SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ziromin 200 mg/5 mL Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

In Each 5 ml:

Azithromycin dihydrate	209.6 mg (equivalent to 200.00 mg azithromycin)

Excipients:

Saccharose	3.63 g/5 ml
Sodium phosphate tribasic	0.09 g/5ml
Sodium benzoate	0.01 g/5 ml

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for Oral Suspension.

Granules that are white colored, cherry scented, liquid, homogeneous, free from particles in pellet form, and form a white or off-white suspension when reconstituted with water.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

It is used for the treatment of pharyngitis/tonsillitis caused by *Streptococcus pyogenes* in presence of penicillin allergy.

ZIROMIN is indicated in men and women for the treatment of sexually transmitted uncomplicated genital infections due to *Chlamydia trachomatis*. Moreover, it is indicated for the treatment of soft tissue ulcer due to *Haemophilus ducreyi* and genital infections without complication due to non-multi-resistant *Neisseria gonorrhoeae*, however, absence of *Treponema pallidum* infection should be confirmed for these cases.

4.2 Posology and method of administration

Posology and frequency/time of administration:

ZIROMIN should be given as a single daily dose.

Adults

For treatment of sexually transmitted diseases due to *Chlamydia trachomatis*, *Haemophilus ducreyi* or susceptible *Neisseria gonorrhoeae*, the dose is 1000 mg taken as one single oral dose.

For treatment of pharyngitis/tonsillitis due to *S. pyogenes*, total dose is given over a period of 5 days with 500 mg on the first day and then 250 mg on next days (2^{nd}, 3^{rd}, 4^{th} and 5^{th} day).

For all other indications the total dose is 1500 mg, to be taken as 500 mg per day for 3 days.

Administration method:

For oral use.

Dose administration period according to infection is given below. ZIROMIN Suspension can be taken with foods.

Preparation

Shake the bottle containing powder.

Then, take boiled and cooled water into the 5 ml syringe and add to bottle content 3 times and shake well. Powder in the bottle should be reconstituted with totally 15 ml boiled and cooled water. After reconstitution, 5 ml measuring cup contains 200 mg azithromycin. Shake the bottle before every time you use.

Take suspension with 5 ml dose graduated syringe calibrated accordingly 0.10 ml intervals.

Additional information for special population:

Renal failure:

No dose adjustment is necessary in patients with mild and moderate level renal impairment (GFR 10-80 mL/min.). Caution should be exercised when azithromycin is administered to patients with severe renal failure (GFR <10 mL/min.). (see section 4.4 - Special warnings and precautions for use).

Liver failure:

The same dose might be administered to the patients with mild and moderate hepatic failure as the patients with normal liver function. Since azithromycin is metabolized in the liver and excreted in the bile, the drug should not be used in patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin (see Section 4.4 Special warnings and precautions for use).

Pediatric population

The adult dosage is administered in children over 45 kg. For any treatment except treatment of pharyngitis/tonsillitis, maximum recommended total dose is 1500 mg administrated for three days (500 mg once daily).

Except treatment of Streptococcal pharyngitis, dose for children is 30 mg/kg in total, as a single dose of 10 mg/kg/day for 3 days or alternatively a single dose of 10 mg/kg for the first day and a single dose of 5 mg/kg for days 2 to 5 for 5 days.

As an alternative to the doses indicated above, a single dose of 30 mg/kg may be administered for treatment of acute otitis media.

Weight (kg)	3-day therapy Administered once a day		5-day therapy Administered once a day		Total Dosage
	Day 1	Day 2 and 3	Day 1	Day 2 to 5	
<15 kg	2.5 ml (100 mg)	2.5 ml (100 mg)	2.5 ml (100 mg)	1.25 ml (50 mg)	30 mg/kg
15-25 kg	5 ml (200 mg)	5 ml (200 mg)	5 ml (200 mg)	2.5 ml (100 mg)	600 mg
26 -35 kg	7.5 ml (300 mg)	7.5 ml (300 mg)	7.5 ml (300 mg)	3.75 ml (150 mg)	900 mg
36-45 kg	10 ml (400 mg)	10 ml (400 mg)	10 ml (400 mg)	5 ml (200 mg)	1200 mg
> 45 kg	Adult dosage				

Since efficacy and safety of azithromycin has not been shown in babies younger than 6 months, it is not recommended to use.

