

AUSTRALIAN PRODUCT INFORMATION – ZITHROMAX[®] (AZITHROMYCIN DIHYDRATE)

1. NAME OF THE MEDICINE

Azithromycin dihydrate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Zithromax capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin.

Zithromax tablets contain azithromycin dihydrate equivalent to 250 mg, 500 mg or 600 mg of azithromycin.

Zithromax powder for oral suspension (POS) contains zithromycin dihydrate equivalent to 200 mg of azithromycin per 5 mL of suspension, when reconstituted.

Excipient(s) with known effect

Excipient(s) with known effect in capsules: sugars as lactose

Excipient(s) with known effect in tablets: lactose

Excipient(s) with known effect in powder for oral suspension: sugars (each 5 mL of reconstituted product contains 3.87 g of sucrose).

For the full list of excipients, see Section 6.1, List of excipients.

3. PHARMACEUTICAL FORM

Zithromax capsules are No.0 capsules with a white body and a white cap printed in black with “Pfizer” and “ZTM-250”.

Zithroax 250 mg tablets are white to off white, unscored, modified capsule shaped film coated tablets, engraved with with “Pfizer” on one side and “ZTM 250” on the other side.

Zithromax 500 mg tablets are white to off white, unscored, modified capsule shaped film coated tablets, engraved with “Pfizer” on one side and “ZTM 500” on the other side.

Zithromax 600 mg tablets are white to off white, scored, modified oval film coated tablets engraved with 'ZTM 600' on one side and 'PFIZER' on the other side.

Zithroax powder for oral suspension (POS) is a white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin is indicated for use in adults for the treatment of the following infections of mild to moderate severity:

Lower respiratory tract infections:

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

Community acquired pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients suitable for outpatient oral treatment.

Community acquired pneumonia caused by susceptible organisms in patients who require initial intravenous therapy. In clinical studies efficacy has been demonstrated against *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*.

Upper respiratory tract infections:

Acute sinusitis due to *Streptococcus pneumoniae* or *Haemophilus influenzae*.

Acute Streptococcal pharyngitis. Note: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin appears to be almost as effective in the treatment of Streptococcal pharyngitis. However, substantial data establishing the efficacy of azithromycin in the subsequent prevention of rheumatic fever are not available at present.

Uncomplicated skin and skin structure infections:

Uncomplicated infections due to *Staphylococcus aureus*, *Streptococcus pyogenes* or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

Sexually transmitted diseases: Uncomplicated urethritis and cervicitis due to *Chlamydia trachomatis*.

Note: At the recommended dose azithromycin cannot be relied upon to treat gonorrhoea or syphilis. As with other drugs for the treatment of non-gonococcal infections, it may mask or delay the symptoms of incubating gonorrhoea or syphilis. Appropriate tests should be performed for the detection of gonorrhoea or syphilis and treatment should be instituted as required.

Azithromycin is also indicated for the treatment of *Chlamydia trachomatis* conjunctivitis and trachoma.

Azithromycin is also indicated for the prevention of infection due to *Mycobacterium avium-intracellulare* complex (MAC) disease, when used as the sole agent or in combination with rifabutin at its approved dose, in adults and children aged more than 12 years with HIV infection and CD4 cell count less than or equal to 75 cells/ μ L (see Section 4.4 Special warnings and precautions for use). Disseminated infection due to *Mycobacterium avium-*

intracellulare complex should be excluded by a negative blood culture prior to commencement of therapy.

Azithromycin is indicated for use in children for the treatment of the following infections:

Acute Streptococcal pharyngitis/tonsillitis:

Note: Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. *The 20 mg/kg azithromycin dose appears to be as effective as penicillin in the treatment of Streptococcal pharyngitis.* However, substantial data establishing the efficacy of azithromycin in the subsequent prevention of rheumatic fever are not available at present.

***Chlamydia trachomatis* conjunctivitis and trachoma in children 12 months or older.**

4.2 Dose and method of administration

Dosage

Azithromycin should be given as a single daily dose.

