Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Azito 500 (Azithromycin Tablets USP 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Azithromycin Dihydrate	USP
Eq. to Azithromycin	500 mg

For full list of excipients see Section 6.1

3. PHARMACEUTICAL FORM

Film Coated Tablets

White, caplet shaped, film coated tablets having break line on one side and plain on other side

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infectious diseases caused by azithromycin-sensitive pathogens:

Ear, nose and throat infections

Pharyngitis, Tonsillitis, Sinusitis, Otitis
(Penicillin is usually the drug of choice for the treatment of Streptococcus pyogenes pharyngitis and includes prophylaxis of rheumatic fever. Azithromycin is generally effective against streptococci in the oropharynx, but there are currently no data to support the effectiveness of azithromycin in preventing pharyngitis prove rheumatic fever.)

Respiratory infections

Bronchitis and pneumonia when oral therapy is indicated based on the clinical course Skin and soft tissue infections of the genital tract caused by chlamydia or gonococci (non-multiresistant strains), with a simultaneous Lues should be ruled out.

Official guidelines for the appropriate use of antibiotics should be taken into account.

Azithromycin tablets® 500 mg film-coated tablets are used in adults or children and adolescents over 45 kg.

4.2 Posology and method of administration

To take the recommended daily dose is to be swallowed whole with or without food as a single dose once a day.

Use in adults
All indications except genital tract infections: 500 mg once daily for 3 days

Infections of the genital tract
Adult genital tract infections caused by chlamydia: 1 g azithromycin (= 2nd film-coated tablets) as a single dose

Combination therapy with ceftriaxone:
Adult genital tract infections caused by gonococci (if susceptible): 1 g or 2 g azithromycin combined with 250 mg or 500 mg ceftriaxone in accordance with local therapeutic guidelines. In patients with penicillin or cephalosporin allergy, local treatment guidelines should be taken into account.

Use in children and adolescents
Children and adolescents over 45 kg receive the adult dose. Azithromycin tablets 200 mg/5 ml - dry juice is available for children and adolescents under 45 kg.

Special dosage instructions

Use in patients with impaired renal function
No dose adjustment is required in patients with mild to moderate renal impairment (GFR 10-80 mL/ min). Caution is advised in patients with severe renal impairment (GFR < 10 ml/min) (see sections 4.4 and 5.2).

Use in patients with impaired liver function
In patients with mild to moderate hepatic impairment, the same dosage as in patients with normal hepatic function can be used with caution.
Since azithromycin is primarily eliminated by the liver, use in patients with severe hepatic impairment is not recommended (see section 4.4).

Use in elderly patients
No dose adjustment is required in elderly patients. Since elderly patients may suffer from proarrhythmic disorders, special caution is required due to the risk of developing cardiac arrhythmias and torsades de pointes (see section 4.4).

Duration of use
In general, the duration of use in children and adolescents is 3 days, as in adults.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of the medicinal product listed in section 6.1, as well as to erythromycin, macrolide and ketolide antibiotics

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolide antibiotics, rare cases of severe allergic reactions, including angioedema and anaphylaxis (rarely fatal), and skin reactions, including acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN; lethal in isolated cases) and drug eruption with eosinophilia and systemic symptoms (DRESS) have been reported. In some cases, the symptoms of these reactions with azithromycin have been recurrent and have required long-term monitoring or treatment.

Treatment.
If an allergic reaction occurs, the drug should be discontinued and appropriate treatment instituted. Physicians should be aware that there may be a recurrence of allergic symptoms when symptomatic treatment is discontinued.

Children and young people

The safety and efficacy for the prophylaxis or treatment of Mycobacterium Avium Complex in children has not been established.

Hepatotoxicity

Since azithromycin is primarily metabolised and eliminated by the liver, caution should be exercised in patients with severe hepatic impairment. Hepatic impairment, hepatitis, cholestatic jaundice, hepatic necrosis and hepatic failure, in some cases fatal, have been reported (see section 4.8). Some patients may have had pre-existing liver disease or treatment with other hepatotoxic drugs.

If symptoms of hepatic dysfunction such as rapidly progressive weakness with jaundice, dark urine, bleeding tendency or hepatic encephalopathy occur, liver function tests/examinations should be performed promptly. Treatment with azithromycin should be discontinued if liver dysfunction occurs.

