APOTEX NZ LTD

NEW ZEALAND DATA SHEET

APO-AZITHROMYCIN

1. APO-AZITHROMYCIN (250mg and 500mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azithromycin 250mg and 500mg (as dihydrate)

Excipient(s) of known effect
APO-AZITHROMYCIN does not contain gluten or lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Apo-Azithromycin 250mg tablets are white, oval, film coated tablets embossed “AZ250” one side and “APO” on the other. Each tablet contains azithromycin dihydrate equivalent to azithromycin 250mg.

Apo-Azithromycin 500mg tablets are white, oval, film coated tablets embossed “AZ500” one side and “APO” on the other. Each tablet contains azithromycin dihydrate equivalent to azithromycin 500mg.”

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:

1. **Lower respiratory tract infections:**

   Acute bacterial bronchitis due to *Streptococcus pneumoniae, Haemophilus influenza* 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*.

2. **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

3. **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, Nessieria gonorrhoea, Mycoplasma hominis*), in patients who require initial intravenous therapy.

4. ***Chlamydia trachomatis* conjunctivitis and trachoma**

5. **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 (refer 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:

1. **Lower respiratory tract infections** (see ADULT INDICATIONS above).

2. **Upper respiratory tract infections** (see ADULT INDICATIONS above).

3. **Uncomplicated skin and skin structural infections** (see ADULT INDICATIONS above).

4. **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 (refer 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.

5. **Acute streptococcal pharyngitis/tonsillitis.**

6. 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.

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

4.2 Dose and method of administration

This product is not able to deliver all approved dose regimens.
Azithromycin should be given as a single daily dose.

Tablets may be taken with food.

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 three weeks (refer section 5.1 Pharmadynamic Properties, Clinical Trials).

Following IV therapy for the treatment of Community Acquired Pneumoniae: 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 *Mycobacterium avium* complex (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: 20mg/kg either as a single dose or once weekly for up to three weeks.

Prevention of disseminated *Mycobacterium avium* complex (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. 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.

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.

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 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 or
- 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 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 *Clostridium 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) and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis (rarely fatal) have been reported in patients on azithromycin therapy (refer 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.

Use in renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment. After oral administration of a single dose of azithromycin 1g 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.

Hepatotoxicity

No dose adjustment is recommended for patients with mild to moderate hepatic impairment (GFR 10 - 80 mL/min). 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 (refer section 5.2 Pharmacokinetics Properties).

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis and hepatic failure have been reported, some of which have resulted in dath. Discontiue 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.

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.

Prolongation of the QT interval
Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide antibiotics 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 such as those with a history of torsades de pointes or congenital long QT syndrome.
– patients taking other medication 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.

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 azithromycin and antacids, the drugs should not be taken simultaneously.

Ergot: The theoretical possibility of ergotism contraindicates the concurrent use of azithromycin with ergot derivatives (refer section 4.4 Special Warnings and Precautions for Use, under *use with caution in the following circumstances* above).

Drugs that require dosage adjustment when administered concomitantly with azithromycin:
Cyclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of 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, cyclosporine 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).

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 cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, 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 15 mg dose of 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: Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects for 2 weeks had no effect on the steady state pharmacokinetics of didanosine as compared with placebo.

Efavirenz: Coadministration of a 600 mg single dose of 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 azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Nelfinavir: 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 is 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 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 azithromycin 500 mg 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 azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfomethoxazole. 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: Some of the macrolide antibiotics have been reported to impair the metabolism of digoxin (in the gut) in some patients. In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin, the possibility of raised digoxin levels should be borne in mind.

Effects on Laboratory Tests
There are no reported laboratory test interactions.

4.6 Fertility, pregnancy and lactation
Use in 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.

Use in Lactation

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterised the pharmacokinetics of azithromycin excretion into human breast milk. Azithromycin should only be used in lactating women where adequate alternatives are not available.

4.7 Effects on ability to drive and use machines

No studies have been conducted.

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, photosensivity, 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 because of a renal function abnormality.

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

	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 hemoglobin 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 & Infestations – moniliasis and vaginitis.

Blood and Lymphatic System Disorders: thrombocytopenia.

Body as a whole - asthenia, anaphylaxis (rarely fatal), fatigue and malaise.

Cardiovascular - hypotension; palpitations and arrhythmias including ventricular tachycardia (as seen with other macrolides) have been reported. There have been rare reports of QT prolongation and torsades de pointes. A causal relationship between azithromycin and these effects has not been established.

Central & Peripheral Nervous system - dizzines, somnolence, headache, syncope, convulsions (as seen with other macrolides), hypoesthesia, paraesthesia and hyperactivity.

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

Genitourinary - acute renal failure, interstitial nephritis.

Liver/Biliary - abnormal liver function including hepatitis and cholestatic jaundice, hepatic necrosis and hepatic failure, which have rarely resulted in death. However, a causal relationship has not been established.

Musculoskeletal - arthralgia.

Psychiatric - aggressive reaction, nervousness, agitation, anxiety.

Skin/Appendages - pruritus, urticaria, oedema, angioedema, serious skin reactions including erythrema multiforme, rash, photosensitivity, Stevens Johnson Syndrome, toxic epidermal necrolysis.

