1.4 Product Information

1.4.1 Prescribing information (Summary of Product Characteristics)

1. **Name of the medicinal product**

Aziwin-500 (Azithromycin Tablets USP 500 mg)

2. Qualitative and quantitative composition

Each film coated tablet contains:
Azithromycin Dihydrate USP eq. To
Azithromycin USP .....500 mg
Colour…….Titanium Dioxide BP

S.No	Ingredients	Pharma copoeial Standard	Quantity per unit dose(mg/Tab)	Functions
Active Substance:				
1.	Azithromycin Dihydrate	USP	524.00	API
Excipients:				
2.	**Anhydrous calcium** Hydrogen Phosphate	BP	50.70	Diluent
3.	Microcrystalline cellulose (PH 101)	BP	79.30	Diluent
4.	Maize starch	BP	77.00	Diluent
5.	Sodium Lauryl Sulphate	BP	6.00	Wetting agent
6.	Povidone (PVP K30)	BP	16.00	Binder
7.	Isopropyl Alcohol^	BP	Q.S	Granulating
8.	Maize Starch	BP	77.00	Diluent
9.	Croscarmellose sodium	USP/NF	18.00	Disintegrant
10.	Sodium starch glycollate	USP/NF	15.00	Disintegrant
11.	Colloidal silicon dioxide	USP/NF	6.00	Glidant
12.	Purified Talc	BP	10.00	Anti-adherent
13.	Sodium Lauryl sulphate	BP	6.00	Wetting agent
14.	Magnesium stearate	BP	10.00	Lubricant
15.	Hypermellose 15 CPS	BP	6.37	Film former
16.	Isopropyl Alcohol**	BP	Q.S	Coating solvent
17.	Methylene chloride** (Dichloromethan)	BP	Q.S	Coating solvent
18.	Titanium Dioxide	BP	14.98	Opacifier
19.	Purified Talc	BP	13.50	Anti-tacking
20.	Polysorbate 80	USP	0.15	Wetting agent
21.	Total		600.00	

3. Pharmaceutical form

Tablet

White oval shaped film coated tablets with a break-line on one surface.

4. Clinical particulars

4.1 Therapeutic indications

Azithromycin is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin.

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas
- Uncomplicated Chlamydia trachomatis urethritis and cervicitis

Consideration should be given to official guidance on the appropriate use of antibacterial agents

4.2 Posology and method of administration

Posology

Azithromycin tablets should be given as a single daily dose. The duration of treatment in each of the infectious diseases is given below.

Adults, elderly, children and adolescents over 45 kg body weight

The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5.

In the case of uncomplicated Chlamydia trachomatis urethritis and cervicitis the dosage is 1000 mg as a single oral dose.

Children and adolescents with a body weight under 45 kg

Azithromycin tablets are not suitable for patients under 45 kg body weight. Other dosage forms are available for this group of patients.

Elderly Patients

For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

Patients with renal impairment

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min)

Patients with hepatic impairment

Dose adjustment is not required for patients with mild to moderate hepatic dysfunction.

Method of administration

For oral use.

The tablets can be taken with or without food.

The tablets should be taken with ½ glass of water.

Paediatric population :

NA

4.3 Method of Administration

For oral administration.

4.4 Contraindications

- Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

4.5 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema 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. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

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.

Since the 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.

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 ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

Superinfections:

As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with non-susceptible micro-organisms like fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.

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.

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

With congenital or documented acquired 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 hypomagnesaemia

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 (MAC) in children have not been established.

The following should be considered before prescribing azithromycin:

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

The selection of azithromycin to treat an individual patient should take into account the appropriateness of using a macrolide antibacterial agent based on adequate diagnosis to ascertain the bacterial etiology of the infection in the approved indications and the prevalence of resistance to azithromycin or other macrolides.

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.

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

In bacterial pharyngitis the use of azithromycin is recommended only in cases where first line therapy with beta-lactams is not possible.

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. pallidium should be excluded.

Neurological or psychiatric diseases:

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

4.6 Paediatric population

NA

4.7 Interactions with other medicinal products and other forms of interaction

Interactions to be used with caution:

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of

antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum levels were reduced by approximately 25%. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

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)

Co-administration 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.

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.

Ergotamine derivatives

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.

Astemizole and alfentanil

No data are available on interactions with astemizole and alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentiation of its effect during concomitant use of the macrolide antibiotic erythromycin.

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 metabolised 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

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 Cmax and AUC0-5 were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz

Co-administration 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

Co-administration 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 co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Indinavir

Co-administration 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 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Nelfinavir

Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically

significant adverse effects were observed and no dose adjustment is required.

Rifabutin

Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established.

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and Cmax, 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

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 DS (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.