Infantile hypertrophic pyloric stenosis (IHPS):

Cases of infantile hypertrophic pyloric stenosis (IHPS) have been reported after administration of azithromycin to neonates (treatment up to 42 days after birth). Parents and caregivers must be instructed to inform the doctor if vomiting or irritation occurs with feeding.

Ergot-Derivate

Ergotism may occur when patients take ergotamine or ergot derivatives concomitantly with certain macrolide antibiotics. Studies on a possible interaction between ergot derivatives and azithromycin are lacking. Because of the theoretical possibility of Ergotism, however, azithromycin should not be administered together with ergot derivatives.

Resistance

As with any antibiotic treatment, monitoring of patients for symptoms of superinfection with resistant microorganisms and/or fungi is recommended. If resistance develops or germ selection occurs, the antibiotic should be changed.

Existing cross-resistance with erythromycin-resistant Gram-positive strains and most strains of methicillin-resistant staphylococci should be taken into account. There is also cross-resistance to lincosamides (including clindamycin) and to group B streptogramins (such as the quinupristin component of quinupristin/dalfopristin).

Clostridium difficile-associated diarrhoea

Clostridium difficile-associated diarrhoea (CDAD) has been reported with almost any antibiotic therapy, including azithromycin, and can range in severity from mild diarrhoea to life-threatening colitis. Antibiotic treatment alters the normal gut flora and can lead to Clostridium difficile overgrowth.

Clostridium difficile produces toxins A and B that contribute to the development of CDAD.
Hypertoxin-producing strains of Clostridium difficile result in increased morbidity and mortality as such infections may not respond to antibiotic therapy and may require colectomy. CDAD must be considered in all patients who develop diarrhoea after antibiotic therapy. Careful medical history is required as CDAD has been reported to occur up to two months after antibiotic administration.

In the event of severe and persistent diarrhoea, the preparation should be discontinued immediately and suitable therapy (e.g. oral vancomycin 4 x 250 mg daily) initiated. Drugs that inhibit peristalsis are contraindicated.

Renal dysfunction

In severe renal impairment (GFR below 10 mL/min), systemic exposure increased by 33%; therefore, caution should be exercised when prescribing azithromycin in these cases (see section 5.2).

Prolongation of the QT interval

Prolongation of cardiac repolarization and QT interval, which is associated with the risk of cardiac arrhythmias and torsades de pointes, has been observed with treatment with macrolides, including azithromycin (see section 4.8). The circumstances listed below may result in an increased risk of ventricular arrhythmias, including torsades de pointes, which could be fatal. Therefore, azithromycin must be used with particular caution in patients with pre-existing proarrhythmic disorders (particularly in women and the elderly), such as B. in patients with congenital or established QT prolongation. Under treatment with other drugs that have a QT-prolonging effect, such as Class IA (quinidine and procainamide) and III (dofetilide, amiodarone and solatol), cisapride and terfenadine, antipsychotics like pimozide, antidepressants like citalopram and fluoroquinolones such as moxifloxacin and levofloxacin with electrolyte disorders, especially hypokalemia and hypomagnesemia with clinically relevant bradycardia, cardiac arrhythmias, or severe heart failure

Elderly patients:
Elderly patients may be more sensitive to drug-associated effects on the QT interval.

Myasthenie

Worsening of symptoms of myasthenia gravis and new onsets of myasthenic syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

Investigations

If syphilis is suspected at the same time as a venereal disease is being treated, suitable diagnostic measures (including dark field examinations) must be taken. Monthly serological tests should be carried out for at least 4 months.

Other ingredients

Azithromycin tablets 500 mg film-coated tablets contain lactose and should not be administered to patients with the rare, hereditary clinical picture of galactose intolerance, total Lapp lactase deficiency or glucose/galactose malabsorption.

This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet. This means it is almost "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Antacid: A study of the effect of a co-administered antacid on the pharmacokinetics of azithromycin revealed no change in overall bioavailability, although peak serum concentrations of azithromycin

were reduced by approximately 24%. Antacids and azithromycin should not be used at the same time
(2-3 hours apart).

Cetirizine: In healthy subjects, 5-day treatment with azithromycin in combination with cetirizine 20 mg at steady state resulted in no pharmacokinetic interactions or significant changes in the QT interval.

