PRODUCT INFORMATION

AZITH POWDER FOR INTRAVENOUS INJECTION

NAME OF THE MEDICINE

Azithromycin monohydrate equivalent to Azithromycin 500 mg.
The structure of azithromycin is shown below:

![Azithromycin structure](image)

DESCRIPTION

Chemical name: 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. Molecular formula: C_{38}H_{72}N_{12}O_{12}. MW: 749.0. CAS: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.
AZITH contains the excipients citric acid and sodium hydroxide.
PHARMACOLOGY

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.

Pharmacokinetics
Absorption/ distribution/ metabolism/ elimination
Following oral administration in humans, azithromycin is widely distributed throughout the body. Bioavailability is approximately 37%. Administration of azithromycin capsules following a substantial meal reduces bioavailability. 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 Cmax ± 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 Cmax, 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 Cmax 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. 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. 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.
Following a single oral dose of azithromycin 1 g, the pharmacokinetics in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/minute) were not affected. Statistically significant differences in AUC(0 to 120) (8.8 versus 11.7 microgram/hour/mL), Cmax (1.0 versus 1.6 microgram/mL) and CLr (2.3 versus 0.2 mL/minute/kg) were observed between subjects with severe renal impairment (GFR< 10 mL/minute) 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.

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.

**Microbiology**

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

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

**Gram negative aerobic bacteria**

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 HIV infections
*Mycobacterium avium-intracellulare* complex.

**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 (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. The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

**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%).
INDICATIONS

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

CONTRAINDICATIONS

Known hypersensitivity to azithromycin, erythromycin or any macrolide or ketolide antibiotic or to any excipients.

PRECAUTIONS

*Allergic reactions*
Rare, serious, allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported in patients on azithromycin therapy (see 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.

*Clostridium difficile associated diarrhea (CDAD)*
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 *Cl. 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.
**Ergotism and macrolide antibiotics**
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.

**Do not administer AZITH IV 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.

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

**QT interval prolongation**
There has been limited assessment of the potential for AZITH IV to prolong the QT interval. In clinical studies no significant ECG abnormalities were reported in subjects who received AZITH IV. Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide products. Azithromycin should be used with caution in patients predisposed to QT interval prolongation or in patients taking other medications known to prolong the QT interval.

**Impaired renal function**
No dose adjustment is needed in patients with mild or moderate renal impairment (glomerular filtration rate (GFR) 10 to 80 mL/minute). 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 hours) and mean Cmax 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.

**Impaired hepatic function**
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 Actions, Pharmacokinetics).
Carcinogenesis, mutagenesis, impairment of fertility
No animal studies have been done to determine the carcinogenic potential of azithromycin. Azithromycin showed no genotoxic potential in a range of standard laboratory tests for gene mutations and chromosomal damage. 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 (Category B1)
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 five to tenfold higher than corresponding maternal plasma concentrations. No animal studies of embryofetal 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 Cmax in both species at the high dose of 200 mg/kg/day. Azithromycin powder for solution for infusion should only be used in pregnant women where adequate alternatives are not available.

Use in lactation
There are no data on the possible secretion of azithromycin into animal or human breast milk. Azithromycin should only be used in breastfeeding women where adequate alternatives are not available.

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.

Effect on ability to drive or operate machinery
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.

Interactions with Other Medicines
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, the concurrent use of azithromycin with ergot derivatives is not recommended.

**Drugs that require dosage adjustment when administered concomitantly with azithromycin**

**Cyclosporin:** In a pharmacokinetic study with healthy volunteers that were administered an oral dose of azithromycin 500 mg/day for three days and were then administered a single oral dose of cyclosporin 10 mg/kg, the resulting Cmax and AUC(0 to 5) were found to be significantly elevated. Consequently, caution should be exercised before concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

**Drugs that have been studied with no clinically significant interaction shown**

**Atorvastatin:** Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG-CoA reductase inhibition assay).

**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 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 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 postmarketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time, when azithromycin is used in patients receiving coumarin type oral anticoagulants.

**Didanosine:** Coadministration of daily doses of azithromycin 1,200 mg with didanosine in six subjects did not appear to affect the pharmacokinetics of didanosine as compared with placebo.

**Efavirenz:** Coadministration 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:** Coadministration with a single dose of azithromycin 1,200 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 coadministration of fluconazole, but a
clinically insignificant decrease in Cmax (18%) of azithromycin was observed. No dose adjustment is necessary when azithromycin is given with fluconazole.

Indinavir: Coadministration of a single dose of azithromycin 1,200 mg had no statistically significant effect on the pharmacokinetics of indinavir 800 mg t.i.d (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, coadministration 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: Coadministration of azithromycin 1,200 mg and nelfinavir at steady state (750 mg three times daily) increases azithromycin concentration. No clinically significant adverse events 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 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 Cmax 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 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: Coadministration of trimethoprim/ sulfamethoxazole DS (160 mg/800 mg) for seven days with azithromycin 1,200 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 1,000 mg doses and multiple 1,200 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 microbial 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.

ADVERSE REACTIONS

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 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.

In postmarketing experience with azithromycin, the following adverse events have been reported:

Infections and infestations. Moniliasis and vaginitis.
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 and peripheral nervous system.** Dizziness, syncope, convulsions (as seen with other macrolides), headache, somnolence, hypoesthesia, paraesthesia and hyperactivity.

**Gastrointestinal.** Vomiting/ diarrhoea (rarely resulting in dehydration), dyspepsia, pancreatitis, anorexia, constipation, pseudomembranous colitis, rare reports of tongue discoloration.

**Genitourinary.** Acute renal failure, interstitial nephritis.

**Haemopoietic.** Thrombocytopenia.

**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, rash, photosensitivity, urticaria, oedema, angioedema, serious skin reactions including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

**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.

**DOSAGE AND ADMINISTRATION**

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

500 mg as a single daily intravenous dose for at least two days. Intravenous therapy should be followed by oral therapy of azithromycin 500 mg administered as a single daily dose to complete a seven to ten day course of therapy. The timing of the conversion to oral 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. 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 hours) and mean Cmax were increased by
approximately 30 and 60%, respectively, when compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to patients with severe renal impairment.

**Use in 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.

**Administration**
AZITH IV 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.
For final infusion solution concentration of 1.0 mg/mL, amount of diluent is 500 mL.
For final infusion solution concentration of 2.0 mg/mL, amount of diluent is 250 mL.

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

AZITH IV 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 deg. C. When diluted according to the instructions the diluted solution is chemically and
physically stable for 24 hours at or below 30 deg. C or for seven days if stored under refrigeration (5 deg. 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 deg. 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 (sodium chloride 0.9%);
- 1/2 normal saline (sodium chloride 0.45%);
- glucose 5% in water;
- lactated Ringer's solution;
- glucose 5% in 1/2 normal saline (sodium chloride 0.45%) with 20 mEq KCl;
- glucose 5% in lactated Ringer's solution;
- glucose 5% in 1/3 normal saline (sodium chloride 0.3%);
- glucose 5% in 1/2 normal saline (sodium chloride 0.45%).

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

**OVERDOSAGE**

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.

Please contact the Poisons Information Centre on 131126 for advice on management.

**PRESENTATION**

10 mL glass vial containing 500 mg azithromycin powder for injection.
Packs of 1 vial.
STORAGE

Store below 25 degrees Celsius and protect from light.

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

POISON SCHEDULE

S4

DATE OF TGA APPROVAL

Approved by the Therapeutic Goods Administration: 15 April 2010