SUMMARY OF PRODUCT CHARACTERISTICS

1.NAME OF MEDICINAL PRODUCTS

ZIROMIN 500 mg Film-Coated Tablets

2. QUALITIVE AND QUANTITATIVE COMPOSITION

Active Substance: Azithromycin dihydrate equivalent to 500 mg azithromycin

Excipients:

Sodium lauryl sulphate	5.0 mg
Croscarmellose sodium	9.0 mg
Lactose, anhydrous	96.0 mg

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Film-Coated Tablets

White coloured, one side scored, on side flat, oblong film-coated tablet. The tablet can be divided into equal doses.

4.CLINICAL PARTICULARS

4.1. Therapeutic indications

ZIROMIN is indicated in the treatment of infections due to susceptible microorganisms; lower respiratory tract infections including bronchitis, mild community-acquired pneumonia caused by *S. pneumoniae* or *H. influenza;* skin and soft tissue infections; upper respiratory tract infections including acute otitis media and sinusitis.

In presence of penicillin allergy, it is used in the treatment of pharyngitis/tonsillitis caused by *Streptococcus pyogenes*

ZIROMIN is indicated in uncomplicated genital inflammatory diseases including sexually transmitted diseases in men and women and caused by *Chlamydia trachomatis.*

Moreover, it is also indicated in soft tissue ulcer due to *Haemophilus ducreyi* and genital inflammatory diseases without complication due to nonmultiresistant *Neisseria gonorrhoeae;* however, concurrent infection with *Treponemapallidum* should be excluded.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

ZIROMIN should be given as a single daily dose.

Duration of dose administration according to infection is given below.

Adults:

For the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis*, *Haemophilus ducreyi* or susceptible *Neisseria gonorrhoeae*, the dosage is 1000 mg as a single oral dose.

In the treatment of *S. pyogenes* tonsillitis/pharyngitis, the total dose (1500 mg) is administered in a period of 5 days with 500 mg on the first day and 250 mg on following days (2^{nd}, 3^{rd}, 4^{th} and 5^{th} day).

For all other indications, the total dose is 1500 mg, administered as 500 mg once daily for 3 days.

Method of administration:

It is taken orally.

Azithromycin can be taken 1 hour before or 2 hours after meals.

Additional information about special populations:

Renal impairment:

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR< 10 ml/min) (see section 4.4 Special warnings and precautions for use).

Hepatic impairment:

In patients with mild and moderate hepatic impairment, the same dose as in patients with normal hepatic functions can be administered. Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be used in patients suffering from severe hepatic

impairment. No studies about azithromycin treatment have been conducted in such patients (see Section 4.4 Special warnings and precautions for use).

Paediatric population:

Adult dose is administered in children weighing more than 45 kg. In children for any treatment except tonsillitis/pharyngitis, the maximum recommended total dose is 1500 mg for 3 days (daily single dose is 500 mg). In the treatment of *S. pyogenes* tonsillitis/pharyngitis, the total dose (1500 mg) is administered in a period of 5 days with 500 mg on the first day and 250 mg on following days (2^{nd}, 3^{rd}, 4^{th} and 5^{th} day).

Oral suspension forms are available for children under 45 kg.

Since efficacy and safety of azithromycin has not indicated in infants under 6 months yet, administration is not recommended.

Geriatric population:

For elderly patients, the same dose as in adults is 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. (see section 4.4).

4.3 Contraindications

ZIROMIN is contraindicated in patients with known hypersensitivity to azithromycin, or any of macrolide or ketolide or erythromycin antibiotics, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

H*ypersensitivity*

As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalized 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 <product name> have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the medicinal product 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.

Hepatic impairment:

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 (see section 4.8). 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.

Infantile hypertrophic pyloric stenosis (IHPS)

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

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 (see section 4.5).

Superinfections:

As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with nonsusceptible microorganisms 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 case of CDAD anti-peristaltics are contraindicated.