Didanosine (dideoxyinosine): Co-administration of azithromycin 1200 mg daily and didanosine 400 mg daily in 6 HIV-positive patients had no effect on the steady-state pharmacokinetics of didanosine compared to placebo.

Digoxin and colchicine (P-glycoprotein substrates): Elevated serum levels of P-glycoprotein substrates have been reported with concomitant treatment with macrolide antibiotics, includingazithromycin, and P-glycoprotein substrates such as digoxin and colchicine. When azithromycin and P- glycoprotein substrates such as digoxin are co-administered, the possibility of increased serum concentrations of the substrate should be considered. It is necessary to conduct clinical monitoring and possibly to measure serum digoxin levels during and after discontinuation of treatment with azithromycin.

Ergot derivatives: There is a theoretical possibility of an interaction between azithromycin and ergot derivatives (see section 4.4).

Zidovudine: The plasma pharmacokinetics and urinary excretion of zidovudine or its glucuronidated metabolite were little affected by azithromycin at single doses of 1000 mg and multiple doses of
1200 mg and 600 mg, respectively. However, administration of azithromycin increased the concentration of phosphorylated zidovudine (the clinically active metabolite) in peripheral blood mononuclear cells. The clinical significance of this fact is unclear, but it may be of benefit to the patient.

Interactions related to cytochrome P-450: Azithromycin has no significant effect on the hepatic cytochromeP-450 system. Therefore, pharmacokinetic interactions observed with erythromycin and other macrolides are not expected for azithromycin.

Azithromycin does not induce or inactivate the hepatic cytochrome P-450 system through the cytochrome metabolite complex.
Pharmacokinetic studies have been performed with Azithromycin tablets and the medicinal products listed below, which are known to be primarily metabolised by cytochrome P-450.

Atorvastatin: Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) had no effect on atorvastatin plasma concentrations (based on HMG-CoA reductase inhibition analysis). However, post-marketing cases of rhabdomyolysis have been reported in patients receiving azithromycin concomitantly with statins.

Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, the serum levels of carbamazepine and its active metabolite were not significantly affected when co-administered with azithromycin.

Cimetidine: In a pharmacokinetic study examining the effect of a single dose of cimetidine, administered two hours before azithromycin, on the pharmacokinetics of azithromycin, no changes in the pharmacokinetics of azithromycin could be detected.

Oral coumarin anticoagulants: In a pharmacokinetic interaction study in healthy volunteers, there was no evidence that azithromycin interfered with the anticoagulant effect of a single 15 mg dose of warfarin. However, there have been post-marketing reports of increased anticoagulation following concomitant use of azithromycin and oral coumarin anticoagulants. Although a causal relationship has not been established, prothrombin time monitoring should be increased in patients treated with coumarin anticoagulants when azithromycin is co-administered.

Cyclosporine: In a pharmacokinetic study in healthy subjects who received oral azithromycin 500 mg daily for 3 days followed by a single oral dose of 10 mg/kg cyclosporine, cyclosporine C_{max} and AUC_{0-5} were significantly increased. Therefore, caution should be exercised when co-administering these medicinal products. If concomitant use is indicated, cyclosporine levels should be monitored and the dose adjusted if necessary.

Efavirenz: Co-administration of a single dose of azithromycin 600 mg and efavirenz 400 mg daily for 7 days resulted in no clinically significant pharmacokinetic interactions.

Fluconazole: Concomitant use of a single 1200 mg dose of azithromycin did not affect the pharmacokinetics of a single 800 mg dose of fluconazole. The total exposure and half-life of azithromycin were unchanged, but a clinically irrelevant decrease in azithromycin C_{max} (18%) was observed.

Indinavir: Co-administration of a single 1200 mg dose of azithromycin had no statistically significant effect on the pharmacokinetics of indinavir 800 mg three times a day 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 subjects, treatment with azithromycin 500 mg daily for three days had no clinically significant effect on the pharmacokinetics and pharmacodynamics of a single concomitant dose of 15 mg midazolam.

Nelfinavir: Concentrations of azithromycin have increased following co-administration of azithromycin (1200 mg) and nelfinavir (750 mg three times daily to steady state). However, no clinically significant adverse effects were observed, so no dose adjustment is necessary.

Rifabutin: Concomitant use of azithromycin and rifabutin had no effect on the serum concentrations of either substance. Neutropenia has been observed with concomitant treatment with azithromycin and rifabutin. Neutropenia has been associated with the use of rifabutin, but a causal relationship with the combination treatment has not been established (see section 4.8).

