NEW ZEALAND DATA SHEET

1. PRODUCT NAME

ZITHROMAX® 250 mg, 500 mg and 600 mg tablets, film-coated

ZITHROMAX® 40 mg/mL powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

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

Powder for oral suspension

Powder for oral suspension (POS) contains azithromycin dihydrate equivalent to 40 mg/mL azithromycin solution following reconstitution.

For the full list of excipients, see section 6.1.

Excipients with known effects

Each mL of POS contains 925.04mg/g of sucrose.

3. PHARMACEUTICAL FORM

Tablets:

White, film-coated, capsular shaped tablets.

Powder for oral suspension

White powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Adults

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 pneumophilia, 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.

Acute otitis media

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* or non multi-resistant *Neisseria gonorrhoeae*.

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

Pelvic inflammatory disease

Caused by susceptible organisms (*Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma hominis*), in patients who require initial intravenous therapy.

Chlamydia trachomatis conjunctivitis and trachoma

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 with HIV infection and CD4 cell count less than or equal to 75 cells/μL (see section 4.4). Disseminated infection due to *Mycobacterium avium-intracellulare* complex should be excluded by a negative blood culture prior to commencement of therapy.

Paediatric population

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

Lower respiratory tract infections

See ADULT INDICATIONS above.

Upper respiratory tract infections

See ADULT INDICATIONS above.

Uncomplicated skin and skin structural infections

See ADULT INDICATIONS above.

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 children aged more than 12 years with HIV infection and CD4 cell count less than or equal to 75 cells/μL (see section 4.4). Disseminated infection due to *Mycobacterium avium-intracellulare* complex should be excluded by a negative blood culture prior to commencement of therapy.

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

Dose

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 or susceptible Neisseria gonorrhoeae

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).

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.

Following IV therapy for the treatment of pelvic inflammatory disease

250 mg as a single daily dose to complete a 7 day course of therapy.

Prevention of disseminated MAC disease in adults with HIV infection

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 taken 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

Conjunctivitis and trachoma due to Chlamydia trachomatis in children 12 months or older

20 mg/kg either as a single dose or once weekly for up to 3 weeks.

Prevention of disseminated MAC disease in children aged more than 12 years with HIV infection

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

Streptococcal pharyngitis and tonsillitis

20 mg/kg once daily for 3 consecutive days providing a total dose of 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.

Acute Otitis Media

Total dose of 30 mg/kg given as 30 mg/kg as a single dose or 10 mg/kg once daily for 3 days or 10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on days 2-5. For children weighing >45 kg dose as per adults.

All other indications

10 mg/kg as a single dose on the first day followed by 5 mg/kg/day on days 2-5. For children weighing >45 kg dose as per adults.

Method of administration

Oral suspension

Oral Suspension in bottles may be taken with food.

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 hypersensitivity to azithromycin, erythromycin, any other macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1.

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).

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). 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.

Hepatotoxicity

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 5.2).

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.

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.

***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.

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 $AUC_{0\text{-}120h}$ 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.

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.

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.

Other

The majority of cases of disseminated *Mycobacterium avium* complex infection occur in patients with CD_4 counts below 50 cells/µL. Some authorities recommend delay of initiation of prophylaxis until the cell count has fallen to 50 cells/µL.

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

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, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 4.4, 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 AUC_{0-5} 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

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.

Pregnancy

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.

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. Azithromycin should only be used in lactating women where adequate alternatives are not available.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect on the patient's ability to drive or operate machinery.

4.8 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.

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 ≥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, anorexia, 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).

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 disorders: acute renal failure, interstitial nephritis.

Skin and subcutaneous tissue disorders: allergic reactions including pruritus, rash, photosensitivity, urticaria, oedema, angioedema, serious skin reactions including erythrema 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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSAGE

Most adverse events experienced in higher than recommended doses were 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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial agent: macrolides

ATC code: J01FA10

Mechanism of action

Azithromycin binds to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology

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

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.

