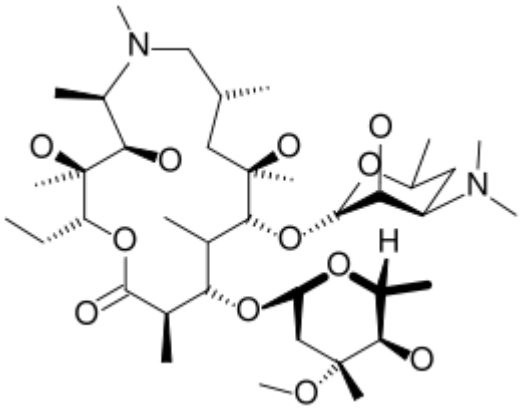
PRODUCT INFORMATION
AZITHROMYCIN SANDOZ® 500mg FILM COATED TABLETS

NAME OF THE MEDICINE

Generic Name: Azithromycin dihydrate
Chemical name : 9-deoxo-9*a*-aza-9*a*-methyl-9*a*-homoerythromycin A, dihydrate.

Chemical Structure:



•2H_2O

CAS: [117772-70-0]
Empirical formula: $C_{38}H_{72}N_2O_{12}$•2$H_2$0
MW: 785.0

DESCRIPTION

Azithromycin dihydrate is a white or almost white powder which is practically insoluble in water, freely soluble in ethanol and in methylene chloride. Azithromycin contains a methyl substituted nitrogen atom at position *9a* of the lactone ring.

Excipients:
Each Azithromycin Sandoz film coated tablet also contains microcrystalline cellulose, maize starch, sodium starch glycollate – type A, colloidal anhydrous silica, magnesium stearate, sodium lauryl sulfate and Opadry OY-L-28900 White (containing lactose monohydrate, hypromellose, titanium dioxide, macrogol 4000 and purified water).

PHARMACOLOGY

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

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

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

Gram-negative Aerobic Bacteria: *Haemophilus influenzae (*including beta-lacatmase producing *Haemophilus influenzae), Haemophilus parainfluenzae, Moraxella catarrhalis, Acinetobacter* species, *Yersinia* species, *Legionella pneumophila, Bordetella pertussis, Bordetella parapertussis, Shigella species, Pasteurella species, Vibrio cholerae* and *parahaemolyticus, Plesiomonas shigelloide*s. Activities against *Escherichia coli, Salmonella enteritidis, Salmonella typhi*, *Enterobacter* species, *Aeromonas hydrophila* and *Klebsiella* species are variable and susceptibility tests should be performed. *Proteus* species, *Serratia* species, *Morganella* species, and *Pseudomonas aeruginosa* are usually resistant.

Anaerobic Bacteria: *Bacteroides fragilis* and *Bacteroides* species, *Clostridium perfringens, Peptococcus* species, *Peptostreptococcus* species, *Fusobacterium necrophorum* and *Propionibacterium acnes*.

Organisms of Sexually Transmitted Diseases: Azithromycin is active against *Chlamydia trachomatis* and also shows good activity against *Treponema pallidum, Neisseria 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 HIV Infections: *Mycobacterium avium-intracellulare complex*.

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

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

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

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

Opportunistic Pathogens Associated with HIV Infections: *Mycobacterium avium-intracellulare complex.*

Note: Erythromycin- and penicillin-resistant Gram-positive isolates may demonstrate cross-resistance to azithromycin.

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 (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg. NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited when the patient is given the recommended dose. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible medicines, 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. **Note:** The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

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

Pharmacokinetics

Tablets: Following oral administration of a 500mg dose, azithromycin is absorbed from the gastrointestinal tract with an absolute bioavailability of 37%. The maximum serum concentration (C_{max}) of 0.2 - 0.6μg/mL is achieved in 2-3 hours with an area under the curve $AUC_{(\infty)}$ of 4.4μg.h/mL.

Food has no significant effect on the bioavailability of azithromycin tablets, even after a high fat meal.

Pharmacokinetics in elderly subjects is substantially the same and no dosage adjustment is necessary. The extent of absorption is unaffected by co-administration with antacid; however, C_{max} is reduced by up to 30%. Administration of an 800mg dose of cimetidine two hours prior to azithromycin had no effect on azithromycin absorption. Azithromycin did not affect the plasma levels or pharmacokinetics of carbamazepine, methylprednisolone, zidovudine or multiple oral doses of theophylline (see Interactions with other medicines).