Tablets and POS may be taken with food.

Administration of capsules with or following a meal significantly reduces the bioavailability. Therefore, capsules must be taken at least 1 hour before or 2 hours after a meal.

Adults

Sexually transmitted uncomplicated urethritis and cervicitis due to *Chlamydia trachomatis*: 1 g as a single dose.

Conjunctivitis and trachoma due to *Chlamydia trachomatis*: 1 g either as a single dose or once weekly for up to 3 weeks (see Section 5.1, Pharmacodynamic properties).

Following IV therapy for the treatment of CAP: 500 mg as a single daily dose to complete a 7 to 10 day course of therapy.

Prevention of disseminated MAC: 1200 mg taken as a single dose once weekly, either alone, or in combination with rifabutin, at its recommended dosage.

All other indications (including outpatients initiated on oral treatment of CAP due to *S. Pneumoniae* or *H. Influenzae*): Total dose of 1.5 g given as 500 mg on day 1, then 250 mg daily on days 2 to 5 or alternatively as 500 mg daily for 3 days.

Children (powder for oral suspension)

Conjunctivitis and trachoma due to *Chlamydia trachomatis*: 20 mg/kg either as a single dose or once weekly for up to 3 weeks.

Streptococcal pharyngitis and tonsillitis: 10 mg/kg or 20 mg/kg once daily for 3 consecutive days providing a total dose of 30 mg/kg or 60 mg/kg over a 3-day treatment period. Do not exceed a daily dose of 500 mg (or 12.5 mL of the reconstituted powder for oral suspension). For children weighing > 45 kg dose as per adults.

Azithromycin powder for oral suspension in the bottle presentation contains azithromycin 200 mg/5mL (40 mg/mL) when mixed with water as directed.

Method of administration

Capsules, tablets and POS: Oral

Oral suspension

Each presentation in bottles contains azithromycin 200 mg/5 mL (40 mg/mL) when mixed with water as described below:

Tap the bottle to loosen the powder.

For the 600 mg presentation, add 9 mL of water. Shake well to produce 15 mL of suspension. Just prior to use, shake well.

After reconstitution, the suspension should be stored below 30°C and any remaining suspension discarded after 10 days.

For children weighing less than 15 kg, ZITHROMAX oral suspension should be measured as closely as possible using the calibrated syringe provided.

A calibrated syringe is provided as the measuring device.

4.3 Contraindications

Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any other macrolide or ketolide antibiotic, or to any of the inactive ingredients in the product (see Section 6.1, List of excipients).

4.4 Special warnings and precautions for use

Use with caution in the following circumstances

In the treatment of pneumonia, azithromycin has been shown to be safe and effective only in the treatment of community-acquired pneumonia (CAP) of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy. 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 nosocomially acquired infections
- patients with known or suspected bacteraemia
- patients requiring hospital admission
- elderly or debilitated patients
- patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

***Clostridium difficile*-associated diarrhoea**

Antibiotic-associated pseudomembranous colitis has been reported with the use of many antibiotics including azithromycin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases may respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

Drugs which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Hypersensitivity

Rare, serious, allergic reactions, including angioedema and anaphylaxis (rarely fatal); dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal); and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients on azithromycin therapy (see Section 4.3, Contraindications). Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

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.

Prolongation of the QT interval

Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide products including azithromycin. Prescribers should consider the risk of QT prolongation (which can be fatal) when weighing the risks and benefits of azithromycin for at-risk groups including:

- patients predisposed to QT interval prolongation
- patients taking other medications known to prolong the QT interval such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones
- patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- elderly patients, as they may be more susceptible to drug-associated effects on the QT interval.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis have been reported in patients receiving azithromycin therapy.

Diabetes

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

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

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

Superinfection

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

Other

The majority of cases of disseminated *Mycobacterium avium* complex infection occur in patients with CD₄ counts below 50 cells/ μ L. Some authorities recommend delay of initiation of prophylaxis until the cell count has fallen to 50 cells/ μ L.