For pediatric streptococcal pharyngitis, it has been shown that administration of azithromycin as single daily dose of 10 mg/kg or 20 mg/kg for 3 days is effective, however daily dose of 500 mg should not be exceeded. In the studies in which these two dose interval has been compared, clinical efficacy is similar, however, higher bacteriological eradication has been observed at dose of 20 mg/kg/day. Penicillin is generally the preferred drug in treatment of pharyngitis caused by *Streptococcus pyogenes* including acute rheumatic fever prophylaxis.

Geriatric population:

The same dose with adults is used in the elderly.

4.3 Contraindications

This medicine is contra-indicated in patients with a known hypersensitivity to azithromycin or any macrolide or ketolide antibiotics, erythromycin, or to any of the excipients listed in Section 6.1 List of excipients.

Due to possible ergotism risk, azithromycin and ergot derivatives should not be used concomitantly.

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis, Stevens Johnson syndrome and toxic epidermal necrosis, have been reported. Death has been reported although it is rare. At the beginning, although it is successful in the treatment of allergic symptoms, when symptomatic treatment is discontinued, allergic reactions might be repeated even there is no exposure to azithromycin. When these reactions occur, a suitable treatment and then a long term observation period should be started. The relation of the long tissue half-life and following antigen exposure of azithromycin with these episodes have not been determined.

If any allergic reaction occurs, suitable treatment should be started. Doctor should be aware of the possibility of reoccurrence of allergic symptoms after treatment is discontinued.

As with other antibiotics, observation of patients for signs of superinfection with non-susceptible organisms, including fungal infection is recommended.

***Clostridium difficile* associated diarrhea (CDAD):**

Clostridium difficile associated diarrhea (CDAD) has been reported with the use of many antibacterial agents, including azithromycin, and may range in severity from mild diarrhea 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. Strains of *C. difficile* which produce excessive toxin cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. Caution should be taken for all diarrhea patients using CDAD antibiotic. Attention should be paid to medical history since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or diagnosed, antibiotic treatment, which has been continuing for a reason other than *C. Difficile treatment*, should be discontinued. Proper liquid and electrolyte administration, protein supplement, proper antibiotic treatment for *C. Difficile* and surgery evaluation should be started in clinically appropriate way.

Exacerbation of the Myasthenia gravis:

Exacerbation of the Myasthenia gravis and a new Myasthenia gravis syndrome have been reported in patients using Azithromycin. (see section 4.8).

Prolongation in QT Interval

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in patient treated with macrolide group including azithromycin. Torsades de pointes cases have been reported spontaneously in post marketing experiences in patients receiving azithromycin.

The benefit-risk ratio have been carried out due to QT prolongation risk which may lead to death when azithromycin is prescribed for patients listed below:

- **Patients with uncompensated heart failure or bradyarrhythmia, prolonged congenital QT syndrome; patients with torsades de pointes story, known prolonged QT interval**
- **Patient who use the drugs which are known to prolong the QT interval,**
- **Patients with proarrhythmic status such as uncorrected hypokalemia or hypomagnesemia, clinically evident bradycardia and the use cases of class IA (quinidine, prokainamide) or class III antiarrhythmic agents (dofetilide, aminodarone, sotalol)**
- **Elderly patients**

can be more sensitive to QT interval prolongation related to the drug.

Gastrointestinal disorder:

As a result of azithromycin administrated to limited number of subjects with GFR < 10 ml/min, gastrointestinal side effects at higher ratio has been observed (in 8 subjects out of 19).

Drug Resistant Bacteria Development

Prescribing ZIROMIN except proved and highly suspected bacterial infections increases drug risk of resistant bacteria development.

Saccharose content:

This medicine contains saccharose. Patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency problems should not use this medicine.

Sodium content:

This medicine contains sodium. It should be considered in patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids:

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid and azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken concomitantly.