Sildenafil: There was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max} of sildenafil and its major metabolite in healthy male subjects.

Terfenadine: Pharmacokinetic studies have not revealed any interactions between azithromycin and terfenadine. Rarely have cases been reported where the possibility of an interaction could not be totally ruled out, but there was no proof of this.

Theophylline: There was no evidence of clinically significant pharmacokinetic interactions in healthy subjects receiving concomitant azithromycin and theophylline.

Triazolam: In 14 healthy subjects, co-administration of azithromycin 500 mg on day 1 or 250 mg on day 2 and triazolam 0.125 mg on day 2 had no significant effect on the pharmacokinetics of triazolam compared to placebo and triazolam.

Trimethoprim/sulfamethoxazole (co-trimoxazole): Co-administration of azithromycin 1200 mg on day 7 of a 7-day treatment with trimethoprim/sulfamethoxazole (160 mg/800 mg) had no significant effect on the maximum concentration, total exposure and urinary excretion of trimethoprim and sulfamethoxazole. The serum concentrations of azithromycin were similar to those in other studies.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited data (results from less than 300 pregnancies) from the use of azithromycin in pregnant women. Animal reproduction studies have shown that azithromycin passes into the placenta, but no teratogenic effects have been observed. There are no adequate well-controlled clinical trials evaluating the effects of azithromycin on pregnancy when used in pregnant women. Since animal reproduction studies are not always conclusive for humans, azithromycin should only be used during pregnancy if the benefit outweighs the risk. As a precaution, the use of azithromycin should be avoided during the first trimester of pregnancy.

Lactation

Limited data from the published literature indicate that azithromycin is present in human milk, with the highest median estimated dose being 0.1 to 0.7 mg/kg/day. Serious adverse effects of azithromycin on the breastfed infants have not been observed.
A decision must be made whether to discontinue breast-feeding or to discontinue treatment with azithromycin, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

In fertility studies in rats, the pregnancy rate was reduced after administration of azithromycin. The relevance of this finding for humans is unknown.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. There is no evidence that azithromycin has a direct effect on a patient's ability to drive or use machines.
However, because of the possible side effects, Azithromycin tablets can impair alertness. Therefore, caution should be exercised when driving or operating machines.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. 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); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness

The following side effects from clinical trials and post-marketing experience may or probably be related to azithromycin:

System Organ Class	**Frequency**	**Adverse reaction**
Infections and infestations	Uncommon	Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis
	Not known	*Pseudomembranous colitis* (see section 4.4)
Blood and lymphatic system disorders	Uncommon	Leukopenia Neutropenia Eosinophilia
	Not known	Thrombocytopenia Haemolytic anaemia

Immune system disorders	Uncommon	Angioedema Hypersensitivity
	Not known	Severe (partly fatal) anaphylactic reaction e.g. anaphylactic shock (see section 4.4)
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Uncommon	Nervousness Insomnia
	Rare	Agitation Depersonalisation
	Not known	*Aggression Anxiety* Delirium Hallucination
Nervous system disorders	Common	Headache
	Uncommon	*Dizziness Somnolence Dysgeusia Paraesthesia*
	Not known	*Syncope, convulsion* Hypoaesthesia *Psychomotor hyperactivity Anosmia Ageusia Parosmia* *Myasthenia gravis* (see section 4.4).
Eye disorders	Uncommon	Visual impairment
	Not known	Blurred vision
Ear and labyrinth disorders	Uncommon	Ear disorder Vertigo
	Not known	Hearing impairment including deafness and/or tinnitus
Cardiac disorders	Uncommon	Palpitations

	Not known	Torsades de pointes (see section 4.4) Arrhythmia (see section 4.4) including ventricular tachycardia electrocardiogram QT prolonged (see section 4.4)
Vascular disorders	Uncommon	Hot flush
	Not known	*Hypotension*
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Vomiting Abdominal pain Nausea
	Uncommon	Constipation, Flatulence, Dyspepsia, Gastritis, Dysphagia, Abdominal distension, Dry mouth, Eructation, Mouth ulceration, Salivary hypersecretion
	Not known	Pancreatitis Tongue Discolouration
Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Hepatic function abnormal Jaundice cholestatic
	Not known	*Hepatic failure* (which has rarely resulted in death) (see section 4.4) *Hepatitis fulminant* *Hepatic necrosis*
Skin and subcutaneous tissue disorders	Uncommon	Rash, Pruritus, Urticaria, Dermatitis, Dry skin, Hyperhidrosis
	Rare	Photosensitivity reaction Acute generalised exanthematous pustulosis (AGEP) DRESS (drug reaction with eosinophilia and systemic symptoms)