No evidence exists from formal studies to determine the need for, and frequency of, repeat dosing in the treatment of trachoma.

Use in hepatic impairment

No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Nonetheless, since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease (see Section 5, Pharmacological properties).

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.

Use in renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment (GFR 10 - 80 mL/min). After oral administration of a single dose of azithromycin 1 g in subjects with severe renal impairment (GFR <10 mL/min), mean AUC_{0-120h} and mean C_{max} were increased by approximately 30% and 60%, respectively when compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to patients with severe renal impairment.

Use in the elderly

See Section 5.2, Pharmacokinetic properties

Paediatric use

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

Effects on laboratory tests

There are no reported laboratory test interactions.

4.5 Interactions with other medicines and other forms of interactions

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

Drugs that should not be concomitantly administered with azithromycin

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by up to 30%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Ergot: Due to the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered (see Section 4.4 Special warnings and precautions for use, Ergot derivatives).

Drugs that require dosage adjustment when administered concomitantly with azithromycin

Cyclosporin

In a pharmacokinetic study with healthy volunteers who 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 cyclosporin, the resulting C_{max} and AUC₀₋₅ were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Drugs that have been studied with no clinically significant interaction shown

Atorvastatin

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

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.

Cetirizine

In healthy volunteers, coadministration of a 5-day regimen of azithromycin with 20 mg cetirizine 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, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-type oral anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of 15 mg warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time, when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Didanosine

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive subjects for 2 weeks had no effect on the steady state pharmacokinetics of didanosine as compared to placebo.

Efavirenz

Coadministration of a single dose of 600 mg azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions. No dose adjustment is necessary when azithromycin is given with efavirenz.

Fluconazole

Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed. No dose adjustment is necessary when azithromycin is given with fluconazole.

Indinavir

Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days. No adjustment of the dose is necessary when azithromycin is given with indinavir.

Methylprednisolone

In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam

In healthy volunteers, coadministration of 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg midazolam.

Nelfinavir

Coadministration of 1200 mg azithromycin and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.

Rifabutin

Coadministration 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. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its major circulating metabolite.

Terfenadine, astemizole

In a study in normal subjects addition of azithromycin did not result in any significant changes in cardiac repolarisation (QTc interval) measured during the steady state dosing of terfenadine. However, there have been cases reported where the possibility of such an interaction could not be entirely excluded.

Theophylline

There is no evidence of any pharmacokinetic interaction when azithromycin and theophylline are coadministered to healthy volunteers.

Triazolam

In 14 healthy volunteers, coadministration of 500 mg azithromycin on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole

Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with 1200 mg azithromycin 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. No dose adjustment is necessary.

Zidovudine

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin 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. The clinical significance of this finding is unclear.

Other interactions

Digoxin and colchicine: Some of the macrolide antibiotics including azithromycin have been reported to impair the metabolism of P-glycoprotein substrates such as digoxin and colchicine (in the gut) in some patients and to result in increased serum levels. In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin, the possibility of raised digoxin levels should be borne in mind. During treatment with azithromycin and after discontinuation thereof, clinical monitoring and measurement of serum digoxin levels may be necessary.

4.6 Fertility, pregnancy and lactation

Effects on fertility

In three fertility and general reproduction studies in rats, there was decreased fertility at doses of 20 and 30 mg/kg/day. The clinical significance of this is unknown.

Use in pregnancy – Category B1

No studies have been carried out in pregnant women. Azithromycin was not fetotoxic or teratogenic in mice and rats at doses that were moderately maternotoxic (up to 200 mg/kg/day). At 200 mg/kg/day, mouse and rat fetal tissues homogenate concentrations were 5 to 10-fold higher than corresponding maternal plasma concentrations.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Use in lactation

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. 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.