Renal impairment

In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Cardiovascular events

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 (see section 4.8). 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.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

Paediatric population

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

The following should be considered before prescribing azithromycin:

Azithromycin 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* (> 30 %) have been reported for azithromycin in some European countries (see section 5.1). This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

Pharyngitis/ tonsillitis

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

Sinusitis

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

Acute otitis media

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

Skin and soft tissue infections

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

Infected burn wounds:

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

Sexually transmitted disease:

In case of sexually transmitted diseases a concomitant infection by *T. 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 total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content

This product contains sodium. This situation should be taken into consideration for the patients on controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids:

In a pharmacokinetic study to the effect of co-administration of antacids and azithromycin, no effect on the total bioavailability was seen, although the peak serum levels were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken concomitantly.

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 patients did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin:

Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in digestive system in some patients. In patients receiving azithromycin and digoxin concomitantly, the possibility of elevated digoxin levels 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.

Ergot

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

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

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the coadministration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with 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, postmarketing 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.

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 postmarketing 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 thefrequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarintypeoral 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 C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz:

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

Fluconazole:

Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and halflife 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 medicinal product. 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 (see section 4.8).

Sildenafil:

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3days) 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. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

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.

Additional information about special populations:

No available data.

Pediatric population:

No available data.

4.6 Pregnancy and lactation

General recommendation:

Pregnancy category: B

Women with childbearing potential/Birth control (Contraception):

The studies performed with mild-moderate maternal toxic doses on animals, are insufficient in terms of directly or indirectly hazardous effects related with pregnancy/embryonal/fetal development/labour or post-natal development. Therefore, appropriate contraceptive method should be used in women who are planning to get pregnant or has doubts about pregnancy.

Pregnancy period

There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed (see section 5.3). The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Lactation period

Azithromycin has been reported to be secreted into human breast milk, The limited information available from published literature indicates azithromycin is present in human milk at an estimated maximum mean daily dose of 0.1 to 0.7 mg / kg / day. No serious side effects have been observed by azithromycin in breast-fed infants.

A decision should be taken whether breastfeeding is discontinued or that treatment with azithromycin is discontinued/initiated or not, taking into account the benefit of breastfeeding for the child and the benefit of treatment for the woman.

Reproduction ability/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.

4.7. 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.

4.8 Undesirable Effects

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, oral candidiasis, vaginal infection

Not known: Pseudomembranous colitis

Blood and lymphatic system disorders

Uncommon: Leukopenia, neutropenia

Not known: Thrombocytopenia, haemolytic anaemia

Immune system disorders

Uncommon: Angioedema, hypersensitivity

Not known: Anaphylactic reactions

Metabolism and nutrition disorders

Common: Anorexia

Psychiatric disorders

Uncommon: Nervousness

Rare: Agitation

Not known: Aggressive responses and anxiety

Nervous system disorders

Common: Dizziness, headache, paraesthesia, dysgeusia

Uncommon: Hypoaesthesia, somnolence, insomnia

Unknown: Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis

Eye disorders

Common: Visual impairment

Ear and labyrinth disorders

Common: Deafness

Uncommon: Hearing impaired, tinnitus

Rare: Vertigo

Cardiac disorders

Uncommon: Palpitations

Not known: *Torsades de pointes,* arrhythmia such as ventricular tachycardia

Vascular disorders

Not known: Hypotension

Gastrointestinal disorders

Very common: Diarrhoea, abdominal pain, nausea, flatulence

Common: Vomiting, dyspepsia

Uncommon: Gastritis, constipation

Not known: Tongue discoloration, pancreatitis

Hepatobiliary disorders

Uncommon: Hepatitis

Rare: Abnormality on hepatic function

Not known: Hepatic failure**, hepatitis fulminant, hepatic necrosis, jaundice cholestatic

Skin and subcutaneous tissue disorders

Common: Pruritus and rash

Uncommon: Stevens-Johnson syndrome, photosensitivity reactions, urticaria

Not known: Toxic epidermal necrolysis, erythema multiforme

Musculoskeletal and connective tissue disorders

Common: Arthralgia

Renal and urinary disorders

Not known: Nephritis interstitial and acute renal failure

General disorders and administration site conditions

Common: Fatigue

Uncommon: Oedema, chest pain, malaise/weakness, asthenia

Investigations

Common: Decrease in lymphocyte count, increase in eosinophil count, increase in blood bicarbonate