Serum concentrations decline in a polyphasic pattern, resulting in an average terminal half-life of 68 hours. The high values for apparent steady-state volume of distribution (31.1L/kg) and plasma clearance (630mL/minute) suggest that the prolonged half-life is due to extensive uptake and subsequent release of drug from tissues. Azithromycin concentrations in the cerebrospinal fluid are very low. Concentrations in the peritoneal fluid are also very low.

Azithromycin is distributed widely throughout the body. Rapid movement of azithromycin from blood into tissues results in significantly higher azithromycin concentrations in tissue than in plasma (from 1-60 times the maximum observed concentration in plasma). It appears to be concentrated intracellularly. Concentrations in tissues, such as lung, tonsil and prostate, etc exceed the MIC_{90} for likely pathogens after a single dose of 500mg, and remain high after serum or plasma concentrations decline to below detectable levels. Mean peak concentrations observed in peripheral leucocytes, the site of MAC infection, were 140μg/mL and remained above 32μg/mL for approximately 60 hours following a single 1200mg oral dose.

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02μg/mL to 7% at 2μg/mL.

Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug following oral administration. Very high concentrations of unchanged drug have been found, together with 10 metabolites, formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

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

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

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

CLINICAL TRIALS

Trachoma:
Trachoma - Children and Adults: Information from clinical trial data and published reports of studies supports the efficacy of 20mg/kg to 1g, taken either as a single dose or once weekly for up to three weeks, in the treatment of trachoma in children and adults. The single dose schedule has not been compared with the three weekly dosing schedule in clinical trials.
Trachoma - Repeat Courses: While the statistically significant superiority of a single dose of azithromycin given as a single dose and repeated at 6 months versus a single dose of azithromycin to adults or children with active trachoma has not been determined, information from clinical trial data suggests that the trachoma free period may be extended by a repeat single dose of azithromycin at 6 months.

Pharyngitis/Tonsillitis:
In a clinical trial (study 96-001), 501 children aged 2 - 12 years with a clinical diagnoses of acute tonsillitis received azithromycin 10mg/kg/day or 20mg/kg/day for 3 days or penicillin V, 50mg/kg (in 3 divided doses) for 10 days. (Note the recommended dose for penicillin V in Australia is 20mg/kg/day). Similar clinical efficacy but greater bacteriological eradication was evident at the 20 mg/kg/day dose (the daily dose did not exceed 500 mg).

Group A Beta -haemolytic streptococci (GABHS) eradication rates and clinical response rates are detailed below:

GABHS Eradication Rates at Day 14 and Day 30		
Treatment	**Day 14**	**Day 30**
Azithromycin 10mg/kg	57.8 %	56.8 %
Azithromycin 20mg/kg	94.2 %	82.8 %
Penicillin V 50mg/kg	84.2 %	81.6 %
Clinical Response Rates (Success) at Day 14		
Treatment	**Day 14**	
Azithromycin 10mg/kg	94.1 %	
Azithromycin 20mg/kg	100.0%	
Penicillin V 50mg/kg	94.5%	

INDICATIONS

Azithromycin is indicated for use in adults for the treatment of the following infections of mild to moderate severity:

- *Lower respiratory tract infections:*
  Acute bacterial bronchitis due to *Streptococcus pneumoniae, Haemophilus influenzae* or *Moraxella catarrhalis.*
  Community acquired pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients suitable for outpatient oral treatment.
  Community acquired pneumonia caused by susceptible organisms in patients who require initial intravenous therapy. In clinical studies efficacy has been demonstrated against *Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophilia, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus* and *Streptococcus pneumoniae*.

- *Upper respiratory tract infections:*
  Acute sinusitis due to *Streptococcus pneumoniae* or *Haemophilus influenzae*.
  Acute streptococcal pharyngitis. Note: Penicillin is the usual drug of choice in the treatment of Streptococcus pyogenes pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin appears to be almost as effective in the treatment of streptococcal pharyngitis. However, substantial data establishing the efficacy of azithromycin in the subsequent prevention of rheumatic fever are not available at present.

- *Uncomplicated skin and skin structure infections:*
  Uncomplicated infections due to *Staphylococcus aureus, Streptococcus pyogenes* or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

- *Sexually transmitted diseases:*
  Uncomplicated urethritis and cervicitis due to *Chlamydia trachomatis*.

Note: At the recommended dose azithromycin cannot be relied upon to treat gonorrhoea or syphilis. As with other medicines for the treatment of non-gonococcal infections, it may mask or delay the symptoms of incubating gonorrhoea or syphilis. Appropriate tests should be performed for the detection of gonorrhoea or syphilis and treatment should be instituted as required.

Azithromycin is also indicated for the treatment of *Chlamydia trachomatis* conjunctivitis and trachoma.

