelf-life
Refer to outer carton for shelf-life.

Special precautions for storage
Tablets: Please refer to outer carton for storage recommendation.

Powder for Oral Suspension: Please refer to outer carton for storage recommendation for the powder and the reconstituted suspension.

Intravenous: Please refer to outer carton for storage recommendation (see **Special precautions for disposal and other handling** for storage information after reconstitution).

Special precautions for disposal and other handling
Tablets: The tablets should be swallowed whole.

Powder for Oral Suspension: Tap the bottle to loosen the powder. To the 600-mg bottle, add 9 mL of water. Shake well. Shake immediately prior to use. The colour of the reconstituted suspension is from white/off-white to orange/brown.

For children weighing less than 15 kg, the suspension should be measured as closely as possible. For children weighing 15 kg or more, the suspension should be administered using an appropriate measuring device.

Intravenous (IV) Solution Preparation for IV Administration:
Reconstitution: Prepare the initial IV solution for infusion by adding 4.8 mL of sterilized Water for Injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since azithromycin IV is supplied under vacuum, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of sterilized Water for Injection is dispensed. Each mL

of reconstituted solution contains 100 mg azithromycin.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours below 30˚C. When diluted according to the instructions, the diluted solution is chemically and physically stable for 24 hours at or below 30°C or for 7 days if stored under refrigeration 5˚C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Dilute this solution further prior to administration as instructed below:
Dilution: To provide azithromycin over a concentration range of 1.0-2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:

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

The Reconstituted Solution can be diluted with:
Normal Saline (0.9% sodium chloride)
½ Normal Saline (0.45% sodium chloride)
5% Dextrose in Water
Lactated Ringer's Solution
5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride) with 20 mEq KCl
5% Dextrose in Lactated Ringer's Solution
5% Dextrose in 1/3 Normal Saline (0.3% sodium chloride)
5% Dextrose in 1/2 Normal Saline (0.45% sodium chloride)
Normosol®-M in 5% Dextrose
Normosol®-R in 5% Dextrose

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

Any unused product or waste material should be disposed of in accordance with local requirements.

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