4.7 Effects on ability to drive and use machines

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Adverse effects (undesirable effects)

Clinical trials

In clinical trials, most of the reported adverse events were mild to moderate in severity and were reversible on discontinuation of the drug. Approximately 0.7% of patients discontinued azithromycin therapy because of treatment-related adverse events. Most of the adverse events leading to discontinuation were related to the gastrointestinal tract, e.g. nausea, vomiting, diarrhoea or abdominal pain. Rare, but potentially serious, adverse events were angioedema (1 case) and cholestatic jaundice (1 case).

Hearing impairment has been reported in investigational studies, mainly where higher doses were used, for prolonged periods of time. In those cases where follow-up information was available the majority of these events were reversible.

Adults

Multiple-dose regimen: The most frequently reported adverse events in patients receiving the multiple-dose regimen of azithromycin were related to the gastrointestinal system with diarrhoea/loose stools (5%), nausea (3%) and abdominal pain (3%) being the most frequently reported. No other side effects occurred in patients on the multiple-dose regimen with a frequency >1%.

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

Allergic: rash, photosensitivity, angioedema.

Cardiovascular: palpitations, chest pain.

Gastrointestinal: dyspepsia, flatulence, vomiting, melaena, cholestatic jaundice.

Genitourinary: moniliasis, vaginitis, nephritis.

Nervous system: dizziness, headache, vertigo, somnolence.

General: fatigue.

Single 1-gram dose regimen: The most frequently reported adverse events in patients receiving a single-dose regimen of 1 gram of azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen. Adverse events that occurred in patients on the single 1-gram dosing regimen of azithromycin with a frequency of 1% or greater included diarrhoea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), vaginitis (2%) and dyspepsia (1%).

Laboratory abnormalities: Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

Incidence >1%: elevated serum creatinine phosphokinase, potassium, ALT (SGPT), GGT and AST (SGOT), lymphocytes and neutrophils; decreased neutrophils.

Incidence <1%: leukopenia, neutropenia, thrombocytopenia; elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate, monocytes, basophils, bicarbonate; decreased sodium, potassium.

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

In multiple-dose trials involving >3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 patient because of a renal function abnormality.

Table 1. Incidence of the Most Frequent (>5% in any Treatment Group) Treatment Related (%) Adverse Events in HIV Infected Patients Receiving Prophylaxis for Disseminated MAC

	Study 155		Study 174		
	Placebo	Azithromycin	Azithromycin	Rifabutin	Combination therapy
Adverse Event	N=91	N=89	N=233	N=236	N=224
Diarrhoea	15.4	52.8	50.2	19.1	50.9
Abdominal pain	6.6	27	32.2	12.3	31.7
Nausea	11.0	32.6	27.0	16.5	28.1
Loose stools	6.6	19.1	12.9	3.0	9.4
Flatulence	4.4	9.0	10.7	5.1	5.8
Vomiting	1.1	6.7	9.0	3.8	5.8
Dyspepsia	1.1	9.0	4.7	1.7	1.8
Rash	2.2	3.4	6.0	8.1	9.8
Pruritus	3.3	0	3.9	3.4	7.6
Headache	0	0	3.0	5.5	4.5
Arthralgia	0	0	3.0	4.2	7.1
Subjects with AE's	31.9	79.8	78.1	59.7	83.5

The most common laboratory test abnormalities were haematological (mainly decreases in haemoglobin and white cell count) and increases in AST and ALT.

Children

The side effect profile in children is comparable with that of adults. No new adverse events have been reported in children. In the treatment of Streptococcal pharyngitis the 20 mg/kg/day dose is associated with a higher rate of adverse events. These are mainly gastrointestinal and remain mild to moderate.

The following adverse events, where a causal relationship to treatment could not be ruled out, were reported at an occurrence of $\geq 1\%$:

Table 2. Adverse events that were reported at an occurrence of $\geq 1\%$

Category of Event	Event	Azithromycin Dose Study 96-001	
		10 mg/kg 3 day (n=169)	20 mg/kg 3 day (n=165)
Gastrointestinal system disorders	Abdominal pain	2%	5%
	Diarrhoea	3%	6%
	Nausea	1%	3%
	Vomiting	7%	9%
General condition disorders	Allergic reaction	2%	-
Skin and accessory structures	Eczema	1%	-
	Rash	1%	-

Post-marketing experience

In post marketing experience, the following adverse events have been reported:

Infections and infestations: moniliasis and vaginitis.