4.8 Additional information on special population.

4.9 Paediatric population: Not applicable

4.10 Fertility, pregnancy and lactation

4.10.1 General principles

4.10.2 Women of childbearing potential/Contraception in males and females.

4.10.3 Pregnancy:

Pregnancy

There are no adequate data from 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.

4.10.4 Breastfeeding:

Azithromycin passes into human breast milk, but there are no adequate and

well-controlled clinical studies in nursing women that have characterised the pharmacokinetics of azithromycin excretion into human breast milk. Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

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

4.11 Effects on ability to drive and use machines

No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery.

However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.12Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency.

The frequency grouping is defined using the following convention: Very common (⩾ 1/10); Common (⩾ 1/100 to <1/10); Uncommon (⩾ 1/1,000 to <1/100); Rare (⩾ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data).

Infections and Infestations

Uncommon : Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis

Not known : Pseudomembranous colitis.

Blood and Lymphatic System Disorders

Uncommon : Leukopenia, neutropenia, eosinophilia

Not Known: Thrombocytopenia, haemolytic anaemia.

Immune System Disorders

Uncommon : Angioedema, hypersensitivity

Not Known : Anaphylactic reaction

Metabolism and Nutrition Disorders

Common : Anorexia

Psychiatric Disorders

Uncommon : Nervousness, insomnia

Rare : Agitation, depersonalization

Not known: Aggression, anxiety, delirium, hallucination.

Nervous System Disorders

Common: Headache, dizziness, paraesthesia, dysgeusia

Uncommon: Hypoaesthesia, somnolence

Not known: Syncope, convulsion, hypoaesthesia, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis.

Eye Disorders

Common: Visual impairment

Ear and Labyrinth Disorders

Common: Deafness

Uncommon: ear disorder, vertigo, hearing impaired, tinnitus

Cardiac Disorders

Uncommon: Palpitations

Not known: Torsades de pointes, arrhythmia including ventricular tachycardia, Electrocardiogram QT prolonged.

Vascular Disorders

Uncommon: Hot flushes

Not Known: Hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, epistaxis

Gastrointestinal Disorders

Very Common: Diarrhoea abdominal pain, nausea, flatulence

Common: Vomiting, dyspepsia

Uncommon: Gastritis, constipation, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion

Not known: Pancreatitis, tongue and teeth discolouration.

Hepatobiliary Disorders

Uncommon: Hepatitis

Rare: Hepatic function abnormal, jaundice cholestatic
Not known: Hepatic failure (which has rarely resulted in death), hepatitis fulminant, hepatic necrosis

Skin and Subcutaneous Tissue Disorders

Common: Rash, pruritus

Uncommon: Steven-Johnson syndrome, photosensitivity reaction, urticaria, dermatitis, dry skin, hyperhidrosis

Rare: Allergic reactions including angioneurotic oedema, Acute generalised exanthematous pustulosis (AGEP)

Not known: Toxic epidermal necrolysis, erytherma multiforme. DRESS (Drug reaction with eosinophilia and systemic symptoms)

Musculoskeletal and Connective Tissue Disorders

Common: Arthralgia.

Uncommon: Osteoarthritis, myalgia, back pain, neck pain

Renal and Urinary Disorders

*Uncommon: D*ysuria, renal pain.

Rare: Renal failure, acute interstitial nephritis.

Reproductive system and breast disorders

Uncommon: Metrorrhagia, testicular disorder.

General Disorders and Administration Site Conditions

Common: Fatigue

Uncommon: Chest pain, face oedema, pyrexia, peripheral pain, oedema, malaise, asthenia

Investigations

Common: Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils increased.

Uncommon: Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal, blood alkaline phosphatase increased, chloride increased , glucose increased, platelets increased, haematocrit decreased, bicarbonate increased, abnormal sodium.

Injury, poisoning and procedural complications

Uncommon: Post procedural complication.

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

Metabolism and Nutrition Disorders

Common: Anorexia

Nervous System Disorders

Common: Dizziness, headache, paraesthesia, dysgeusia.

Uncommon: Hypoaesthesia

Eye Disorders

Common: Visual impairment

Ear and Labyrinth Disorders

Common: Deafness

Uncommon: Hearing impaired tinnitus.

Cardiac Disorders

Uncommon: Palpitations

Gastrointestinal Disorders

Very Common: Diarrhoea, abdominal pain, nausea, flatulence, abdominal discomfort, loose stools

Hepatobiliary Disorders

Uncommon: Hepatitis

Skin and Subcutaneous Tissue Disorders

Common: Rash, pruritus

Uncommon: Stevens-Johnson syndrome, photosensitivity reaction

Musculoskeletal and Connective Tissue Disorders

Common: Arthralgia

General Disorders and Administration Site Conditions

Common: Fatigue

Uncommon: Asthenia, malaise.

4.13 Overdose

Symptoms

The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Management

In the event of overdose, general symptomatic and supportive measures are indicated as required.