Didanosine (Dideoxynosine):

When 1200 mg/day azithromycin is administrated with 400 mg/day didanosine concomitantly to 6 HIV-positive patients, no difference in the steady state pharmacokinetic properties of didanosine is detected as compared with placebo.

Digoxin:

Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the digestive system in some patients. In patients receiving digoxin with azithromycin, the possibility of raised digoxin levels should be kept in mind.

Cetirizine:

In healthy volunteers, when 20 mg cetirizine is administered concomitantly with 5 days azithromycin treatment, any pharmacokinetic interaction in steady state has not been observed and any significant change in QT interval did not occur.

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 beneficial for 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 during azithromycin use.

Ergot:

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

Pharmacokinetic studies of azithromycin have been conducted with following drugs known to undergo significant cytochrome P450 mediated metabolism.

Atorvastatin:

Co-administration of atorvastatin (10 mg/day) and azithromycin (500 mg/day) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition test).

Efavirenz:

As a result of co-administration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days, any clinically significant pharmacokinetic interaction did not occur.

Fluconazole:

As a result of co-administration of a single dose of 1200 mg azithromycin with 800 mg, azithromycin do not alter the pharmacokinetics fluconazole. Although co-administration with fluconazole does not lead a change in total exposure and half-life of azithromycin, a clinically insignificant decrease in C_{max} (18%) of azithromycin was recorded.

Indinavir:

Co-administration of 1200 mg of single dose azithromycin with 800 mg indinavir 3 times a day for 5 days did not cause any statistically significant effect on pharmacokinetic properties of indinavir.

Carbamazepine:

In a pharmacokinetic interaction study that azithromycin and carbamazepine are given concurrently, carried out with healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolites.

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. In the post-marketing period, after co-administration azithromycin with coumarin-type oral anticoagulants, there are reports that anticoagulant activity is potentiated. 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.

Methylprednisolone:

In a pharmacokinetic interaction study performed in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam*:*

In healthy volunteers, co-administration of azithromycin 500 mg/day for 3 days and a single dose of 15 mg midazolam did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of midazolam.

Nelfinavir:

According to a study carried out with healthy volunteers using 1200 mg azithromycin and nelfinavir at steady state (750 mg three times daily) concomitantly, it is resulted in 100% increase in absorption and bioavailability of azithromycin. No evident effect on absorption rate and clearance rate was observed. No clinically significant adverse effects were observed and no dose adjustment was required. Result of this interaction is unknown, caution should be exercised when azithromycin is prescribed to patients receiving nelfinavir.

Rifabutin:

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

Neutropenia was observed in patients receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a certain relationship regarding azithromycin combination has not been established.(see Section 4.8. Undesirable effects).

Cyclosporine:

In a pharmacokinetic study carried out with healthy volunteers, a dose of 500 mg azithromycin for 3 days and then a single 10 mg/kg dose of cyclosporine were given and this resulted in a significant increase (by 24% and 21% respectively) in C_{max} and AUC_{0-5} of cyclosporine, with this, however no significant changes were seen in $AUC_{0-\infty}$. Therefore, caution should be exercised in the concurrent use of relevant drugs. If co-administration of these drugs is mandatory, cyclosporine levels should be monitored and the dose adjusted as required.

Sildenafil:

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days), sildenafil or its major circulating metabolite on the AUC and Cmax values.

Cimetidine:

In a 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 observed.

Theophylline:

A clinically significant pharmacokinetic interaction has not been found when azithromycin and theophylline were co-administered to healthy volunteers. Theophylline levels may be elevated in patients taking ZIROMIN.

Triazolam*:*

In 14 healthy volunteers, co-administration 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 placebo.

Trimethoprim/sulfamethoxazole:

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

Additional information for special populations:

There is no sufficient information.

Pediatric population:

There is no sufficient information.

4.6 Pregnancy and lactation

General recommendation:

Pregnancy Category: B

Women have childbearing potential /Birth Control (Contraception)

Studies carried out with animals with mild to moderate maternal toxic doses are insufficient in terms of direct or indirect harmful effects related to pregnancy / embryonal / fetal growth/ birth or postnatal growth. For this reason, suitable birth control methods should be performed in women, who are planning to get pregnant or with pregnancy doubt.

