AUSTRALIAN PRODUCT INFORMATION – AZITHROMYCIN VIATRIS (AZITHROMYCIN DIHYDRATE) TABLETS

1 NAME OF THE MEDICINE

Azithromycin dihydrate.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

AZITHROMYCIN VIATRIS tablets contain azithromycin dihydrate equivalent to 500 mg of azithromycin.

Excipients with known effect: lactose monohydrate.

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

3 PHARMACEUTICAL FORM

AZITHROMYCIN VIATRIS tablets are white, oblong, biconvex, film coated tablets, scored on one side.

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.

3. Uncomplicated skin and skin structure infections:
   Uncomplicated infections due to *Staphylococcus aureus, Streptococcus pyogenes* or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.
4. Sexually transmitted diseases: Uncomplicated urethritis and cervicitis due to *Chlamydia trachomatis*.
   Note: At the recommended dose azithromycin cannot be relied upon to treat gonorrhoea or syphilis. As with other drugs for the treatment of non-gonococcal infections, it may mask or delay the symptoms of incubating gonorrhoea or syphilis. Appropriate tests should be performed for the detection of gonorrhoea or syphilis and treatment should be instituted as required.
   Azithromycin is also indicated for the treatment of *Chlamydia trachomatis* conjunctivitis and trachoma.
   Azithromycin is also indicated for the prevention of infection due to *Mycobacterium avium-intracellulare Complex* (MAC) disease, when used as the sole agent or in combination with rifabutin at its approved dose, in adults and children aged more than 12 years with HIV infection and CD4 cell count less than or equal to 75 cells/µL (see 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. 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.
2. *Chlamydia trachomatis* conjunctivitis and trachoma in children 12 months or older.

4.2 DOSE AND METHOD OF ADMINISTRATION

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*: 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 (see 5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials).

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

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

Children (powder for oral suspension)[#]

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

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

[#]Azithromycin powder for oral suspension is unavailable in AZITHROMYCIN VIATRIS brand however is available in other brands. Where correct dosing requires oral suspension in paediatric or adult patients, the oral suspension available from other suppliers should be used. Refer to the specific product information for azithromycin oral suspension for guidance on administrations and precautions.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with caution in the following circumstances

In the treatment of pneumonia, azithromycin has been shown to be safe and effective only in the treatment of community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following:

- patients with cystic fibrosis
- patients with nosocomially acquired infections
- patients with known or suspected bacteraemia
- patients requiring hospital admission
- elderly or debilitated patients
- patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Clostridium difficile-associated diarrhoea

Antibiotic associated pseudomembranous colitis has been reported with 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 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 4.3 CONTRAINDICATIONS). Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at present.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Prolongation of the QT interval

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

- patients predisposed to QT interval prolongation
- patients taking other medications known to prolong the QT interval such as antiarrhythmics of classes IA and III; antipsychotic agents; antidepressants; and fluoroquinolones
- patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- 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 symptoms of myasthenia gravis have been reported in patients receiving azithromycin therapy.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by co-administration 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 VIATRIS and ergot derivatives should not be co-administered.

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.

Use in hepatic impairment

No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Nonetheless, since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease (see 5.2 PHARMACOKINETIC PROPERTIES).

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

Use in renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment (GFR 10 – 80 mL/min). After oral administration of a single dose of azithromycin 1 g in subjects with 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 GFR >80 mL/min. Caution should be exercised when azithromycin is administered to patients with GFR <10 mL/min.

Use in the elderly

No data available.

Paediatric use

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

Effects on laboratory tests

There are no reported laboratory test interactions.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Drugs that should not be concomitantly administered with azithromycin

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

Ergot: Due to the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered (see 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Ergot derivatives).

Drugs that require dosage adjustment when administered concomitantly with azithromycin

Cyclosporin: In a pharmacokinetic study with healthy volunteers 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 co-administration 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: Co-administration 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, co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Cimetidine: 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 co-administration 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: Co-administration 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: Co-administration 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 co-administration 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: Co-administration 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, co-administration 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: Co-administration 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: Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment with azithromycin and rifabutin. 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 co-administered to healthy volunteers.

Triazolam: In 14 healthy volunteers, co-administration 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: Co-administration 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 sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies. No dose adjustment is necessary.

Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin did not affect the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear.

Other interactions

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy – Pregnancy Category B1

Azithromycin was not foetotoxic 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 foetal tissues homogenate concentrations were 5 to 10-fold higher than corresponding maternal plasma concentrations.

There are no adequate and well-controlled studies in pregnant women.

Data exists from published observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period.

