AUSTRALIAN PRODUCT INFORMATION

AZITH

(Azithromycin (as monohydrate)) powder for intravenous injection

1 NAME OF THE MEDICINE

Azithromycin (as monohydrate).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each AZITH 500 mg vial contains azithromycin monohydrate as active ingredient equivalent to 500 mg azithromycin, providing 100 mg/mL solution following reconstitution.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Injection, powder for intravenous infusion.

AZITH is a white powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

The dose of AZITH for the treatment of adult patients with community acquired pneumonia is:

Azithromycin 500 mg as a single daily intravenous dose for at least two days. Intravenous therapy should be followed by oral therapy of 500 mg azithromycin administered as a single daily dose to complete a 7 to 10 day course of therapy. The timing of the conversion to oral azithromycin therapy should be done at the discretion of the doctor and in accordance with clinical response.

After reconstitution and dilution, the recommended route of administration for intravenous azithromycin is by IV infusion only. Do not administer as an intravenous bolus or intramuscular injection.

Use in the elderly

No dose adjustment is necessary in elderly patients requiring azithromycin therapy.

Use in patients with renal impairment

No dose adjustment is needed in patients with mild or moderate renal impairment GFR 10–80mL/min. After oral administration of a single dose of azithromycin 1 g in subjects with severe renal impairment GFR < 10 mL/minute, mean $AUC_{0\ to\ 120}$ 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 severe renal impairment GFR <10mL/min.

Use in patients with hepatic impairment

The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment.

Use in children

The safety and effectiveness of azithromycin powder for solution for infusion for the treatment of infections in children have not been established (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Paediatric Use).

AZITH after reconstitution and dilution is for administration by intravenous infusion. Not to be given as a bolus or as an intramuscular injection.

The infusate concentration and rate of infusion for azithromycin powder for solution for infusion should be either 1 mg/mL over three hours or 2 mg/mL over one hour.

Preparation of the solution for intravenous administration is as follows:

Reconstitution

Prepare the initial solution of azithromycin powder for solution for infusion by adding sterilised water for injections 4.8 mL to the 500 mg vial and shaking the vial until all of the drug is dissolved. It is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of sterilised water for injections is dispensed. Each mL of reconstituted solution contains azithromycin 100 mg.

If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

Dilute this solution further prior to administration as instructed below.

Dilution

To provide azithromycin over a concentration range of 1.0 to 2.0 mg/mL, transfer 5 mL of the azithromycin 100 mg/mL solution into the appropriate amount of any of the diluents listed below.

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

It is recommended that a 500 mg dose of azithromycin powder for solution for infusion, diluted as above, be infused over a period of not less than 60 minutes.

AZITH is supplied in single use vials. The vial contents are reconstituted with sterilised water for injections 4.8 mL (azithromycin 100 mg/mL). For administration, the required volume of the reconstituted solution is added to a compatible infusion solution to produce a final azithromycin solution of 1.0 to 2.0 mg/mL.

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

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

However, as this product contains no antimicrobial agent, to reduce microbiological hazard, use as soon as practicable after reconstitution/ preparation. If storage is necessary, hold at 2° to 8° C for not more than 24 hours.

This product is for single use in one patient only. Discard any residue.

The reconstituted solution can be diluted with:

- normal saline (0.9% sodium chloride);
- ½ normal saline (0.45% sodium chloride);

- 5% Glucose in water;
- Lactated Ringer's solution;
- 5% Glucose in ½ normal saline (0.45% sodium chloride) with 20 mEq KCl;
- 5% Glucose in Lactated Ringer's solution;
- 5% Glucose in ⅓ normal saline (0.3% sodium chloride);
- 5% Glucose in ½ normal saline (0.45% sodium chloride).

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 excipients (see Section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

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

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

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.

Clostridioides difficile associated diarrhoea (CDAD)

Antibiotic associated pseudomembranous colitis has been reported with the use of many antibiotics including azithromycin. A toxin produced by *Clostridioides 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 *Clostridioides difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

Prolongation of the QT interval

There has been limited assessment of the potential for AZITH to prolong the QT interval. In clinical studies, no significant ECG abnormalities were reported in subjects who received AZITH. 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. Azithromycin should be used with caution in patients:

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

Myasthenia gravis

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

Administration Precaution

Do not administer AZITH as a bolus or as an intramuscular injection. Reconstitute and dilute the powder for infusion as directed and administer as an intravenous infusion over not less than 60 minutes. All patients who received infusate concentrations above 2.0 mg/mL experienced local infusion site reactions and, therefore, higher concentrations should be avoided.