Pregnancy period

There are no adequate data regarding use of Azithromycin in pregnant women. Studies have been carried out with animals with mild to moderate maternal toxic doses. In these studies, no evidence about the harm of azithromycin to fetus has been found. Potential risk for human is unknown. It should be used in pregnant women if it is certainly necessary.

Lactation period

It is not known whether azithromycin is excreted into human breast milk or not.

Benefit of lactation for children and of ZIROMIN treatment for lactating mother should be taken into consideration while deciding whether breast-feeding or ZIROMIN will be stopped or treatment will be avoided.

Reproduction ability/Fertility

There is no sufficient information.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

ZIROMIN is well tolerated with a low incidence of side effects.

The section below lists the adverse reactions in accordance with the following categories:

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

Unknown: *Pseudomembranous colitis*

Blood and Lymphatic System Disorders

Uncommon: Leukopenia, neutropenia

Unknown: *Thrombocytopenia, haemolytic anaemia*

Immune System Disorders

Uncommon: Angioedema, hypersensitivity

Unknown: Anaphylactic reaction

Metabolism and Nutrition Disorders

Common: Anorexia

Psychiatric Disorders

Uncommon: Nervousness

Rare: Agitation

Unknown*:* Aggressive reactions and anxiety

Nervous System Disorders

Common: Dizziness, headache, paraesthesia, dysgeusia

Uncommon: Hypoesthesia, somnolence, insomnia

Unknown*:* Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis

Eye Disorders

Common: Visual disorder

Ear and Labyrinth Disorders

Common: Deafness

Uncommon: Hearing impairment, tinnitus

Rare: Vertigo

Cardiac Disorders

Uncommon: Palpitations

Unknown: Torsades de pointes, arrhythmia such as ventricular tachycardia

Vascular Disorders

Unknown: *Hypotension*

Gastrointestinal Disorders

Very common: Diarrhea, abdominal pain, nausea, gas

Common: Vomiting, dyspepsia

Uncommon: Gastritis, constipation

Unknown: Pancreatitis, color change on tongue

Hepatobiliary Disorders

Uncommon: Hepatitis

Rare: Hepatic function abnormalities

Unknown: Hepatic failure**, hepatitis fulminant hepatitis, hepatic necrosis, cholestatic jaundice

Skin and Subcutaneous Tissue Disorders

Common: Pruritus and rash

Uncommon: Stevens-Johnson syndrome, photosensitivity reaction, urticaria

Unknown: Toxic epidermal necrolysis, erythema multiform

Musculoskeletal, Connective Tissue and Bone Disorders

Common: Arthralgia

Renal and Urinary Disorders

Unknown: Interstitial nephritis and acute renal failure

General disorders and Administration Site Conditions

Common: Tiredness

Uncommon: Oedema, chest pain, malaise, 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

Unknown: QT prolongation in electrocardiogram

** results in death rarely.

4.9 Overdose and treatment

Adverse effects experienced at higher doses than recommended ones were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhea. In the case of overdose, the administration of medicinal charcoal and general symptomatic and supportive treatment are indicated as required.

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 azalid 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 means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

Cardiac Electrophysiology:

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial performed with 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-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) 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.

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 entrance and modification of the antibiotic structure.

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

Susceptibility Breakpoints

Azithromycin susceptibility breakpoints for typical bacterial pathogens are:

National Committee for Clinical Laboratories Standards (NCCLS):

• Susceptible ≤ 2mg/l; resistant ≥ 8mg/l

• *Haemophilus* spp: susceptible ≤ 4mg/l

• *Streptococcus pneumoniae* and *Streptococcus pyogenes:*

Susceptible ≤ 0.5 mg/l; resistant ≥ 2 mg/l

Susceptibility

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

Table: Antibacterial spectrum of Azithromycin

Commonly susceptible species
Aerobic Gram-positive microorganisms
Staphylococcus aureus Methicillin-susceptible
Streptococcus pneumoniae Penicillin-susceptible
Streptococcus pyogenes (Group A)
Aerobic Gram-negative microorganisms
Haemophilus influenzae *Haemophilus parainfluenzae*
Legionella pneumophila
Moraxella catarrhalis
Pasteurella multocida
Anaerobic microorganisms
Clostridium perfringens