CONTRAINDICATIONS

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

PRECAUTIONS

Use with caution in the following circumstances:

In the treatment of pneumonia, azithromycin has been shown to be safe and effective only in the treatment of community-acquired pneumonia of mild severity due to *Streptococcus*

pneumoniae or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following:

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

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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.
Medicines which delay peristalsis e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Rare, serious, allergic reactions, including angioedema and anaphylaxis (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.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased

risk for prolonged cardiac repolarization (see ADVERSE EFFECTS), therefore caution is required when treating patients:

- with congenital or documented QT prolongation
- currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine
- with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia
- with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see ADVERSE EFFECTS).

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.

Impaired renal function

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 1g in subjects with severe renal impairment (GFR < 10mL/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.

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 PHARMACOLOGY, Pharmacokinetics). Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see ADVERSE EFFECTS). Liver function tests/investigations should be performed in cases where signs and symptoms of liver dysfunction occur such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy.

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

The majority of cases of disseminated *Mycobacterium Avium* complex infection occur in patients with CD_4 counts below 50cells/μL. Some authorities recommend delay of initiation of prophylaxis until the cell count has fallen to 50cells/μL.

No evidence exists from formal studies to determine the need for, and frequency of, repeat dosing in the treatment of trachoma.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No studies have been done to determine the carcinogenic potential of azithromycin in animals. Azithromycin showed no genotoxic potential in a range of standard laboratory tests for gene mutations and chromosomal damage. In three fertility and general reproduction studies in rats, there was decreased fertility at doses of 20 and 30mg/kg/day. The clinical significance of this is unknown.

Serious infections
Azithromycin is not intended to treat suitable severe infections, where fast high blood concentrations of antibiotic have to be achieved.

Use in Pregnancy [Category B1]
No studies have been carried out in pregnant women. Azithromycin was not foetotoxic or teratogenic in mice and rats at doses that were moderately maternotoxic (up to 200mg/kg/day). At 200mg/kg/day, mouse and rat foetal tissues homogenate concentrations were 5 to 10-fold higher than corresponding maternal plasma concentrations.

Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Australian categorisation definition of Category B1:
Medicines 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.

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.

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.

Medicines that should not be concomitantly administered with azithromycin:

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

Ergot: The theoretical possibility of ergotism contraindicates the concurrent use of azithromycin with ergot derivatives (see PRECAUTIONS).

Medicines that require dosage adjustment when administered concomitantly with azithromycin:

Cyclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500mg/day oral dose of azithromycin for 3 days and were then administered a single 10mg/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 medicines. If coadministration of these medicines is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Medicines that have been studied with no clinically significant interaction shown:

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

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

Cetirizine: In healthy volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20mg 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 15mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time, when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Didanosine: Co-administration of 1200mg/day azithromycin with 400mg/day didanosine in 6 HIV-positive subjects for 2 weeks had no effect on the steady state pharmacokinetics of didanosine as compared with placebo.

Efavirenz: Coadministration of a 600mg single dose of azithromycin and 400mg 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 1200mg azithromycin did not alter the pharmacokinetics of a single dose of 800mg fluconazole. Total exposure and half life of azithromycin were unchanged by the coadministration of fluconazole however a clinically

insignificant decrease in C_{max} (18%) of azithromycin was observed. No dose adjustment is necessary when azithromycin is given with fluconazole.

Indinavir: Coadministration of a single dose of 1200mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800mg three times daily for 5 days. No adjustment of the dose is necessary when azithromycin is given with indinavir.

Methylprednisolone: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam: In healthy volunteers, coadministration of azithromycin 500mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15mg dose of midazolam.

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

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

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

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

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

Triazolam: In 14 healthy volunteers, coadministration of azithromycin 500mg on Day 1 and 250mg on Day 2 with 0.125mg 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 (160mg/800mg) for 7 days with azithromycin 1200mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfomethoxazole. Azithromycin serum concentrations were similar to those seen in other studies. No dose adjustment is necessary.

Zidovudine: Single 1000mg doses and multiple 1200mg or 600mg doses of azithromycin had little effect on 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, but it may be of benefit to patients.

Other Interactions:

Digoxin: Some of the macrolide antibiotics have been reported to impair the metabolism of 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.

Effects on laboratory tests
There are no reported laboratory test interactions.

ADVERSE EFFECTS

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

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

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

Side effects that occurred with a frequency of 1% or less included the following:
Allergic: rash, photosensitivity, angioedema.
Cardiovascular: palpitations, chest pain.
Gastrointestinal: dyspepsia, flatulence, vomiting, melaena, cholestatic jaundice.
Genitourinary: moniliasis, vaginitis, nephritis.
Nervous system: dizziness, headache, vertigo, somnolence.
General: fatigue.