While most of these studies do not suggest an association with adverse foetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy.

Azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Use in lactation.

Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

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

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

Adults

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

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

Allergic: rash, photosensitivity, angioedema.

Cardiovascular: palpitations, chest pain.

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

Genitourinary: moniliasis, vaginitis, nephritis.

Nervous system: dizziness, headache, vertigo, somnolence.

General: fatigue.

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

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

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

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

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

In multiple-dose trials involving > 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 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, constipation, pseudomembranous colitis, rare reports of tongue discolouration.

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

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

Immune system disorders: anaphylaxis (rarely fatal).

Metabolism and nutritional disorders: anorexia.

Musculoskeletal and connective tissue disorders: arthralgia.

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

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

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

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

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

4.9 OVERDOSE

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

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

Microbiology

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

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

Gram-negative Aerobic Bacteria – *Haemophilus influenzae (*including beta-lactamase producing *Haemophilus influenzae), Haemophilus parainfluenzae, Moraxella catarrhalis, Acinetobacter* species, *Yersinia* species, *Legionella pneumophila*, *Bordetella pertussis, Bordetella parapertussis, Shigella species, Pasteurella species, Vibrio cholerae* and *parahaemolyticus, Plesiomonas 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 gonorrhoea*e and *Haemophilus ducreyi*.

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

Opportunistic Pathogens Associated with human immunodeficiency virus (HIV) Infections – *Mycobacterium avium- intracellulare complex (MAC)*.

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

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

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

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

Opportunistic Pathogens Associated with HIV Infections - *MAC*.

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

Susceptibility Testing

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited when the patient is given the recommended dose. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body site where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation.

A report of "Resistant" indicates that the pathogen is not likely to be inhibited when the patient is given the recommended dose; other therapy should be selected.

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

Clinical trials

Disseminated MAC Disease Prophylaxis

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

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 – 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%

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 2-3 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 AZITHROMYCIN VIATRIS 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 (see 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.

Distribution

Azithromycin is distributed widely throughout the body. Rapid movement of azithromycin from blood into tissues results in significantly higher azithromycin concentrations in tissues than in plasma (from 1-60 times the maximum observed concentration in plasma). It appears to be concentrated intracellularly. Concentrations in tissues, such as lung, tonsil and prostate, etc exceed the 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.

Metabolism

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.

Excretion

Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug following oral administration. 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 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 GFR < 10 mL/min and subjects with GFR >80 mL/min.

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

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

Powder for oral suspension[#]

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

[#]Azithromycin powder for oral suspension is unavailable in AZITHROMYCIN VIATRIS brand however is available in other brands.

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

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

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

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

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

AZITHROMYCIN VIATRIS tablets 500 mg are packaged in blister packs of 2 and 3 and 15* tablets.

Azithromycin 500mg film-coated tablets are packed in blisters, transparent PVC film sealed with aluminium foil.

*Not currently marketed in Australia.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

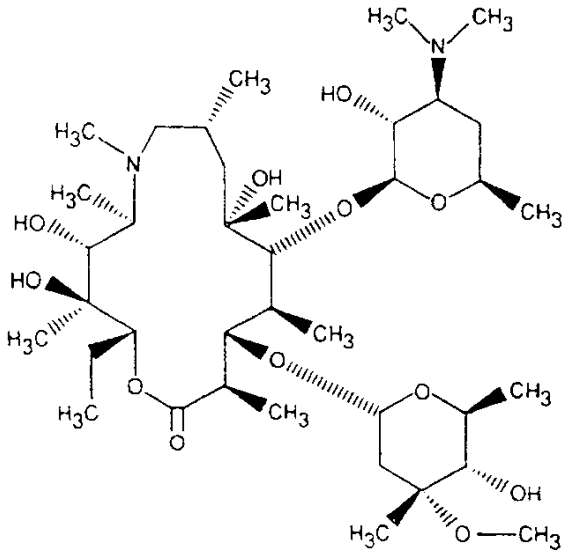
6.7 PHYSICOCHEMICAL PROPERTIES

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

Azithromycin dihydrate is a white crystalline powder with a chemical formula of $C_{38}H_{72}N_2O_{12}.2H_20$ and a molecular weight of 785.0.

Azithromycin dihydrate is practically insoluble in water, freely soluble in ethanol and in methylene chloride.

Chemical structure



CAS number

CAS: 83905-01-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Medicine)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

28 October 2022

10 DATE OF REVISION

18 January 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Addition of information to Use in Renal Impairment section
4.6	Addition of information to Use in Pregnancy and Use in Lactation sections
5.2	Addition of information to Excretion section