Uncommon: Increase in aspartate aminotransferase, increase in alanine aminotransferase, increase in blood bilirubin, increase in blood urea, increase in blood creatinine, abnormal blood potassium

Not known: QT prolongation in the electrocardiogram

** Rarely result in death.

4.9 Overdose and its treatment

The undesirable effects at doses in excess of those recommended were similar to those after normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhea. In cases of overdose, administration of medicinal charcoal and general symptomatic treatment as well as measures to support vital functions are indicated where necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use

ATC code: J01FA10.

Mechanism of action:

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 azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the ribosomal 50S sub-unit and inhibition the translocation of peptides.

Cardiac Electrophysiology:

QT interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with oral azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QT interval in a dose- and concentration- dependent manner. In comparison 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 the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

PK/PD relationship:

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

Mechanism of resistance:

The two most frequently occurring mechanisms of resistance to macrolides, such as azithromycin, its target modification (most often due to methylation of 23S rRNA) and active efflux. The occurrence of these mechanisms of resistance varies by species and within a species varies the frequency of the resistance of each 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 (erythromycin ribosome methylase) 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.

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.

Azithromycin demonstrates cross resistance with erythromycin-resistant gram-positive isolates. As discussed above, some ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the

lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin).

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.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

	MIC breakpoint (mg/L)	
Pathogens	Susceptible (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	Note[1]	Note[1]
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Note[1]: 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

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 *Bacteroides fragilis-group*

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

Paediatric population

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:

After oral administration bioavailability of azithromycin is approximately 37%. When ZIROMIN is given after a nutritious meal, bioavailability reduces at least by 50%. Peak plasma levels are reached after 2-3 hours.

Distribution:

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.

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

Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

In 1st day and 2nd day following oral administration of azithromycin at daily doses of 600 mg, the average maximum plasma concentration (Cmax) is 0.33 µg/mL and 0.55 µg/mL, respectively.

Biotransformation:

No available data.

Elimination:

The terminal plasma elimination half-life closely reflects the elimination half-life from tissues (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. Unchanged drug at high concentrations has been found in human bile.

Ten metabolites have been identified in human bile. Microbiological Assays and HPLC comparisons in tissues suggest that the metabolites do not play a role in the microbiological activity of azithromycin.

Linearity/Non-linear case:

No available data.

Characteristic properties in the patients

Elderly:

In elderly volunteers (> 65 years) higher AUC values have been measured after a 5 day treatment than in younger volunteers (< 40 years). These differences are not regarded as clinically relevant; dose adjustment is therefore not recommended.

Renal Impairment:

Following a single dose (1 g) of immediate-release azithromycin administration, pharmacokinetic properties of azithromycin did not change in subjects with mild to moderate renal impairment (GFR (Glomerular Filtration Rate) 10-80 ml/min). Statistically significant differences in AUC 0-120 (8.8 μg·hr/ml vs. 11.7 μg·hr/ml), Cmax (1.0 μg/ml vs. 1.6 μg/ml) and renal clearance (CLr) (2.3 ml/min/kg vs. 0.2 ml/min/kg) were observed between the group with severe renal impairment (GFR < 10 ml/min) and the group with normal renal function.

Hepatic insufficiency:

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

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 it has mild QT prolongation potential.

Carcinogenic potential:

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

Mutagenic potential:

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

Reproductive toxicity:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core

Pregelatinized starch
Hydroxypropyl cellulose
Calcium hydrogen phosphate dihydrate
Sodium lauryl sulphate
Croscarmellose sodium
Anhydrous lactose
Colloidal anhydrous silica
Magnesium stearate

Film Coating

Opadry white Y-1-7000 (Hypromellose 2910 5cp, polyethylene glycol 400 and Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of packaging

It is packaged in Alu-PVC/PVdC blister containing 3 film coated tablets.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be destroyed according to "Medical Material Control Regulation'' and "Packaging and Packaging Waste Control Regulation''.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorisation:
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10. DATE OF REVISION OF THE TEXT