1. NAME OF THE MEDICINAL PRODUCT

ZINICHE (AZITHROMYCIN TABLETS USP 500MG)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Azithromycin Dihydrate USP

Eq.to Azithromycin.....500mg

Colour: Quinoline Yellow Lake

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Azithromycin Tablet USP 500 mg available as Yellow color caplet shape film coated tablets having break line on one side of the tablet

<The scoreline is only to facilitate breaking for ease of swallowing and not to divide into equal doses.>

4. Clinical particulars

4.1 Therapeutic indications

AZITHROMYCIN TABLETS USP 500MG is indicated for the treatment of the following infections, when caused by microorganisms sensitive 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 USP 500MG 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 dosage of azithromycin is 1500 mg which is spread over three days (500 mg once daily). Alternatively, the dosage can be spread over five days (500 mg as a single dose on the first day and thereafter 250 mg once daily).

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

For sinusitis, treatment is indicated for adults and adolescents 16 years of age and over.

Children and adolescents 45 kg and under body weight

Tablets are not indicated for these patients. Other pharmaceutical forms of azithromycin, e.g. suspensions may be used.

Elderly

No dose adjustments are required for elderly patients. 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

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 30-80 ml/min/1.73 m^2).

Patients with hepatic impairment

A dose adjustment is not necessary for patients with mild to moderately impaired liver function (Child-Pugh class A or B).

Method of administration

For oral use.

The tablets can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance, to erythromycin or any macrolide or ketolide antibiotic.or to any of the excipients

4.4 Special warnings and precautions for use

Allergic reactions

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal) have been reported alongside dermatological reactions, including acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms). A certain number of these reactions resulted in recurring symptoms and required an extended period of observation and treatment.

If an allergic reaction occurs, use of this medicinal product must be discontinued and the appropriate treatment initiated. Doctors must be aware that allergic symptoms can recur if symptomatic treatment is discontinued.

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance > 40 ml/min). In patients with severe renal function impairment (GFR < 10 mL/min), a 33% increase in systemic exposure to azithromycin has been observed.

Hepatic impairment

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, or 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.

Liver function disorders, hepatitis, cholestatic jaundice, liver necrosis and renal failure have been reported and have been fatal in a number of cases. Discontinue the use of azithromycin if signs and symptoms of hepatitis occur.

Pseudomembranous colitis has been reported following use of macrolide antibiotics. This diagnosis should therefore be taken into consideration in patients who develop diarrhoea after starting treatment with azithromycin.

Infantile hypertrophic pyloric stenosis

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Ergot alkaloids and azithromycin

The concurrent use of ergot alkaloids and macrolide antibiotics has been found to accelerate the development of ergotism. The interactions between ergot alkaloids and azithromycin have not been studied. The development of ergotism is however possible, so that azithromycin and ergot alkaloid derivatives should not be administered simultaneously.

QT prolongation

Prolonged cardiac repolarisation and a prolonged 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.
- Patients currently receiving treatment with other active substances that 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.

- Patients with a disrupted electrolyte balance, particularly in cases of hypokalaemia and hypomagnesaemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Myasthenia gravis and azithromycin

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Superinfections

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

Clostridium difficile associated diarrhoea

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.

The following should be considered before prescribing azithromycin:

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

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*.

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.

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.

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. pallidum* should be excluded.

Neurological or psychiatric diseases

Azithromycin should be administered with caution to patients suffering from neurological or psychiatric diseases.

Long-term use

There is no experience regarding the safety and efficacy of long-term use of azithromycin for the mentioned indications. In case of rapid recurrent infections, treatment with another antibiotic should be considered.

Due to cross-resistance existing among macrolides, in areas with a high incidence of erythromycin resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other macrolides.

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

Paediatric population

Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex in children have not been established.

This medicinal product contains soya oil

Azithromycin contains soya oil. Patients who are allergic to peanut or soya, must not use this medicinal product.

Azithromycin contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'

4.5 Interaction with other medicinal products and other forms of interaction

Antacids

When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma reduced by approximately 25 %. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

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 and colchicine (P-gp substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, 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. During treatment with azithromycin and after discontinuation, clinical monitoring, and possible follow-up of serum digoxin levels, is required.

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 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 medicinal products 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.

Ciclosporin

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 ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these medicinal products. If coadministration of these medicinal products is necessary, ciclosporin 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 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

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 active. 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

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.

Protease inhibitors

There are no data available about a possible interaction with protease inhibitors

4.6 Pregnancy and Lactation

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.