Single 1 gram dose regimen: The most frequently reported adverse events in patients receiving a single-dose regimen of 1 gram of azithromycin were related to the

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

Laboratory abnormalities: Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:
Incidence >1%: elevated serum creatinine phosphokinase, potassium, ALT (SGPT), GGT and AST (SGOT), lymphocytes and neutrophils; decreased neutrophils.
Incidence < 1%: leukopenia, neutropenia, thrombocytopenia; elevated serum alkaline phosphatase, bilirubin, BUN, creatinine, blood glucose, LDH, and phosphate, monocytes, basophils, bicarbonate; decreased sodium, potassium,.
When follow-up was provided, changes in laboratory tests appeared to be reversible.
In multiple-dose trials involving > 3000 patients, 3 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

HIV infected patients receiving prophylaxis for disseminated MAC. The most frequent adverse events are as follows:

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

	Study 155		**Study 174**		
	Placebo	**Azithromycin**	**Azithromycin**	**Rifabutin**	**Combination therapy**
Adverse Event	**N=91**	**N=89**	**N=233**	**N=236**	**N=224**
Diarrhoea	15.4	52.8	50.2	19.1	50.9
Abdominal pain	6.6	27	32.2	12.3	31.7
Nausea	11.0	32.6	27.0	16.5	28.1
Loose stools	6.6	19.1	12.9	3.0	9.4
Flatulence	4.4	9.0	10.7	5.1	5.8
Vomiting	1.1	6.7	9.0	3.8	5.8
Dyspepsia	1.1	9.0	4.7	1.7	1.8
Rash	2.2	3.4	6.0	8.1	9.8
Pruritus	3.3	0	3.9	3.4	7.6
Headache	0	0	3.0	5.5	4.5
Arthralgia	0	0	3.0	4.2	7.1
Subjects with AE's	31.9	79.8	78.1	59.7	83.5

The most common laboratory test abnormalities were haematological (mainly decreases in haemoglobin and white cell count) and increases in AST and ALT.

The following adverse events, where a causal relationship to treatment could not be ruled out, were reported at an occurrence of ≥ 1%:			
		Azithromycin Dose Study 96-001	
Category of event		**10 mg/kg 3 day (n=169)**	**20 mg/kg 3 day (n=165)**
	Event		
Gastrointestinal system disorders			
	Abdominal Pain	2%	5%
	Diarrhoea	3%	6%
	Nausea	1%	3%
	Vomiting	7%	9%
General condition disorders			
	Allergic reaction	2%	-
Skin and accessory structures			
	Eczema	1%	-
	Rash	1%	-

Post marketing experience:
In post marketing experience, the following adverse events have been reported:

Infections and Infestations: moniliasis and vaginitis.

Blood and Lymphatic System Disorders: thrombocytopenia.

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, somnolence, headache, syncope, convulsions (as seen with other macrolides), hypoesthesia, paraesthesia, psychomotor hyperactivity and myasthenia gravis.

Eye disorders: visual impairment.

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

Genitourinary: acute renal failure, interstitial nephritis

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

Musculoskeletal: arthralgia.

Psychiatric: aggressive reaction, nervousness, agitation, anxiety.

Skin/Appendages: pruritus, urticaria, oedema, angioedema, serious skin reactions including erythema multiforme, rash, photosensitivity, Stevens Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS).

Special senses: vertigo, hearing disturbances* including hearing loss, deafness and/or tinnitus; vertigo. Taste/smell perversion and/or loss; however a causal relationship has not been established.
NOTE: * Hearing impairment has been reported with macrolide antibiotics.

DOSAGE AND ADMINISTRATION

Azithromycin should be given as a single daily dose. The tablets may be taken with food.

Adults:
Sexually transmitted uncomplicated urethritis and cervicitis due to Chlamydia trachomatis: 1g as a single dose.

Conjunctivitis and trachoma due to Chlamydia trachomatis: 1g either as a single dose or once weekly for up to three weeks (see CLINICAL TRIALS).

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

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

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

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

As with many cationic amphiphilic medicines, 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.

PRESENTATION AND STORAGE CONDITIONS

Azithromycin Sandoz 500mg tablets - white, film-coated, oval shaped, plain on one side, with a breaking notch and 'A500' embossed on the other side.
Available in blister packs of 2 and 3 tablets.

Store below 25°C.
Protect from light and moisture.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 29/04/2009

Date of most recent amendment: 01/11/2016