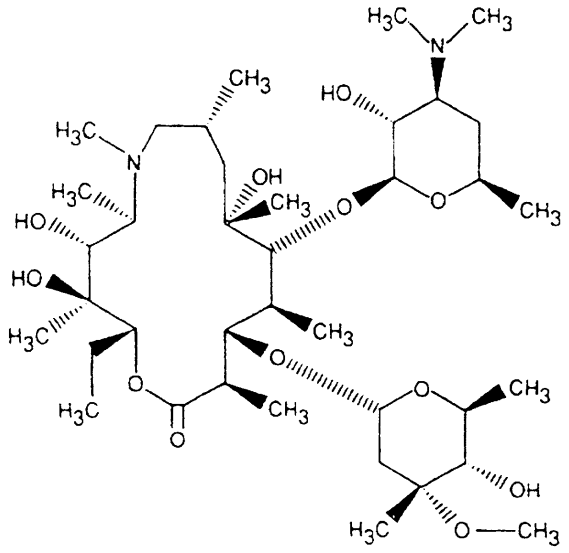
PRODUCT INFORMATION

ZITHROMAX® IV

(azithromycin powder for injection)

NAME OF THE MEDICINE

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. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The structural formula is:



CAS:83905-01-5

Azithromycin has a chemical formula of $C_{38}H_{72}N_2O_{12}$ and a molecular weight of 749.0.

DESCRIPTION

Powder for solution for infusion: One vial containing 500 mg of azithromycin, providing 100 mg/mL solution following reconstitution. The formulation also contains anhydrous citric acid and sodium hydroxide.

Pharmacotherapeutic group: Antibacterial agent: macrolide ATC code: J 01 FA 10.

PHARMACOLOGY

Pharmacodynamics

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 to most strains of methicillin-resistant Staphylococci.

Gram-negative aerobic bacteria – *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 (oral) 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.

Azithromycin (IV) demonstrates activity *in vivo* against the following bacteria*:*

Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila.

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 (e.g. 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.

Pharmacokinetics

Absorption/distribution

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 2-3 hours. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. In elderly volunteers (>65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (<40 years), but 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 (IV) infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean C_{max} ± S.D. achieved was 3.63 ± 1.60 μg/mL, while the 24-hour trough level was 0.20 ± 0.15 μg/mL, and the AUC24 was 9.60 ± 4.80 μg·h/mL. The mean C_{max}, 24-hour trough and AUC_{24} values were 1.14 ± 0.14 μg/mL, 0.18 ± 0.02 μg/mL, and 8.03 ±0.86 μg h/mL, respectively, in normal volunteers receiving a 3-hour IV infusion of 500 mg azithromycin at a concentration of 1 mg/mL.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg IV azithromycin 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 MIC90 for likely pathogens after a single dose of 500 mg. High concentrations of azithromycin were found in gynaecological tissue 96 hours after a single 500 mg oral dose of azithromycin.

Metabolism/elimination

In a multiple-dose study in 12 normal volunteers utilising a 500 mg (1 mg/mL) one-hour IV-dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the 1st dose and 14% after the 5th 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 10 metabolites, formed by N- and O-demethylation, hydroxylation of the desosamine and aglycone rings, and cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Following a single oral dose of azithromycin 1 gram, the pharmacokinetics in subjects with mild to moderate renal impairment (GFR 10 – 80 mL/min) were not affected. Statistically significant differences in AUC_{0-120} (8.8 μg.hr/mL vs. 11.7 μg.hr/mL), C_{max} (1.0 μg/mL vs. 1.6 μg/mL) and CLr (2.3 mL/min/kg vs. 0.2 mL/min/kg) were observed between subjects with severe renal impairment (GFR < 10 mL/min) and subjects with normal renal function.

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

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.

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 as a single dose for 2 – 5 days, followed by 500 mg/day orally to complete 7 to 10 days of therapy) was compared to cefuroxime (2.225 g/day in 3 divided doses administered IV for 2 to 5 days followed by 1 g/day in 2 divided doses to complete 7 to 10 days therapy), with erythromycin as required. Two hundred and ninety one patients were evaluable for efficacy. Clinical success (cure + improvement) at 10 to 14 days post therapy was 77.4% in the azithromycin group vs 74.1 % in the comparator group.

In a separate open, non-comparative study, 94 patients received azithromycin by IV infusion (for 2 to 5 days) followed by azithromycin orally (to complete a total of 7 to 10 days therapy) for the treatment of CAP. The clinical success rates (cure + improvement) at 10 to 14 days post therapy was 88% (74/84) and at 4 to 6 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 4 to 6 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 L*egionella* 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 pneumophilia*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Staphylococcus aureu*s and *Streptococcus pneumoniae.*

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 DESCRIPTION).

PRECAUTIONS

Hypersensitivity

Rare, serious, allergic reactions, including angioedema and anaphylaxis (rarely fatal); dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal); and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients on azithromycin therapy (see 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.