Fusobacterium spp.
Prevotella spp.
Porphyromonas spp.
Other microorganisms
Chlamydia trachomatis
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae Penicillin-intermediate- susceptible Penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis
Staphylococci **MRSA, MRSE***
Anaerobic microorganisms
Bacteroides fragilis group

* Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of azithromycin after oral administration is approximately 37%. The bioavailability of ZIROMIN after a nutritive meal will be decreased by at least 50%: The time required for achieving peak plasma level is 2 to 3 hours.

Distribution

Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities. Concentrations in the targeted tissues, such as lungs, tonsil and prostate are higher than the MRC_{90} 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% for 0.5 microgram/ml up to 52% for 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) was calculated as 31.1 l/kg.

Following oral Azithromycin intake at 600mg daily dose, the mean highest plasma concentrations (Cmax) are respectively 0.33 μg/ml and 0.55 μg/ml on day 1 and day 2.

Biotransformation:

There is no sufficient information.

Elimination

The terminal plasma elimination half-life closely reflects the half-life of azithromycin in tissues (2 - 4 days.)

Approximately 12% of an intravenously administered dose, the most significant part occurs during the first 24 hours, is excreted as main drug in urine within the following three days. High concentrations of unchanged drug was found in human bile. At the same time, its 10 metabolites were also detected in human bile. Microbiological assays in tissues and HPLC comparisons have shown that metabolites do not have a role on the microbiological efficacy of azithromycin.

Linearity/Non-Linear status:

There is no sufficient information.

Characteristic properties in patients:

Elderly:

After 5 day administration in elderly volunteers (> 65 years old), a little bit higher AUC values has been seen in comparison with young volunteers (<40 years old), however, these values are not accepted as clinically significant values, therefore any dose adjustment is not recommended.

Renal impairment

Following a single dose (1g) of sudden release azithromycin, the pharmacokintetic properties of azithtomycin has not been changed in individuals with mild to moderate renal impairment [GFH (glomerular filtration rate of 10-80 ml/min]. Statistically meaningful difference in with respect to AUC_{0-120} (11.7 µg.hour/mL against 8.8 µg.hour/mL), C_{max} (1.6 µg/mL against 1-0 g/mL) and CL_r (0.2 µL/min.kg against 2.3 mL/min./kg) have been noted between the group with severe renal impairment (GFH < 10 mL/min) and the group with normal renal functions.

Hepatic impairment

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 clearance of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

5.3 Preclinical safety data

In animal tests in which the dosages used amounted to 40 times the dose expected to be administered in clinical practice, azithromycin was found to have caused reversible phospholipidosis, generally without noticeable toxicological results, normal use of azithromycin in human and an evidence of it is not present.

Electrophysiological investigations have shown that there is QT prolonge potential in mild level.

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 performed for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day caused mild retardation in fetal 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 in fetal ossification and in maternal weight gain.

6. Pharmaceutical particulars

6.1 List of excipients

Saccharose
Sodium phosphate tribasic
Sodium benzoate
Hydroxypropyl cellulose
Xanthan gum
Cherry flavor
Banana flavor

6.2 Incompatibilities

There is not any known incompatibility.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. It can be stored within 5 days at the room temperature after reconstitution.

6.5 Nature and contents of container

ZIROMIN 200 mg/5 ml Powder for Oral Suspension is packaged in 60 ml natural HDPE bottle closed with polypropylene cap with white colored induction foil, 1 dose graduated syringe (5 ml) in cardboard box with 1 patient information leaflet.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

World Medicine İlaç San. ve Tic. A.Ş.
Bağcılar/Istanbul, TURKEY

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization:
Renewal of the authorization:

10. DATE OF REVISION OF THE SPC