Breast-feeding

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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

	Very common	Common	Uncommon	Rare	Very rare	Not Known
Infections and Infestations			Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis			Pseudomembranous colitis
Blood and Lymphatic System Disorders			Leukopenia, neutropenia, eosinophilia			Thrombocytopenia, haemolytic anaemia

Immune System Disorders			Angioedema, hypersensitivity			Hypotension
Metabolism and Nutrition Disorders			Anorexia			
Psychiatric Disorders			Nervousness, insomnia	Agitation Irritability		Aggression, anxiety, delirium, hallucination
Nervous System Disorders		Headache, dizziness, somnolence, dysgeusia, paraesthesia	Hypoaesthesia			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis (see section 4.4)
Eye Disorders		Visual impairment				
Ear and Labyrinth Disorders		Deafness	Ear disorder, vertigo, hearing impairment including hearing loss, tinnitus			
Cardiac Disorders			Palpitations			Torsades de pointes, arrhythmia including ventricular tachycardia, Electrocardiogram QT prolonged
Vascular Disorders			Hot flushes			Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis			
Gastrointestinal Disorders	Diarrhoea, abdominal pain, nausea, flatulence	Vomiting, dyspepsia	Constipation, gastritis, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration,			Pancreatitis, tongue discolouration, tooth discolouration

			salivary hypersecretion			
Hepatobiliary Disorders			Hepatitis, abnormal hepatic function	Cholestatic jaundice		Hepatic failure (which has rarely resulted in death), fulminant hepatitis, hepatic necrosis
Skin and Subcutaneous Tissue Disorders		Rash, pruritus	Urticaria, dermatitis, dry skin, hyperhidrosis, Stevens-Johnson syndrome, Photosensitivity reaction	Acute generalised exanthematous pustulosis (AGEP)	DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms)	Toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and Connective Tissue Disorders		Arthralgia	Osteoarthritis, myalgia, back pain, neck pain			
Renal and Urinary Disorders			Dysuria, renal pain			Acute renal failure, interstitial nephritis
Reproductive system and breast disorders			Metrorrhagia, testicular disorder			
General Disorders and Administration Site Conditions		Fatigue	Oedema, asthenia, malaise, face oedema, chest pain, pyrexia, pain, peripheral oedema			
Investigations		Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils increased	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			Post procedural complication			
*Post-marketing rare events of angioedema, anaphylaxis and anaphylactic shock have been reported.						

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:

	Very Common	**Common**	**Uncommon**
Metabolism and Nutrition Disorders		Anorexia	
Nervous System Disorders		Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia
Eye Disorders		Visual impairment	
Ear and Labyrinth Disorders		Deafness	Hearing impaired, tinnitus
Cardiac Disorders			Palpitations
Gastrointestinal Disorders	Diarrhoea, abdominal pain, nausea, flatulence, abdominal discomfort, loose stools		
Hepatobiliary Disorders			Hepatitis
Skin and Subcutaneous Tissue Disorders		Rash, pruritus	Stevens-Johnson syndrome, photosensitivity reaction
Musculoskeletal and Connective Tissue Disorders		Arthralgia	
General Disorders and Administration Site Conditions		Fatigue	Asthenia, malaise

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. Characteristic symptoms of overdose with macrolide antibiotics include the following: reversible hearing loss, severe nausea, vomiting and diarrhoea.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antibacterials 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. The chemical name of azithromycins is 9-deoxy-9a-aza-9a-methyl-9a-homo-erythromycin A. The molecular weight is 749.0.

Mechanism of action

Azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other by binding to the 50S ribosomal subunit. As a result, RNA-dependent protein synthesis in susceptible organisms is inhibited.

Cardiac electrophysiology :

QTc interval prolongation was studied in a randomised, placebo-controlled parallel trial in 116 healthy subjects, who received chloroquine (1000 mg), either alone or in combination with azithromycin (500 mg, 1000 mg and 1500 mg once daily). Concomitant administration of azithromycin increased the QTc interval in a dose and concentration-dependent manner. Compared to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with concomitant administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

Mechanism of resistance

The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most commonly by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species, and within a single species, the frequency of resistance varies by geographical location.

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N6)-dimethylation of adenine at nucleotide A2058 (*Escherichia coli* numbering system) of the 23S rRNA by methylases encoded by *erm* (*e*rythromycin *r*ibosome *m*ethylase) genes. Ribosomal modifications often determine cross resistance (MLSB phenotype) to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different *erm* genes are present in different bacterial species, in particular Streptococci and Staphylococci. Susceptibility to macrolides can also

be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA, or in the large subunit ribosomal proteins L4 and L22.

Efflux pumps occur in a number of species, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher MICs) and Staphylococci. In Streptococci and Enterococci, an efflux pump that recognises 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef* (A) genes.

A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, beta-haemolytic streptococci of group A, *Enterococcus* spp. and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA).

A decrease in macrolide susceptibility over time has been noted particularly in *Streptococcus pneumoniae* and *Staphylococcus aureus* and is also observed in Streptococcus viridans and in *Streptococcus agalactiae*.

Penicillin-sensitive *S. pneumoniae* are more likely to be susceptible to azithromycin than are penicillin-resistant strains of *S. pneumoniae*. Methicillin-resistant *S. aureus* (MRSA) is less likely to be susceptible to azithromycin than methicillin-sensitive *S. aureus* (MSSA).

