Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azithromycin Krka 250 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg azithromycin (as azithromycin dihydrate).

Excipient with known effect
Azithromycin Krka 250 mg film-coated tablets
Each film-coated tablet contains up to 0.50 mg sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White or almost white, capsule-shaped film-coated tablets (length: 13.8–14.2 mm, width: 6.3–6.7 mm), inscribed "S19" on one side and blank on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin Krka is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin (see sections 4.4 and 5.1):
- 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 Krka should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below.

Children and adolescents with a body weight 45 kg or over, adults and the elderly:
The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg as a single dose on the first day and 250 mg once daily on day 2 to 5.

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

Children and adolescents with a body weight below 45 kg:
Azithromycin Krka tablets are not suitable for patients under 45 kg body weight. Other dosage forms are available for this group of patients.

Elderly patients:

The same dosage as in adult patients is used in the elderly. 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).

Patients with renal impairment:
Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min) (see section 4.4). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min) (see section 4.4 and 5.2).

Patients with hepatic impairment:
Dose adjustment is not required for patients with mild to moderate hepatic dysfunction (Child-Pugh class A or B). Since azithromycin is metabolised in the liver and excreted in the bile, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. No studies have been conducted regarding treatment of such patients with azithromycin (see section 4.4).

Method of administration
The tablets can be taken with or without food. The tablets should be taken with water.

4.3 Contraindications

Hypersensitivity to the azithromycin, erythromycin, any macrolide or ketolide antibiotic or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity
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 (see section 4.8) Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death.
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 derivatives
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 ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be coadministered.

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

Clostridioides difficile associated diarrhea
Clostridioides difficile associated diarrhea (CDAD) has been reported with use of nearly all 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. 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (Glomerular Filtration Rate [GFR] 10–80 ml/min). In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Prolongation of the QT interval
Prolonged cardiac repolarization 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 (possibly fatal). Azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes 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; and chloroquine or hydroxychloroquine
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

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).

Streptococcal infections
Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.

Paediatric population
Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex (MAC) in children have not been established.

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

The following should be considered before prescribing azithromycin:

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

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* have been reported for azithromycin in some European countries (see section 5.1). This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

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

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

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

Sexually transmitted disease:
In case of sexually transmitted diseases a concomitant infection by *T. pallidium* should be excluded.

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

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium-free.

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 with 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 simultaneously. Co-administration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.

Cetirizine: In healthy volunteers, coadministration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine): 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: 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-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

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 (see section 4.4).

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 co-administration of these medicines with azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid 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 metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Cyclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin Cmax and AUC0-5 were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If 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 half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (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 drug.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8).

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

Terfenadine: Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

Theophylline: There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers. 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.

Substances that prolong the QT interval: Azithromycin should not be used concomitantly with other active substances that prolong the QT interval e.g. hydroxychloroquine and chloroquine (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breast-feeding
Azithromycin has been reported to be secreted into human breast milk. Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery. However, due to the occurrence of side effects (see section 4.8), the ability to react may be altered and the ability to actively participate in road traffic and to operate machinery may be impaired.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and postmarketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention:

- Very common (≥ 1/10)
- Common (≥ 1/100 to < 1/10)
- Uncommon (≥ 1/1,000 to < 1/100)
- Rare (≥ 1/10,000 to < 1/1,000)
- Very rare (< 1/10,000)
- Not known (cannot be estimated from the available data)Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

	Very common	Common	Uncommon	Rare		Not known
Infections and infestations			Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorder, rhinitis, oral candidiasis			Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders			Leukopenia, neutropenia, eosinophilia			Thrombocytopenia, haemolytic anaemia
Immune system disorders			Angioedema, hypersensitivity			Anaphylactic reaction (see section 4.4)
Metabolism and nutrition disorders			Anorexia			
Psychiatric disorders			Nervousness, insomnia	Agitation		Aggression, anxiety, delirium, hallucination
Nervous system disorders		Headache	Dizziness, somnolence, dysgeusia, paraesthesia			Syncope, convulsion, hypoestheia, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis (see section 4.4).
Eye disorders			Visual impairment			
Ear and labyrinth disorders			Ear disorder, vertigo			Hearing impairment including deafness and/or tinnitus
Cardiac disorders			Palpitations			Torsades de pointes (see section 4.4), arrhythmia (see section 4.4) including ventricular tachycardia, electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea, epistaxis			
Gastrointestinal disorders	Diarrhea	Vomiting, abdominal pain, nausea	Constipation, flatulence, dyspepsia, gastritis, dysphagia, abdominal, distension, dry mouth eructation, mouth ulceration, salivary hypersecretion			Pancreatitis, tongue discolouration
Hepatobiliary disorders				Hepatic function abnormal, jaundice		Hepatic failure (which has rarely resulted in death) (see section 4.4) hepatitis fulminant, hepatic necrosis

				cholestatic		
Skin and subcutaneous tissue disorders			Rash, pruritus urticaria, dermatitis, dry skin, hyperhidrosis	Photosensitivity reaction, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (see section 4.4)		Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis, myalgia, back pain, neck pain			Arthralgia
Renal and urinary disorders			Dysuria, renal pain			Renal failure acute, nephritis interstitial
Reproductive system and breast disorders			Metrorrhagia, testicular disorder			
General disorders and administration site conditions			Oedema, asthenia, malaise, fatigue, face edema, chest pain, pyrexia, pain, peripheral edema			
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, hematocrit decreased, bicarbonate increased, abnormal sodium			

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 (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to < 1/100)
Metabolism and Nutrition Disorders		Anorexia	
Nervous System Disorders		Dizziness, Headache, Paraesthesia, Dysgeusia	Hypoesthesia
Eye Disorders		Visual impairment	
Ear and Labyrinth Disorders		Deafness	Hearing impaired, Tinnitus
Cardiac Disorders			Palpitations
Gastrointestinal Disorders	Diarrhea, 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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Symptoms
Adverse events experienced in higher than recommended doses 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 diarrhoea.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Macrolides, ATC code: J01FA10.