Hepatotoxicity

No dose adjustment is recommended for patients with mild to moderate hepatic impairment. Nonetheless, since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease (see Section 5.2 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 GFR 10 - 80 mL/min. After oral administration of a single dose of azithromycin 1 g in subjects with GFR < 10 mL/min, mean $AUC_{0 \text{ to } 120}$ 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 dose adjustment is necessary in elderly patients requiring azithromycin therapy. Also see *Prolongation of the QT interval* above

Paediatric Use

The safety and effectiveness of azithromycin powder for solution for infusion for the treatment of infections in children have not been established.

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

No data available.

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 administered concomitantly with azithromycin

Antacids:

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

Ergot:

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

Drugs that require dosage adjustment when administered concomitantly with azithromycin

Ciclosporin:

In a pharmacokinetic study with healthy volunteers that were administered an oral dose of 500 mg/day azithromycin for three days and were then administered a single oral dose of ciclosporin 10 mg/kg, the resulting C_{max} and $AUC_{0\ to\ 5}$ 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, ciclosporin 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 five-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 two hours before azithromycin on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin type oral anticoagulants:

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of warfarin 15 mg 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 daily doses of azithromycin 1200 mg with didanosine in six subjects did not appear to affect the pharmacokinetics of didanosine as compared with placebo.

Efavirenz:

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

Fluconazole:

Co-administration with a single dose of azithromycin 1200 mg did not alter the pharmacokinetics of a single dose of fluconazole 800 mg. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, but 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 azithromycin 1200 mg had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for five days. No adjustment of the dose of azithromycin is necessary when 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 three days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of midazolam 15 mg.

Nelfinavir:

Co-administration of azithromycin 1200 mg and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse events 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 of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Sildenafil:

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for three 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 triazolam 0.125 mg 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 seven days with azithromycin 1200 mg on the seventh day 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 microbial metabolism of P-glycoprotein substrates such as digoxin and colchicine (in the gut) in some patients and to result in increased serum levels of the P-glycoprotein substrate.

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

No animal studies of fertility have been conducted by the IV route. In three oral 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

Category B1: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful

effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage

Studies in mice and rats have demonstrated that azithromycin crosses the placenta. Following an oral dose of 200 mg/kg/day, azithromycin concentrations in mouse and rat fetal tissue homogenates were 5 to 10 fold higher than corresponding maternal plasma concentrations. No animal studies of embyrofetal development have been conducted by the IV route. Azithromycin was not fetotoxic or teratogenic in mice and rats at oral doses that were moderately maternotoxic. Plasma levels for azithromycin were lower than the clinical C_{max} in both species at the high dose of 200 mg/kg/day.

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 studies do not suggest an association with adverse fetal 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 powder for solution for infusion 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

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials

In clinical studies of azithromycin given by the intravenous route followed by the oral route in community acquired pneumonia, the most frequent treatment related events occurring at an incidence of greater than or equal to 1% in azithromycin treated patients (n = 871) were diarrhoea (4.7%), IV site pain (4.4%), nausea (4.2%), abdominal pain (2.8%), rash (1.5%), vomiting (1.4%), dyspepsia (0.9%) and LFTs abnormal (0.7%). Local inflammation at the infusion site has also been reported.

In clinical studies, the incidence of IV site disorders (infection/ inflammation/ oedema/ pain/ reactions) associated with the 1 mg/mL and 2 mg/mL infusion solution concentration was 4.2 and 5.6%, respectively.

A total of 2.4% patients discontinued azithromycin therapy either by the intravenous or oral route due to treatment related clinical or laboratory adverse events.

Treatment related laboratory abnormalities occurred in 0.6% of patients.

Adults

Multiple dose regimen (oral)

The most frequently reported adverse events in patients receiving a multiple dose regimen of azithromycin orally were diarrhoea/ loose stools (5%), nausea (3%) and abdominal pain (3%). No other adverse events occurred in patients on the multiple dose regimen with a frequency > 1%.

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

*Allergic***.** Rash, photosensitivity and angioedema.

Cardiovascular. Palpitations, chest pain.

Gastrointestinal. Dyspepsia, flatulence, vomiting, melaena and cholestatic jaundice.

*Genitourinary***.** Moniliasis (candidiasis), vaginitis and nephritis.

*Nervous system***.** Dizziness, headache, vertigo and somnolence.

General. Fatigue.

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.

Post-marketing experience

In post-marketing experience with azithromycin, 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 (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.

*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. However, a causal relationship has not been established.

Immune system disorder. Anaphylaxis (rarely fatal).

Metabolism and nutrition disorders**.** Anorexia.

Musculoskeletal and connective tissue disorders. Arthralgia.

Nervous system disorders. Dizziness, convulsions (as seen with other macrolides), headache, hyperactivity, hypoesthesia, paraesthesia, somnolence and syncope.