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-bacterials for systemic use; macrolides

ATC code: J01FA10.

Azithromycin is a macrolide antibiotic belonging to the azalide group.
The molecule is constructed by adding a nitrogen atom to the Lactone ring of

erythromycin A.

Mechanism 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.

Pharmacokinetic/pharmacodynamic 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, betahaemolytic 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)

	MIC breakpoint (mg/l)	
Pathogens	Suspectible (mg/l)	Resistant (mg/l)
Staphylococcus spp.	< 1	> 2
Streptococcus spp. (Group A, B, C, G)	< 0.25	> 0.5
Streptococcus pneumoniae	< 0.25	> 0.5
Haemophilus influenzae	< 0.125	> 4
Moraxella catarrhalis	< 0.25	> 0.5
Neisseria gonorrhoeae	< 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 Suspectibility

Commonly susceptible species
Aerobic Gram-negative microorganisms

Haemophilus influenzae* Moraxella catarrhalis* Other microorganisms Chlamydophila pneumoniae Chlamydia trachomatis Legionella pneumophila Mycobacterium avium Mycoplasma pneumonia*
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms Staphylococcus aureus* Streptococcus agalactiae Streptococcus pneumoniae* Streptococcus pyogenes* Other microorganisms Ureaplasma urealyticum
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 Bacteroides fragilis-group

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

5.2 Pharmacokinetic properties

Absorption:

Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (Cmax) after a single dose of 500 mg is approximately 0.4 µg/ml.

Distribution:

Orally administered azithromycin is widely distributed throughout the body.

Pharmacokinetic studies have demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (up to 50 times the maximum observed

concentration in plasma) than those measured in plasma. This indicates that the agent strongly binds to tissues (steady-state distribution volume approx. 31 l/kg).

At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 µ g/g, 0,6-2,3 µ g/g, 2,0-2,8 µ g/g and 0-0,3 µ g/ml have been measured in resp. lung, prostate, tonsil and serum.

In experimental in vitro and in vivo studies azithromycin accumulates in phagocytes. Release is stimulated by active phagocytosis. In animal models this process contributes to the accumulation of azithromycin in tissue.

Binding of azithromycin to serum proteins is variable and varies from 52% at 0,05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration.

Elimination:

The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

Approximately 12% of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µ g/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile. Ten metabolites have been identified (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggest that the metabolites do not play a role in the microbiological activity of azithromycin.

Pharmacokinetics in special populations

Renal insufficiency:

Following a single oral dose of azithromycin 1g, mean Cmax and AUC0-120 increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment, the mean Cmax and AUC0-120 increased 61% and 35% 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.

In elderly volunteers (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

Infants, toddlers, children and adolescents:

Pharmacokinetics has 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 Cmax achieved is slightly lower than adults with 224 µg/l in children aged 0.6-5 years and after 3 days dosing and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

Paediatric population:

Not applicable

5.3 Pharmacokinetic properties

Absorption:

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Pharmacokinetics in special populations

Renal insufficiency:

Following a single oral dose of azithromycin 1g, mean Cmax and AUC0-120 increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment, the mean Cmax and AUC0-120 increased 61% and 35% 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.

In elderly volunteers (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

Infants, toddlers, children and adolescents:

Pharmacokinetics has 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 Cmax achieved is slightly lower than adults with 224 µg/l in children aged 0.6-5 years and after 3 days dosing and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

Paediatric population:

Not applicable

5.4 Preclinical safety data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a

rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential:

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

Reproductive toxicity:

No teratogenic effects were observed in embryo toxicity studies in rats after oral administration of azithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/day led to mild retardations in fetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6. Pharmaceutical Particulars

6.1 List of excipients

Anhydrous Calcium Hydrogen Phosphate	BP
Microcrystalline cellulose (PH 101)	BP
Maize starch	BP
Sodium Lauryl Sulphate	BP
Povidone (PVP K 30)	BP
Isopropyl Alcohol	BP
Croscarmellose Sodium	USP/NF
Sodium starch glycollate	USP/NF
Colloidal silicon dioxide	USP/NF
Purified talc	BP
Magnesium stearate	BP
Hypromellose (15 CPS)	BP
Methylene Chloride (Dichloromethane)	BP
Titanium Dioxide	BP
Polysorbate 80	USP

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30^0C.

6.5 Nature and contents of container

Pack size : 1X3's Alu-PVC blister

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder and manufacturing site address

Bal Pharma Limited.
21 & 22 - Bommasandra Industrial Area
Bangalore - 560099 Karnataka, India.
E-mail: regulatory@balpharma.com

8. Marketing authorisation number(s)

Not applicable

9. Date of first authorisation/renewal of the authorisation.

Not applicable

10. Date of revision of the text

Not applicable