Special senses - vertigo, hearing disturbances* including hearing loss, deafness and/or tinnitus, Taste/smell perversion and/or loss; however a causal relationship has not been established.

* Hearing impairment has been reported with macrolide antibiotics.

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 Overdose

Most adverse events experienced in higher then 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.

Contact the Poisons Information Centre on 0800 POISON (0800 764 766) for advice on management of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: antibacterials for systemic use, macrolides, azithromycin, ATC code: J01FA10

Mechanism of Action
Azithromycin acts by binding to the 50S ribosomal subunit of susceptible organisms, thus interfering with microbial protein synthesis and inhibiting the assembly of the 50S

ribosomal subunit. Nucleic acid synthesis is not affected.

Clinical trials

<u>Disseminated MAC Disease Prophylaxis</u>

In a placebo-controlled study, patients receiving azithromycin were less than one-half as likely to develop MAC bacteremia as those on placebo. The one-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 bacteremia 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 bacteremia as those patients receiving either agent alone. The one-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.

<u>Trachoma</u>

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.

<u>Pharyngitis/Tonsillitis</u>

In a clinical trial (study 96-001), 501 children aged 2 - 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%

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 (N6)-dimethylation of adenine at nucleotide A2058 (*E. 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 that of the macrolides: the lincosamides (including clindamycin), and the streptogramins 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 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.

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.

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, results 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	-	-
Neisseria meningitides	≤ 2	-	-**b**
Staphylococcus aureus	≤ 2	4	≥ 8
Streptococci[a]	≤ 0.5	1	≥ 2

[a] Includes *Streptococcus pneumoniae,* β-hemolytic 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, 2012. ; CLSI, 2010

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 meningitides	≥ 20	-	-
Staphylococcus aureus	≥ 18	14 - 17	≤ 13
Streptococci[a]	≥ 18	14 - 17	≤ 13

[a] Includes *Streptococcus pneumoniae,* β-hemolytic streptococci and viridans streptococci.
Incubation in ambient air.

CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration;
mm = Millimeters.
Source: CLSI, 2012. 8), CLSI, 2010

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 (CLSI)

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.
CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration;
mm = Millimeters.
Source: CLSI, 2012.

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has also stablished 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-hemolytic 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.

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 minimal inhibitory concentration (MIC) values against *Mycobacterium avium complex* (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.

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 that of the macrolides: the lincosamides (including clindamycin), and the streptogramins 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 in *Streptococcus agalactiae.*

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

Gram-positive Aerobic Bacteria - *Staphylococcus aureus, Streptococcus pyogenes* (group A beta-hemolytic 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 most strains of methicillin-resistant staphylococci.

Gram-negative Aerobic Bacteria - *Haemophilus influenzae (*including beta-lacatmase 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 shigelloide*s. 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 HIV Infections - *Mycobacterium avium-intracellulare complex*.

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

Gram-positive Aerobic Bacteria - *Staphylococcus aureus*, *Streptococcus agalactiae, 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 - *Mycobacterium avium-intracellulare complex* and the eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.

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.

5.2 Pharmacokinetics Properties

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 2-3 hours with an area under the curve $AUC_{(0-24)}$ of 2.6 µg hr/mL.

Food has no significant effect on the bioavailability of the APO-AZITHROMYCIN 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 co-administration 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 (refer section 4.5 Interactions with other medicines and other forms of interactions).

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 tissue 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.

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. Very high concentrations of unchanged drug have been found, together with 10 metabolites, formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by 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.

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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been done to determine the carcinogenic potential of azithromycin in animals. Azithromycin showed no genotoxic potential in a range of standard laboratory tests for gene mutations and chromosomal damage. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APO-AZITHROMYCIN tablets contain the following excipients:

- Calcium hydrogen phosphate dihydrate
- Hydroxypropyl cellulose
- Croscarmellose sodium
- Magnesium stearate (Intragranular)
- Magnesium stearate (Extragranular)
- Opadry II 31K58875 white

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

Apo-Azithromycin 250mg
Bottle packs – 36 months from the date of manufacture
Blister packs – 36 months from the date of manufacture

Apo-Azithromycin 500mg
Bottle packs – 24 months from the date of manufacture
Blister packs – 36 months from the date of manufacture

6.4 Special precautions for storage

Store at or below 25ºC. Keep out of reach of children.

6.5 Nature and contents of container

APO-AZITHROMYCIN 250mg and 500mg: Bottles of 30 and 500 tablets and in blisters of 2 tablets.
Not all strengths and packs sizes may be available.

6.6 Special precautions for disposal

No special requirements for disposal.

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Apotex NZ Ltd
32 Hillside Road
Glenfield
Private Bag 102-995
North Shore Mail Centre
Auckland
Telephone: (09) 444 2073
Fax: (09) 444 2951

9. DATE OF FIRST APPROVAL

18 March 2010

10. DATE OF REVISION OF THE TEXT

28 August 2018

Summary Table of Changes

Section changed	Summary of new information
6.3 Shelf Life	Revised shelf life for Apo-Azithromycin 250mg bottle packs from 24 to 36 months