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N_6)-dimethylation of adenine at nucleotide A2058 (*Escherichia coli* numbering system) of the 23S rRNA by methylases encoded by *erm* (*e*rythromycin *r*ibosome *m*ethylase) genes. Ribosomal modifications often determine cross resistance (MLS_B phenotype) to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different *erm* genes are present in different bacterial species, in particular Streptococci and Staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA, or in the large subunit ribosomal proteins L4 and L22.

Efflux pumps occur in a number of species, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher minimal inhibitory concentrations [MICs]) and Staphylococci. In Streptococci and Enterococci, an efflux pump that recognises 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef* (A) genes.

Microbiology

Methodology for determining the in vitro susceptibility of bacteria to azithromycin

Susceptibility testing should be conducted using standardized laboratory methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (MIC determination) and disk susceptibility methods. Both CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretive criteria for these methods.

Based on a number of studies, it is recommended that the in vitro activity of azithromycin be tested in ambient air to ensure physiological pH of the growth medium. Elevated CO_2 tensions, as often used for Streptococci and anaerobes, and occasionally for other species, result in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides.

The CLSI susceptibility breakpoints, based on broth microdilution or agar dilution testing, with incubation in ambient air, are given in the table below.

CLSI Dilution Susceptibility Interpretive Criteria

	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≤ 4	-	-[b]
Moraxella catarrhalis	≤ 0.25	-	-

CLSI Dilution Susceptibility Interpretive Criteria

	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Neisseria meningitidis	≤ 2	-	-[b]
Staphylococcus aureus	≤ 2	4	≥ 8
Streptococci [a]	≤ 0.5	1	≥ 2

[a] Includes *Streptococcus pneumoniae*, β-haemolytic Streptococci and viridans Streptococci.
[b] The current absence of data on resistant strains precludes defining any category other than susceptible. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.
Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration.
Source: CLSI M45, 2015. CLSI M100, 2018.

Susceptibility can also be determined by the disk diffusion method, measuring inhibition zone diameters after incubation in ambient air. Susceptibility disks contain 15 µg of azithromycin. Interpretive criteria for inhibition zones, established by the CLSI on the basis of their correlation with MIC susceptibility categories, are listed in the table below.

CLSI Disk Zone Interpretive Criteria

	Disk inhibition zone diameter (mm)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≥ 12	-	-
Moraxella catarrhalis	≥ 26	-	-
Neisseria meningitidis	≥ 20	-	-
Staphylococcus aureus	≥ 18	14 - 17	≤ 13
Streptococci [a]	≥ 18	14 - 17	≤ 13

[a] Includes *Streptococcus pneumoniae*, β-haemolytic Streptococci and viridans Streptococci.
Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; mm = Millimeters.
Source: CLSI M45, 2015. CLSI M100, 2018.

The validity of both the dilution and disk diffusion test methods should be verified using quality control (QC) strains, as indicated by the CLSI. Acceptable limits when testing azithromycin against these organisms are listed in the table below.

Quality Control Ranges for Azithromycin Susceptibility Tests

Broth microdilution MIC	
Organism	**Quality control range (mg/L azithromycin)**
Haemophilus influenzae ATCC 49247	1 - 4
Staphylococcus aureus ATCC 29213	0.5 - 2
Streptococcus pneumoniae ATCC 49619	0.06 - 0.25
Disk inhibition zone diameter (15 µg disk)	
Organism	**Quality control range (mm)**
Haemophilus influenzae ATCC 49247	13 - 21
Staphylococcus aureus ATCC 25923	21 - 26
Streptococcus pneumoniae ATCC 49619	19 - 25

Incubation in ambient air.
MIC = Minimal inhibitory concentration; mm = Millimeters.
Source: CLSI M100, 2018.

EUCAST has also established susceptibility breakpoints for azithromycin based on MIC determination. The EUCAST susceptibility criteria are listed in the table below.