Blood and lymphatic system disorders: thrombocytopenia.

Cardiovascular disorders: hypotension; palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes.

Gastrointestinal disorders: vomiting/diarrhoea (rarely resulting in dehydration), dyspepsia, pancreatitis, constipation, pseudomembranous colitis, rare reports of tongue discolouration.

General disorders and administration site conditions: asthenia, fatigue and malaise.

Hepatobiliary disorders: abnormal liver function including hepatitis and cholestatic jaundice, hepatic necrosis and hepatic failure, which have resulted in death.

Immune system disorders: anaphylaxis (rarely fatal).

Metabolism and nutritional disorders: anorexia.

Musculoskeletal and connective tissue disorders: arthralgia.

Nervous system disorders: dizziness, convulsions, headache, hyperactivity, hypoesthesia, paraesthesia, somnolence, syncope.

Psychiatric disorders: aggressive reaction, nervousness, agitation, anxiety.

Renal and urinary tract disorders: acute renal failure, interstitial nephritis.

Skin and subcutaneous tissue disorders: allergic reactions including pruritus, rash, photosensitivity, urticaria, oedema, angioedema, serious skin reactions including erythema multiforme, acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson

syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS).

Special senses: hearing disturbances and/or impairment including hearing loss, deafness and/or tinnitus, vertigo. Taste/smell perversion and/or loss.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Most adverse events experienced in higher than recommended doses are similar in type and may be more frequent than those seen at normal doses. The incidence of tinnitus and ototoxicity is more frequent in overdosage than at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

As with many cationic amphiphilic drugs, phospholipidosis has been observed in some tissues of mice, rats and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems in dogs administered doses which, based on pharmacokinetics, are as low as 2-3 times greater than the recommended human dose and in rats at doses comparable to the human dose. This effect is reversible after cessation of azithromycin treatment. The significance of these findings for humans with overdose of azithromycin is unknown.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use. ATC code: J01FA10

Mechanism of action

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

Microbiology

Azithromycin demonstrates activity *in vitro* against a wide range of bacteria including:

Gram-positive aerobic bacteria – *Staphylococcus aureus*, *Streptococcus pyogenes* (group A beta-haemolytic Streptococci), *Streptococcus pneumoniae*, alpha-haemolytic Streptococci (viridans group) and other Streptococci, and *Corynebacterium diphtheriae*. Azithromycin demonstrates cross-resistance with erythromycin-resistant Gram-positive strains, including *Streptococcus faecalis* (Enterococcus) and to most strains of methicillin-resistant Staphylococci.

Gram-negative aerobic bacteria – *Haemophilus influenzae* (including beta-lactamase producing *Haemophilus influenzae*), *Haemophilus parainfluenzae*, *Moraxella catarrhalis*, *Acinetobacter* species, *Yersinia* species, *Legionella pneumophila*, *Bordetella pertussis*, *Bordetella parapertussis*, *Shigella* species, *Pasteurella* species, *Vibrio cholerae* and *parahaemolyticus*, *Plesiomonas shigelloides*. Activities against *Escherichia coli*, *Salmonella enteritidis*, *Salmonella typhi*, *Enterobacter* species, *Aeromonas hydrophila* and *Klebsiella* species are variable and susceptibility tests should be performed. *Proteus* species, *Serratia* species, *Morganella* species, and *Pseudomonas aeruginosa* are usually resistant.

Anaerobic bacteria – *Bacteroides fragilis* and *Bacteroides* species, *Clostridium perfringens*, *Peptococcus* species, *Peptostreptococcus* species, *Fusobacterium necrophorum* and *Propionibacterium acnes*.