Psychiatric disorders. Aggressive reaction, nervousness, agitation, anxiety.

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

Skin and subcutaneous tissue disorders. Allergic reactions including pruritus, rash, photosensitivity, urticaria, oedema, angioedema, serious skin reactions including erythema multiforme, acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS).

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

*Hearing impairment has been reported with macrolide antibiotics.

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 were similar to those 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 two to three 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

Pharmacotherapeutic group: Antibacterial agent: macrolide ATC code: J01 FA 10.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

The mode of action of azithromycin is inhibition of protein synthesis in bacteria by binding to the 50S ribosomal subunit and preventing translocation of peptides.

Microbiology

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

Gram positive aerobic bacteria

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

Gram negative aerobic bacteria

Haemophilus influenzae, H. parainfluenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Acinetobacter sp., Yersinia sp., Legionella pneumophila, Bordetella pertussis, Bordetella parapertussis, Shigella sp., Pasteurella sp., Vibrio cholerae and Vibrio parahaemolyticus, Plesiomonas shigelloides. Activities against Escherichia coli, Salmonella enteritidis, Salmonella typhi, Enterobacter sp., Aeromonas hydrophila and Klebsiella sp. are variable and susceptibility tests should be performed. Proteus sp., Serratia sp., Morganella sp. and Pseudomonas aeruginosa are usually resistant.

Anaerobic bacteria

Bacteroides fragilis and Bacteroides sp., Clostridium perfringens, Peptococcus sp. and Peptostreptococcus sp., 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 H. ducreyi.

Other organisms

Borrelia burgdorferi (Lyme disease agent), Chlamydia pneumoniae, Mycoplasma pneumoniae, Mycoplasma hominis, Ureaplasma urealyticum, Campylobacter sp. and Listeria monocytogenes.

Opportunistic pathogens associated with Human Immunodeficiency Virus (HIV) infections

Mycobacterium avium-intracellulare complex (MAC).

Oral azithromycin demonstrates activity in vivo against the following bacteria:

Gram positive aerobic bacteria

Staph. aureus, Strep. pyogenes (group A beta-haemolytic Streptococci), *Strep. pneumoniae,* alpha-haemolytic Streptococci (viridans group) and other Streptococci.

Gram negative aerobic bacteria

H. influenzae (including beta-lactamase producing H. influenzae), H. parainfluenzae, Moraxella catarrhalis.

Other organisms

Chlamydia trachomatis, Chlamydia pneumoniae, Mycoplasma pneumoniae.

Opportunistic pathogens associated with HIV infections

Mycobacterium avium-intracellulare complex.

Intravenous azithromycin demonstrates activity *in vivo* against the following bacteria:

Staph. aureus, Strep. pneumoniae, H. influenzae, Moraxella catarrhalis, Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila.

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

Susceptibility testing

Dilution or diffusion techniques, either quantitative (minimal inhibitory concentration [MIC]) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. CLSI). 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 sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation.

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

Clinical Trials

Community Acquired Pneumonia (CAP)

The efficacy of azithromycin in the treatment of CAP was assessed in an open, randomised comparative trial, conducted in the US between 1993 and 1995. Azithromycin (500 mg IV (intravenously) as a single dose for two to five days, followed by 500 mg/day orally to complete seven to ten days of therapy) was compared to cefuroxime (2.225 g/day in three divided doses administered IV for two to five days followed by 1 g/day in two divided doses to complete seven to ten days therapy), with erythromycin as required. 291 patients were evaluable for efficacy. Clinical success (cure + improvement) at 10 to 14 days post-therapy was 77.4% in the azithromycin group versus 74.1% in the comparator group.

In a separate open, non-comparative study, 94 patients received azithromycin by IV infusion (for two to five days) followed by azithromycin orally (to complete a total of seven to ten days therapy) for the treatment of CAP. The clinical success rate (cure + improvement) at 10 to 14 days post-therapy was 88% (74/84) and at four to six weeks was 86% (73/85) among evaluable patients.

These two studies indicated an overall cure rate for patients serologically positive for *Legionella pneumophila* of 84% (16/19). Additionally, in an open, non-comparative study, patients diagnosed as positive for *Legionella pneumophila* (serogroup 1) using a specific urinary antigen test were treated with azithromycin IV followed by oral azithromycin. At 10 to 14 days, 16 out of 17 evaluable patients were clinically cured and at four to six weeks, 20 out of 20 evaluable patients were clinically cured.