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 PHARMACOLOGY, Pharmacokinetics).

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

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

Superinfection

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi, is recommended.

Clostridium difficile-associated diarrhoea

Antibiotic-associated pseudomembranous colitis has been reported with the use of many antibiotics including azithromycin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life-threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy).

Mild cases may respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *C difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Hypertoxin-producing strains of *C difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

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 severe renal impairment (GFR <10 mL/min), mean $AUC_{0\text{-}120h}$ and mean C_{max} were increased by approximately 30% and 60%, respectively when compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to patients with severe renal impairment.

Prolongation of the QT interval

There has been limited assessment of the potential for ZITHROMAX IV to prolong the QT interval. In clinical studies no significant ECG abnormalities were reported in subjects who received ZITHROMAX IV. Ventricular arrhythmias associated with prolonged QT interval, including ventricular tachycardia and torsades de pointes have been reported with macrolide products including azithromycin. Prescribers should consider the risk of QT prolongation (which can be fatal) when weighing the risks and benefits of azithromycin for at-risk groups including:

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

Myasthenia gravis

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

Administration precautions

Do not administer ZITHROMAX IV as a bolus or as an intramuscular injection. Reconstitute and dilute the powder for infusion as directed and administer as an IV 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.

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

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 foetal 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. 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 lactating women where adequate alternatives are not available.

Paediatric use

The safety and effectiveness of azithromycin powder for solution for infusion for the treatment of infections in children have not been established. Azithromycin powder for oral suspension is recommended for the treatment of paediatric patients.

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.

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.

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.

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.

The following information on drug interactions refers to oral azithromycin:

Drugs that should not be concomitantly administered 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 co-administered (see PRECAUTIONS, Ergot derivatives).

Drugs that require dosage adjustment when administered concomitantly with azithromycin

Cyclosporin: In a pharmacokinetic study with healthy volunteers who were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Drugs that have been studied with no clinically significant interaction shown

Atorvastatin: Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

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

Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-type oral anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of 15 mg warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated

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

Didanosine: Coadministration of daily doses of 1200 mg azithromycin with didanosine in six subjects did not appear to affect the pharmacokinetics of didanosine as compared to placebo.

Efavirenz: Coadministration of a single dose of 600 mg azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions. No dose adjustment is necessary when azithromycin is given with efavirenz.

Fluconazole: Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed. No dose adjustment is necessary when azithromycin is given with fluconazole.

Indinavir: Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days. No adjustment of the dose 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 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg midazolam.

Nelfinavir: Coadministration of 1200 mg azithromycin and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.

Rifabutin: Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment with azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Sildenafil: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its major circulating metabolite.

Terfenadine, astemizole: In a study in normal subjects addition of azithromycin did not result in any significant changes in cardiac repolarisation (QTc interval) measured during the steady state dosing of terfenadine. However, there have been cases reported where the possibility of such an interaction could not be entirely excluded.

Theophylline: There is no evidence of any pharmacokinetic interaction when azithromycin and theophylline are coadministered to healthy volunteers.

Triazolam: In 14 healthy volunteers, coadministration of 500 mg azithromycin on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole: Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with 1200 mg azithromycin on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies. No dose adjustment is necessary.

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

Other interactions

Digoxin: Some of the macrolide antibiotics including azithromycin have been reported to impair the metabolism of P-glycoprotein substrates such as digoxin (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.

ADVERSE EFFECTS

Clinical trials

In clinical studies of azithromycin given by the IV route followed by the oral route in community acquired pneumonia, the most frequent treatment related events occurring at an incidence of ≥ 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 IV 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:

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, 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 nutrition 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.

DOSAGE AND ADMINISTRATION

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

500 mg as a single daily IV dose for at least two days. IV 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 physician and in accordance with clinical response.

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

Use in 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/min), mean $AUC_{0\text{-}120h}$ and mean C_{max} were increased by approximately 30% and 60%, respectively when compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to patients with severe renal impairment.

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.

ZITHROMAX IV after reconstitution and dilution is for administration by IV 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 3 hours or 2 mg/mL over 1 hour.

Preparation of the solution for IV administration is as follows:

Reconstitution

Prepare the initial solution of azithromycin powder for solution for infusion by adding 4.8 mL of sterilised Water For Injections 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 100 mg azithromycin.

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 mg/mL to 2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin 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.

ZITHROMAX IV is supplied in single use vials. The vial contents are reconstituted with 4.8 mL sterilised Water for Injections (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 mg 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).

It is recommended that a 500 mg dose of azithromycin powder for solution for infusion, 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 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 Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

ZITHROMAX IV is packaged in 10 mL Type I flint glass tubular vial and closed with a grey butyl rubber stopper and aluminium over-seal with a flip-off cap.

Store below 30°C.

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

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
ABN 50 008 422 348
38-42 Wharf Road
WEST RYDE NSW 2114

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

19 November 2002

DATE OF MOST RECENT AMENDMENT

01 June 2017