Organisms of sexually transmitted diseases – Azithromycin is active against *Chlamydia trachomatis* and also shows good activity against *Treponema pallidum*, *Neisseria gonorrhoeae* and *Haemophilus ducreyi*.

Other organisms – *Borrelia burgdorferi* (Lyme disease agent), *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, *Campylobacter* species and *Listeria monocytogenes*.

Opportunistic pathogens associated with human immunodeficiency virus (HIV) infections – *Mycobacterium avium-intracellulare* complex (MAC).

Azithromycin demonstrates activity *in vivo* against the following bacteria:

Gram-positive aerobic bacteria - *Staphylococcus aureus*, *Streptococcus pyogenes* (group A beta-haemolytic Streptococci), *Streptococcus pneumoniae*, alpha-haemolytic Streptococci (viridans group) and other Streptococci.

Gram-negative aerobic bacteria - *Haemophilus influenzae* (including beta-lactamase producing *Haemophilus influenzae*), *Haemophilus parainfluenzae*, *Moraxella catarrhalis*.

Other organisms - *Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*.

Opportunistic pathogens associated with HIV infections - MAC.

In Australia, macrolide resistance for *Streptococcus pneumoniae* and *Staphylococcus aureus* has been increasing since the late 1990's. Resistance rates of 15% or more are regularly reported. The use of macrolides should be guided by culture susceptibility results and practice guidelines.

Susceptibility testing

Dilution or Diffusion techniques – either quantitative (minimal inhibitory concentration [MIC]) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited when the patient is given the recommended dose. 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 site 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 when the patient is given the recommended dose; other therapy should be selected.

Susceptibility testing for Mycobacterium avium complex (MAC)

The disk diffusion techniques and dilution methods for susceptibility testing against Gram-positive and Gram-negative bacteria should not be used for determining azithromycin MIC values against mycobacteria. *In-vitro* susceptibility testing methods and diagnostic products currently available for determining MIC values against MAC organisms have not been established or validated. Azithromycin MIC values will vary depending on the susceptibility testing method employed, composition and pH of media and the utilization of nutritional supplements. Breakpoints to determine whether clinical isolates of *M. avium* or *M. intracellulare* are susceptible to azithromycin have not been established.

Clinical trials

Disseminated MAC disease prophylaxis

In a placebo-controlled study patients receiving azithromycin were less than one-half as likely to develop MAC bacteraemia as those on placebo. The 1-year cumulative incidence rate of disseminated MAC disease was 8.24% on azithromycin and 20.22% on placebo.

In a comparative study the risk of developing MAC bacteraemia in patients receiving azithromycin was less than that observed for patients receiving rifabutin. Patients on a combination of azithromycin and rifabutin were approximately one-third as likely to develop MAC bacteraemia as those patients receiving either agent alone. The 1-year cumulative incidence rate of disseminated MAC disease was 7.62% on azithromycin, 15.25% on rifabutin and 2.75% on azithromycin and rifabutin. However, patients receiving the combination were more likely to discontinue therapy due to poor tolerability.

Trachoma

Trachoma – children and adults

Information from clinical trial data and published reports of studies supports the efficacy of 20 mg/kg to 1 g, taken either as a single dose or each week for three weeks, in the treatment of trachoma in children and adults. The single dose schedule has not been compared with the three weekly dosing schedule in clinical trials.

Trachoma - repeat courses

While the statistically significant superiority of a single dose of azithromycin given as a single dose and repeated at 6 months versus a single dose of azithromycin to adults or children with active trachoma has not been determined, information from clinical trial data suggests that the trachoma free period may be extended by a repeat single dose of azithromycin at 6 months.