Mechanism of action
Azithromycin Krka 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 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.

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

Mechanism of resistance:
Resistance of gram-positive organisms to the macrolides usually involves an alteration of the antimicrobial binding site. The mlSB type of resistance (see below), which may be constitutive in staphylococci or induced in staphylococci and

streptococci by exposure to certain macrolides, is mediated by a variety of acquired genes (*erm* family) encoding methylases targeted at the peptidyl transferase centre of 23*S* ribosomal RNA.

Methylation impedes binding of antibacterials to the ribosome and gives rise to cross-resistance to macrolides (all macrolides when constitutive), lincosamides and type B streptogramins but not to type A streptogramins. Less frequent mechanisms of resistance include antimicrobial degradation by inactivating enzymes such as esterases and active efflux of the antimicrobial from the bacteria.

Gram-negative organisms may be intrinsically resistant to the macrolides because of the inability of the macrolide to effectively penetrate the outer cell membrane. Macrolides having a better penetration may have activity against some gram-negative organisms.

Gram-negative organisms may also produce ribosomal methylase or macrolide-inactivating enzymes.

Breakpoints
Azithromycin susceptibility breakpoints for typical bacterial pathogens:
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	≤ 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.

Table of susceptibilities

Commonly susceptible species
Aerobic Gram-positive
Mycobacterium avium°
Streptococcus pyogenes[1]
Aerobic Gram-negative
Haemophilus influenzae[$]
Moraxella catarrhalis°
Neisseria gonorrhoeae
Other microorganisms
Chlamydophila pneumoniae°
Chlamydia trachomatis°
Legionella spp. °
Mycoplasma pneumoniae°
Species for which acquired resistance may be a problem.
Aerobic Gram-positive
Staphylococcus aureus (methicillin-susceptible)
Staphylococcus aureus (methicillin-resistant)[+]
Streptococcus pneumoniae
Streptococcus agalactiae
Inherently resistant organisms

Aerobic Gram-negative
Escherichia coli.
Klebsiella spp.
Pseudomonas aeruginosa

°At the time of publication there are no current data. In primary literature, standard works and treatment guidelines susceptibility is assumed.
[1]Resistance rate in some studies ≥10%.
[$]Species that show natural intermediate susceptibility (in the absence if acquired mechanism of resistance)
[+]Resistance rate more than 50% in at least one region within the EU.

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
Bioavailability after oral administration is approximately 37%. Peak concentrations in the plasma are attained 2-3 hours after taking the medicinal product. The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 microgram/ml.

Distribution
Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin in tissues are noticeably higher (as much as 50 times) than those in plasma, which indicates that the agent binds strongly to tissues. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released than are released from inactive phagocytes. Consequently, in animal tests the azithromycin concentrations measured in inflammation foci were high.

Binding to serum proteins varies according to concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram/ml. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

Biotransformation and elimination
Terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days. Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Ten metabolites were also detected in bile, which were formed through N- and O-demethylation, hydroxylation of desosamine and aglycone rings and degradation of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

Pharmacokinetics in special populations:

Renal impairment
Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR>80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively compared to normal.

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

Elderly
The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

In elderly volunteers (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger volunteers (<40 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

Paediatric population
Pharmacokinetics has been studied in paediatric patients 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, C_{max} achieved was slightly lower than in adults with 224 microgram/l in infants, toddlers and children aged 0.6-5 years after 3 days dosing and 383 microgram/l in children and adolescents aged 6-15 years. The $t_{1/2}$ of 36 h in the older children and adolescents was within the expected range for adults.

5.3 Preclinical safety data

In animal tests in which the dosages used amounted to 40 times the therapeutic dosage, azithromycin was found to have caused reversible phospholipidosis, but as a rule, no true toxicological consequences were observed.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic Potential:
Long-term studies in animals to evaluate carcinogenic potential have not been performed because the drug is indicated for short-term treatment only. No signs indicative of carcinogenic activity have been observed in other studies.

Mutagenic Potential:
There was no evidence of a potential for genetic and chromosomal mutations in *in vivo* and *in vitro* test models.

Reproductive Toxicity:
In studies of the embryotoxic effects of azithromycin in mice and rats, no teratogenic effect has been observed. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and maternal weight gain. In peri- and post-natal studies in rats, mild retardation was observed following treatment with 50 mg/kg/day azithromycin and above.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E460)
Pregelatinised potato starch
Sodium laurilsulfate
Hypromellose (E464)
Croscarmellose sodium (E468)
Colloidal anhydrous silica (E551)
Magnesium stearate (E470b)

Film coating
Hypromellose 5 cP (E464)
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (opaque white PVC/PVdC-film, Alu-foil): 4 and 6 film-coated tablets, in a box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/047/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 9th May 2014
Date of last renewal: 18th April 2019

10 DATE OF REVISION OF THE TEXT

September 2022