EUCAST Susceptibility Breakpoints for Azithromycin

	MIC (mg/L)	
	Susceptible	**Resistant**
Staphylococcus species	≤ 1	> 2
Streptococcus pneumoniae	≤ 0.25	> 0.5
β-haemolytic Streptococci [a]	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

[a] Includes Groups A, B, C, G.
EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = Minimal inhibitory concentration.
Source: EUCAST website.
EUCAST Clinical Breakpoint Table v. 8.0, valid from 2018-01-01
www.eucast.org/.../EUCAST.../Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf

Antibacterial spectrum

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive isolates. As discussed above, some ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin) and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in viridans streptococci and *Streptococcus agalactiae.*

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible isolates): *S. aureus*, *Streptococcus agalactiae*,* *S. pneumonia*,* *Streptococcus pyogenes*,* other β-haemolytic streptococci (Groups C, F, G), and viridans Streptococci. Macrolide-resistant isolates are encountered relatively frequently among aerobic and facultative Gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP).

Aerobic and facultative Gram-negative bacteria: *Bordetella pertussis*, *Campylobacter jejuni, Haemophilus ducreyi,** *Haemophilus influenza,** *Haemophilus parainfluenzae,** *Legionella pneumophila*, *Moraxella catarrhalis,** and *Neisseria gonorrhoeae.** *Pseudomonas* spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* infections.

Anaerobes: *Clostridium perfringens*, *Peptostreptococcus* spp. and *Prevotella bivia*.

Other bacterial species: *Borrelia burgdorferi*, *Chlamydia trachomatis*, *Chlamydophila pneumonia,** *Mycoplasma pneumonia,** *Treponema pallidum,* and *Ureaplasma urealyticum*.

Opportunistic pathogens associated with HIV infection: *Mycobacterium avium* complex (MAC),* and the eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.

∗The efficacy of azithromycin against the indicated species has been demonstrated in clinical trials.

Clinical efficacy and safety

Disseminated MAC disease prophylaxis

In a placebo-controlled study patients receiving azithromycin were less than one-half as likely to develop MAC bacteremia 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 diagnoses 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:

GABHS Eradication Rates at Day 14 and Day 30

Treatment	Day 14	Day 30
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 %

Clinical Response Rates (Success) at Day 14

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

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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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).

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.

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 MIC_{90} 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.

Distribution

Azithromycin is distributed widely throughout the body.

Biotransformation

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.

Elimination

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 AUC_{0-120} (8.8 µg.hr/mL vs. 11.7 µg.hr/mL), C_{max} (1.0 µg/mL vs. 1.6 µg/mL) and CLr (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.

<u>Powder for oral suspension</u>

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.

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

Tablets

Pregelatinised maize starch-, calcium hydrogen phosphate, croscarmellose sodium, magnesium stearate, and sodium lauryl sulfate. The coating of the tablets contains lactose, hypromellose, titanium dioxide and glycerol triacetate. Powder for oral suspension

Sucrose, sodium phosphate-tribasic, hyprolose, xanthan gum, cherry flavour, banana flavour and vanilla flavour.

6.2 Incompatibilities

Incompatibilities with other medicines - None known.

6.3 Shelf life

Tablet 250 mg - 36 months

Tablet 500 mg – 60 months

Tablet 600 mg – 24 months

Powder for oral suspension 200 mg/5 mL – 60 months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Tablets are embossed with "ZTM 500" on one side, and with "Pfizer" on the other, and are scored. ZITHROMAX tablets 500 mg are packaged in blister packs of 2, 3 and 15[†] tablets and bottles of 30[†] tablets.

There are four pack sizes: 600 mg/15 mL, 900 mg/22.5 mL[†], 1200 mg/30 mL[†] and 1500 mg/37.5 mL[†] packaged in HDPE bottles.

[†] Not currently marketed in New Zealand.

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine.

8. SPONSOR

Pfizer New Zealand Limited
PO Box 3998
Auckland, New Zealand

Toll Free number: 0800 736 363

9. DATE OF FIRST APPROVAL

Tablet 250 mg and 500 mg – 16 October 1997

Tablet 600 mg – 13 July 2000

Powder for oral suspension 200 mg/5 mL – 16 December 1993

10. DATE OF REVISION OF THE TEXT

26 July 2018

Summary of updates (26 July 2018)

Section	Update
Section 4.5	Update for Drug Interaction with colchicine
Section 4.6	Update to lactation information
Section 5.1	Update to Clinical and Laboratory Standards Institute references and EUCAST reference