Pharyngitis/tonsillitis

In a clinical trial (study 96-001), 501 children aged 2 to 12 years with a clinical diagnosis of acute tonsillitis received azithromycin 10 mg/kg/day or 20 mg/kg/day for 3 days or penicillin V, 50 mg/kg (in 3 divided doses) for 10 days. (Note the recommended dose for penicillin V in Australia is 20 mg/kg/day). Similar clinical efficacy but greater bacteriological eradication was evident at the 20 mg/kg/day dose (the daily dose did not exceed 500 mg). Group A beta-haemolytic Streptococci (GABHS) eradication rates and clinical response rates are detailed below:

Table 3. GABHS Eradication Rates at Day 14 and Day 30

<u>Treatment</u>	<u>Day 14</u>	<u>Day 30</u>
Azithromycin 10 mg/kg	57.8 %	56.8 %
Azithromycin 20 mg/kg	94.2 %	82.8 %
Penicillin V 50 mg/kg	84.2 %	81.6 %

Table 4. Clinical Response Rates (Success) at Day 14

<u>Treatment</u>	<u>Day 14</u>
Azithromycin 10 mg/kg	94.1 %
Azithromycin 20 mg/kg	100.0%
Penicillin V 50 mg/kg	94.5%

5.2 Pharmacokinetic properties

Absorption

Capsules and tablets

Following oral administration of a 500 mg dose, azithromycin is absorbed from the gastrointestinal tract with an absolute bioavailability of 37%. Maximum serum concentration (C_{max}) of 0.3 - 0.4 µg/mL is achieved in 2 to 3 hours with an area under the curve $AUC_{(0-24)}$ of 2.6 µg hr/mL.

Food decreases the bioavailability of ZITHROMAX capsules by 50% but has no significant effect on the bioavailability of the ZITHROMAX tablets, even after a high fat meal.

Pharmacokinetics in elderly subjects are substantially the same and no dosage adjustment is necessary. The extent of absorption is unaffected by coadministration with antacid; however, C_{max} is reduced by up to 30%. Administration of an 800 mg dose of cimetidine two hours prior to azithromycin had no effect on azithromycin absorption. Azithromycin did not affect the plasma levels or pharmacokinetics of carbamazepine, methylprednisolone, zidovudine or multiple oral doses of theophylline (see Section 4.5, Interactions with other medicines and other forms of interactions).

Distribution

Serum concentrations decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. The high values for apparent steady-state volume of distribution (31.1 L/kg) and plasma clearance (630 mL/min) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues. Azithromycin concentrations in the cerebro-spinal fluid are very low. Concentrations in the peritoneal fluid are also very low.

Azithromycin is distributed widely throughout the body. Rapid movement of azithromycin from blood into tissues results in significantly higher azithromycin concentrations in tissues than in plasma (from 1-60 times the maximum observed concentration in plasma). It appears to be concentrated intracellularly. Concentrations in tissues, such as lung, tonsil and prostate, etc exceed the MIC90 for likely pathogens after a single dose of 500 mg, and remain high after serum or plasma concentrations decline to below detectable levels. Mean peak concentrations observed in peripheral leucocytes, the site of MAC infection, were 140 µg/mL and remained above 32 µg/mL for approximately 60 hours following a single 1200 mg oral dose.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 2 µg/mL.

Metabolism

Very high concentrations of unchanged drug have been found, together with 10 metabolites, formed by N- and O-demethylation, hydroxylation of the desosamine and aglycone rings, and cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Excretion

Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug following oral administration.

Following a single oral dose of azithromycin 1 gram, the pharmacokinetics in subjects with mild to moderate renal impairment (GFR 10 – 80 mL/min) were not affected. Statistically significant differences in AUC₀₋₁₂₀ (8.8 µg.hr/mL vs. 11.7 µg.hr/mL), C_{max} (1.0 µg/mL vs. 1.6 µg/mL) and CL_r (2.3 mL/min/kg vs. 0.2 mL/min/kg) were observed between subjects with severe renal impairment (GFR <10 mL/min) and subjects with normal renal function.

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients.

Powder for oral suspension

Bioavailability studies in the fed and fasted state have been conducted with azithromycin. Administration of azithromycin immediately following a high fat meal resulted in a slight increase in the rate of absorption but no change in the fraction of the dose absorbed. This effect is probably of no clinical significance. A separate bioavailability study has confirmed bioequivalence between the powder for suspension and sachet.