Susceptibility test breakpoints:

The EUCAST susceptibility criteria are listed in the table below.

EUCAST Susceptibility Breakpoints for Azithromycin.

EUCAST

	MIC (mg/L)	
Pathogens	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (Group A, B, C, G)	≤ 0.25	> 0.5
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 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 1: Antibacterial spectrum of azithromycin

	Species
	Commonly susceptible species
	Aerobic Gram-positive
	Corynebacterium diphteriae
	Streptococcus pneumoniae
	Erythromycin-sensitive
	Penicillin-sensitive
	Streptococcus pyogenes
	Erythromycin-sensitive
	Aerobic Gram-negative
	Bordetella pertussis
	Escherichia coli-ETEC
	Escherichia coli-EAEC
	Haemophilus influenzae *Haemophilus ducreyi*
	Legionella spp.
	Moraxella catarrhalis
	Erythromycin-sensitive
	Erythromycin-intermediate
	Pasteurella multocida
	Anaerobic
	Fusobacterium nucleatum *Fusobacterium necrophorum*
	Prevotella spp.
	Porphyromonas spp.
	Propionibacterium spp
	Other micro-organisms
	Chlamydia pneumoniae
	Chlamydia trachomatis
	Listeria spp.
	Mycobacterium avium Complex
	Mycoplasma pneumoniae
	Species for which acquired resistance may be a problem
	Aerobic Gram-positive
	Staphylococcus aureus
	Methicillin-susceptible
	Coagulase-neg. staphylococci
	Methicillin-susceptible^{+}
	Streptococcus pneumoniae
	Penicillin-intermediate
	Penicillin-resistant
	Erythromycin-intermediate
	Streptococcus pyogenes
	Erythromycin-intermediate
	Streptococci viridans group
	Penicillin-intermediate
	erobic Gram-negative
	Moraxella catarrhalis Erythromycin-resistant
	Anaerobic
	Peptostreptococcus spp.
	Inherently resistant organisms
	Aerobic Gram positive
	Corynebacterium spp.

	Enterococcus spp.
	Staphylococci MRSA, MRSE
	Streptococcus pneumoniae
	Erythromycin-resistant
	Penicillin & Erythromycin resistant
	Streptococcus pyogenes
	Erythromycin-resistant
	Streptococci viridans group
	Penicillin-resistant
	Erythromycin-resistant
	Aerobic Gram-negative
	Pseudomonas aeruginosa
	Anaerobic
	Bacteroides fragilis group

[8] Resistance is greater than 50%.

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

5.2 Pharmacokinetic properties

Absorption

Following oral administration the bio-availability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours. The mean maximum concentration observed (C_{max}) 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 shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma). This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). The mean maximum observed serum concentration (C_{max}) after a single dose of 500 mg is approx. 0.4 mg/mL, 2-3 hours after administration. With the recommended dosage no accumulation in the serum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than in the serum/plasma. Three days after administration of 500 mg as a single dose or in split doses, concentrations of 1.3 to 4.8 mg/g, 0.6 to 2.3 mg/g, 2.0 to 2.8 mg/g and 0 to 0.3 mg/mL were detected in lung, prostate, tonsil and serum respectively. Concentrations in these target tissues exceed the MIC90 for likely pathogens.

In experimental *in vitro* and *in vivo* studies, azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appears to contribute to the accumulation of azithromycin in tissue.

The binding of azithromycin to plasma proteins is variable and varies from 52% at 0.005 µg/ml to 18% at 0.5 µg/ml, depending on the serum concentration.

Biotransformation and Excretion

The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 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 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile, together with 10 metabolites (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggests that the metabolites do not play a role in the micro-biological activity of azithromycin.

Pharmacokinetics in special populations

Renal impairment

Following a single oral dose of azithromycin 1g, 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 30-80 ml/min/1.73m^2) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment (GFR < 30 ml/min/1.73m^2), the mean C_{max} and AUC_{0-120} increased 61% and 35% respectively compared to normal.

Hepatic impairment

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. There are no data on azithromycin use in cases of more severe hepatic impairment.

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.

Paediatric population

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 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 $t_{1/2}$ of 36h in the older children was within the expected range for adults

5.3 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 embryotoxicity 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

Maize Starch
Calcium Hydrogen Phosphate Dihydrate
Microcrystalline Cellulose (Plain)
Ethyl Cellulose
Colloidal Anhydrous Silica
Croscarmellose Sodium (Vivasol)
Magnesium Stearate
Purified Talc (Talcum)
Hypromellose (H.P.M.C.E 15)
Quinoline Yellow Lake
Talcum (Purified Talc)
Titanium Dioxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months from the date of manufacture

6.4 Special precautions for storage

Store below 30ºC. protect from light

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

10 Tablets packed in 1 Alu-Pvc blister. Such 10 Alu-Pvc blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

6.6 Special precautions for disposal <and other handling>

No special requirements

7. APPLICANT/MANUFACTURER

Globela Pharma Pvt. Ltd.

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