

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product

AZITHROMYCIN 500

(Azithromycin Capsules USP 500 mg)

2. Quality and Quantitative Composition

Qualitative Composition:

Each capsule Contains:

Azithromycin Dihydrate USP

Eq. to Azithromycin Anhydrous 500 mg

Excipients.....Q.S.

Approved color used in capsule shells

Sr. No.	Ingredients	Standard
1	Microcrystalline Cellulose	BP
2	Magnesium Stearate	BP
3	Purified Talc	BP
4	Hard gelatin capsule shells, Size 0. Cap: Faint Green Body: Dark Green	IH

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

Quantitative Composition:

Each capsule Contains:

Azithromycin Dihydrate USP

Eq. to Azithromycin Anhydrous 500 mg

Excipients.....Q.S.

Approved color used in capsule shells

Sr. No	Ingredients	Specification	Quantity /Capsule
1.	Microcrystalline Cellulose	BP	8.00 mg
2.	Magnesium Stearate	BP	11.00 mg
3.	Purified Talc	BP	4.00 mg
4.	Hard gelatin capsule shells, Size 0. Cap: Faint Green Body: Dark Green	IH	---

3. Pharmaceutical Form

Solid Dosage form (Capsules)

Dark green cap and Light green body, “0” size capsules, containing white crystalline powder.

5. Clinical Particulars

4.1 Therapeutic indications

Treatment of the following bacterial infections induced by micro-organisms susceptible to azithromycin:

- Bronchitis
- Community-acquired pneumonia
- Sinusitis

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

- Pharyngitis/tonsillitis (see 4.4 regarding streptococcal infections)
- Otitis media
- Infections of the skin and soft tissues
- Uncomplicated genital infections due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae*

4.2 Posology and method of administration

Posology

Azithromycin capsules should be given as a single daily dose.

In common with many other antibiotics Azithromycin Capsules should be taken at least 1 hour before or 2 hours after food.

Children and adolescents with a body weight above 45 kg, adults and the elderly:

The total dose of azithromycin is 1500 mg, which should be given over three days (500 mg once daily).

In the case of uncomplicated *genital infections due to Chlamydia trachomatis*, the dose is 1000 mg as a single oral dose. For susceptible *Neisseria gonorrhoeae* the recommended dose is 1000 mg or 2000 mg of azithromycin in combination with 250 mg or 500 mg ceftriaxone according to local clinical treatment guidelines. For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

Paediatric population:

Children and adolescents with a body weight below 45 kg:

Azithromycin Capsules are not suitable for children under 45kg.

Renal impairment:

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min)

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

Hepatic impairment:

Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin.

Method of administration

Azithromycin Capsules are for oral administration only.

4.3 Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients used.

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

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. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests / investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

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

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

Clostridium difficile associated diarrhoea (CDAD) has been reported with the 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.

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including azithromycin.

Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia 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.

Safety and efficacy for the prevention or treatment of (*Mycobacterium avium* complex) in children have not been established.

The following should be considered before prescribing azithromycin:

Azithromycin powder for oral solution is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* (> 30 %) have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

Pharyngitis/ tonsillitis

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by *Streptococcus pyogenes*. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis

Often, azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media

Often, azithromycin is not the substance of first choice for the treatment of acute otitis media.

Skin and soft tissue infections

The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Infected burn wounds

Azithromycin is not indicated for the treatment of infected burn wounds.

Sexually transmitted disease

In case of sexually transmitted diseases a concomitant infection by *T. palladium* should be excluded.

Neurological or psychiatric diseases

Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.70 g of sucrose.

Patients with rare hereditary problems of fructose intolerance, glucose-galactosemalabsorption or sucrase-isomaltase insufficiency should not take this medicine since it contains sucrose.

Azithromycin 200mg/5 ml contain aspartame which is a source of phenylalanine. It may be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction

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 approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine

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

Didanosine (Dideoxyinosine)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin (P-gp substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

Zidovudine

Single 1000 mg doses and multiple 1200 mg or 600 mg 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.

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.

Ergot

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

Ergotamine derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin.

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

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.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Cimetidine

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

Coumarin-Type Oral Anticoagulants

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

Cyclosporin

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin 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.

Efavirenz

Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

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 C_{max} (18%) of azithromycin was observed.

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.

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 3 did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

Nelfinavir

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

Rifabutin

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 3 days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.

Terfenadine

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

Theophylline

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

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

Trimethoprim/sulfamethoxazole

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

Substances that prolong the QT interval

Azithromycin should not be used concurrently with other active substances that prolong the QT interval.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore Azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Lactation

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

Fertility

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Stomach upset, diarrhea/loose stools, nausea, vomiting, or abdominal pain may occur. If any of these effects persist or worsen, tell your doctor or pharmacist promptly.