Azithromycin has similar pharmacokinetic characteristics in adults and children. There is a linear relationship between AUC and C_{max} and dose, for doses between 10 and 20 mg/kg daily in children.

5.3 Preclinical safety data

Genotoxicity

Azithromycin showed no genotoxic potential in a range of standard laboratory tests for gene mutations and chromosomal damage.

Carcinogenicity

No studies have been done to determine the carcinogenic potential of azithromycin in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Zithromax capsules contain the following inactive ingredients: gelatin, lactose, magnesium stearate, maize starch, sodium lauryl sulfate, TekPrint SW-9008 Black Ink (ARTG PI No 2328) and titanium dioxide.

Zithromax tablets contain the following inactive ingredients: pregelatinised maize starch, calcium hydrogen phosphate, croscarmellose sodium, magnesium stearate, and sodium lauryl sulfate. The coating of the tablets contains lactose monohydrate, hypromellose, titanium dioxide and triacetin.

Zithromax powder for oral suspension contains the following inactive ingredients: sucrose, tribasic sodium phosphate, hypolose, xanthan gum, Spray Dried Artificial Cherry 11929 (ARTG PI No 2470), Spray Dried Artificial Banana 15223 (ARTG PI No 2469) and Crema Vaniglia N11489 Polvere SC613737 AR (ARTG PI No 117797).

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

Powder for oral suspension

After reconstitution, the suspension should be stored below 30°C and any remaining suspension discarded after 10 days.

6.5 Nature and contents of container

ZITHROMAX capsules 250mg[†] are packaged in PVC/aluminium blister packs of 4 or 6 capsules.

ZITHROMAX tablets 250 mg[†] are packaged in PVC/aluminium blister packs of 2, 4, 6 and 30 tablets.

ZITHROMAX tablets 500 mg are packaged in PVC/aluminium blister packs of 2, 3 and 15[†] tablets.

ZITHROMAX 600 mg are packaged in PVC/aluminium blister packs of 2[†], 8 and 24[†] tablets.

ZITHROMAX powder for oral suspension is supplied in four pack sizes: 600 mg/15 mL, 900mg /22.5 mL[†], 1200 mg/30 mL[†] and 1500 mg/37.5 mL[†] (when reconstituted) packaged in HDPE bottles.

[†] Not currently marketed in Australia.

6.6 Special precautions for disposal

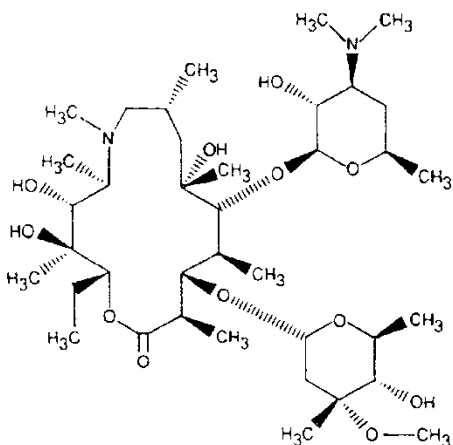
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Azithromycin is the first of a new class of antibiotics designated chemically as azalides, a subclass of macrolides, available for oral administration. Azithromycin, chemically 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, contains a methyl substituted nitrogen atom at position 9A of the lactone ring.

Azithromycin dihydrate is a white crystalline powder with a chemical formula of C₃₈H₇₂N₂O₁₂.2H₂O and a molecular weight of 785.0.

Chemical structure



CAS number

117772-70-0.

7. MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4).

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
SYDNEY NSW 2000

Toll Free Number: 1800 675 229.
www.pfizer.com.au.

9. DATE OF FIRST APPROVAL

8 April 1994.

10. DATE OF REVISION

16 July 2021

Summary Table of Changes

Section changed	Summary of new information
2	Sucrose content corrected
6.7	CAS number corrected to refer to Azithromycin Dihydrate