	Not known	Steven-Johnson syndrome Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and connective tissue disorders	Uncommon	Osteoarthritis Myalgia Back pain Neck pain
	Not known	Arthralgia
Renal and urinary disorders	Uncommon	Dysuria Renal pain
	Not known	Renal failure acute Nephritis interstitial
Reproductive system and breast disorders	Uncommon	Metrorrhagia Testicular disorder
General disorders and administration site conditions	Uncommon	Oedema, Asthenia, Malaise, Fatigue, Face oedema, Chest pain, Pyrexia, Pain, Peripheral oedema
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, Hematocrit decreased, Bicarbonate increased, Abnormal sodium
Injury and Poisoning	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:

System Organ Class	Frequency	Adverse reaction
Metabolism and nutrition disorders	Common	Anorexia
Nervous system disorders	Common	Dizziness Headache Paraesthesia Dysgeusia
	Rare	Hypoaesthesia
Eye disorders	Common	Visual impairment
Ear and labyrinth disorders	Common	Deafness
	Rare	Hearing impaired Tinnitus
Cardiac disorders	Uncommon	Palpitations
Gastrointestinal disorders	Very common	Diarrhoea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools
Hepatobiliary disorders	Rare	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash Pruritis
	Rare	Steven-Johnson syndrome Photosensitivity reaction
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Common	Fatigue
	Rare	Asthenia Malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report to www.zim.in

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

Symptoms

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

Treatment

In the event of overdose the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties

Pharmacotherapeutic group: Antibacterials for systemic use; macrolides; azithromycin, 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.

Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non- inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

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.

Breakpoint
EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens	**Susceptible (mg/l)**	**Resistant**
Staphylococcus spp.[1]	≤ 1	> 2
Streptococcus spp. (Group A, B, C, G)[1]	≤ 0.25	> 0.5
Streptococcus pneumoniae[1]	≤ 0.25	> 0.5
Haemophilus influenzae	Note[2]	Note[2]
Moraxella catarrhalis[1]	≤ 0.25	> 0.5
Neisseria gonorrhoeae	Note[3]	Note[3]

1. Erythromycin can be used to determine susceptibility to azithromycin.
2. Clinical evidence for the efficacy of macrolides in H. influenzae respiratory infections is conflicting due to high spontaneous cure rates. Should there be a need to test any macrolide against this species, the epidemiological cut-offs (ECOFFs) should be used to detect strains with acquired resistance. The ECOFF for azithromycin is 4 mg/L.
3. Azithromycin is always used in conjunction with another effective agent. For testing purposes with the aim of detecting acquired resistance mechanisms, the ECOFF is 1 mg/L.

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

*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
Anaerobic Gram-negative microorganisms

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

5.2 Pharmacokinetic properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately

0.4 mg/l).

Distribution
Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg. In experimental *in vitro* and *in vivo* studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis.
In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue. In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Excretion
Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchangedform, is a major route of elimination.
The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.
After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

<u>Pharmacokinetics in special populations</u>

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 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

In high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Carcinogenic potential:

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

Mutagenic potential:

Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Reproductive toxicity:

No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri-/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

Tablet Core:
Colloidal anhydrous silica
Maize Starch
Lactose
Sodium starch Glycolate (Type A)
Povidone

Sodium Benzoate
Magnesium stearate
Purified talc

Tablet Coat:
Opadry White

6.2 Incompatibilities

Not Applicable

6.3 Shelf-life

36 months

6.4 **Special precautions for storage**

Store at temperature not exceeding 30°C. Protect from moisture.

6.5 Nature and content of container

1 × 3 Tablets Normal Blister Pack

6.6 Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zim Laboratories Limited.
Sadoday Gyan (Ground Floor),
Opp. NADT, Nelson Square,
Nagpur – 440013
India.

8. MARKETING AUTHORISATION NUMBERS

05674/07693/REN/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/02/2021

10. DATE OF REVISION OF THE TEXT

03/07/2023