In patients that were treated with azithromycin with a pathogen identified the clinical success rates observed were *Streptococcus pneumoniae* 98/102 (92.5%), *Haemophilus influenzae* 54/62 (87.1%), *Staphylococcus aureus* 8/10 (90%), *Mycoplasma* 40/43 (93%), *Chlamydia pneumoniae* 39/44 (88.6%) and Legionella 34/39 (87.2%).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Bioavailability is approximately 37%. The time taken to peak plasma levels is two to three hours. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of two to four days. In elderly volunteers (> 65 years), slightly higher AUC values were seen after a five-day regimen than in young volunteers (< 40 years). These are not considered clinically significant, and hence no dose adjustment is recommended.

In patients hospitalised with community acquired pneumonia receiving single daily one hour intravenous infusions for two to five days of azithromycin 500 mg at a concentration of 2 mg/mL, the mean C_{max} ± S.D. achieved was 3.63 ± 1.60 microgram/mL, while the 24 hour trough level was 0.20 ± 0.15 microgram/mL, and the AUC_{24} was 9.60 ± 4.80 microgram.hour/mL. The mean C_{max}, 24 hour trough and AUC_{24} values were 1.14 ± 0.14 microgram/mL, 0.18 ± 0.02 microgram/mL, and 8.03 ± 0.86 microgram.hour/mL, respectively, in normal volunteers receiving a three hour intravenous infusion of azithromycin 500 mg at a concentration of 1 mg/mL.

Comparison of the plasma pharmacokinetic parameters following the first and fifth daily doses of intravenous azithromycin 500 mg showed only an 8% increase in C_{max} but a 61% increase in AUC_{24} reflecting a threefold rise in C_{24} trough levels.

Pharmacokinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the drug is heavily tissue bound. Concentrations in target tissues, such as lung, tonsil and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg. High concentrations of azithromycin were found in gynaecological tissue 96 hours after a single oral dose of azithromycin

Distribution

Following oral administration in humans, azithromycin is widely distributed throughout the body.

Metabolism

Very high concentrations of unchanged drug have been found in human bile, together with ten 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.

Excretion

In a multiple dose study in 12 normal volunteers utilising a 500 mg (1 mg/mL) one-hour intravenous dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the first dose and 14% after the fifth dose. These values are greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin. Biliary excretion is a major route of elimination for unchanged drug, following oral administration.

Following a single oral dose of azithromycin 1 g, the pharmacokinetics in subjects with GFR 10 - 80 mL/min were not affected. Statistically significant differences in AUC (0 to 120) (8.8 versus 11.7 microgram/hour/mL), C_{max} (1.0 versus 1.6 microgram/mL) and CLr (2.3 versus 0.2 mL/minute/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.

In animal studies, high azithromycin concentrations have been observed in phagocytes. In experimental models, higher concentrations of azithromycin are released during active phagocytosis than from non-stimulated phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

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 animal studies have been done to determine the carcinogenic potential of azithromycin.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

AZITH contains citric acid and sodium hydroxide.

6.2 INCOMPATIBILITIES

AZITH reconstituted solution may be diluted using the instructions and compatible infusion solutions provided in Section 4.2 DOSE AND METHOD OF ADMINISTRATION. Other intravenous substances, additives or medications should not be added to AZITH or infused simultaneously through the same intravenous line.

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. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type:	10mL clear Type I, tubular flint glass vial and closed with dark grey bromobutyl lyo slotted stopper and grey, aluminium flip-off seal.
Pack sizes:	Packs of 1 and 5 vials.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 146755 – AZITH azithromycin (as monohydrate) 500mg powder for injection vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

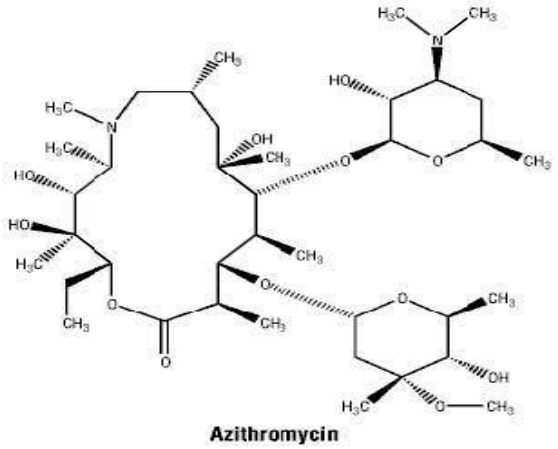
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Chemical name : 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A

Structural formula :



Azithromycin

Molecular formula : $C_{38}H_{72}N_2O_{12}$ Molecular weight : 749.0

CAS Number

83905-01-5

Azithromycin is the first of a class of antibiotics designated chemically as azalides, a subclass of macrolides. Chemically it is derived by insertion of a nitrogen atom into the lactone ring of erythromycin A.

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

01/06/2009

10 DATE OF REVISION

18/09/2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
4.4	Clostridium replaced with Clostridioides as per updated classification
4.6	Addition of safety warning relating to use in pregnancy

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