Remember that your doctor has prescribed this medication because he or she has judged that the benefit to you is greater than the risk of side effects. Many people using this medication do not have serious side effects.

Tell your doctor right away if any of these unlikely but serious side effects occur: hearing changes (such as decreased hearing, deafness), eye problems (such as drooping eyelids, blurred vision), difficulty speaking/swallowing, muscle weakness, signs of liver problems (such as unusual tiredness, persistent nausea/vomiting, severe stomach/abdominal pain, yellowing eyes/skin, dark urine).

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolides; azithromycin,

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

ATC code: J01FA10

Mode of action

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

PK/PD relationship

For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

Mechanism of resistance

Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Complete cross resistance exists among *Streptococcus pneumoniae*, beta-haemolytic streptococcus of group A, *Enterococcus faecalis* and *Staphylococcus aureus*, including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens	susceptible (mg/l)	resistant (mg/l)
<i>Staphylococcus</i> spp.	≤ 1	> 2
<i>Streptococcus</i> spp. (Group A, B, C, G)	≤ 0.25	> 0.5
<i>Streptococcus pneumoniae</i>	≤ 0.25	> 0.5
<i>Haemophilus influenzae</i>	≤ 0.125	> 4

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

<i>Moraxella catarrhalis</i>	≤ 0.5	> 0.5
<i>Neisseria gonorrhoeae</i>	≤ 0.25	> 0.5

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Pathogens for which resistance may be a problem: prevalence of resistance is equal to or greater than 10% in at least one country in the European Union.

Table of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms <i>Haemophilus influenzae</i> * <i>Moraxella catarrhalis</i> * Other microorganisms <i>Chlamydia pneumoniae</i> <i>Chlamydia trachomatis</i> <i>Legionella pneumophila</i> <i>Mycobacterium avium</i> <i>Mycoplasma pneumoniae</i> *
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms <i>Staphylococcus aureus</i> *

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

Streptococcus agalactiae

*Streptococcus pneumoniae**

*Streptococcus pyogenes**

Other microorganisms

Ureaplasmaurealyticum

Inherently resistant organisms

Aerobic Gram-positive microorganisms

Staphylococcus aureus – methicillin resistant and erythromycin resistant strains

Streptococcus pneumoniae – penicillin resistant strains

Aerobic Gram-negative microorganisms

Escherichia coli

Pseudomonas aeruginosa

Klebsiella spp.

Anaerobic Gram-negative microorganisms

Bacteroidesfragilis-group

* Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indications.

5.2 Pharmacokinetic properties

Absorption

The biological availability of azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.

Distribution

After oral administration, azithromycin is distributed throughout the entire body. Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities.

Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.

The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.

Elimination

The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days.

Approximately 12% of an intravenously administered dose of azithromycin is, over a period of 3 days, excreted unchanged in the urine. High concentrations of unchanged azithromycin were found in human bile. In this, ten metabolites were also detected (formed by N- and O- desmethylation, by hydroxylation of the desosamin and aglycon rings and by splitting the cladinose conjugate). A comparison of fluid chromatography and microbiological assessment methods shows that the metabolites are microbiologically inactive.

In animal models high concentrations of azithromycin were found in phagocytes. Also it has been shown that during active phagocytosis higher concentrations of azithromycin are released than during inactive phagocytosis. In animal models this process was shown to contribute to the accumulation of azithromycin in infectious tissue.

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 33% respectively compared to normal.

Hepatic insufficiency

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

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension.. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and humans is unknown.

Carcinogenic potential:

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

Mutagenic potential:

There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

Reproductive toxicity:

In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

6.0 Pharmaceutical Particulars

6.1 List of excipients

Sr. No.	Ingredients	Standard
1	Microcrystalline Cellulose	BP
2	Magnesium Stearate	BP
3	Purified Talc	BP
4	Hard gelatin capsule shells, Size 0. Cap: Faint Green Body: Dark Green	IH

6.2 Incompatibilities

Not applicable.

AZITHROMYCIN 500 (Azithromycin Capsules USP 500 mg)

MODULE 1 (Administrative & Prescribing Information)

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C, protected from light.

Keep medicines out of reach of children.

6.5 Nature and contents of container

Alu/PVC Blister pack of 1 x 4 Capsules.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing Authorization Holder

Emzor Pharmaceutical Industries Limited

8. Marketing Authorization Numbers

9. Date of first authorization/renewal of the authorization

10. Date of revision of the text
