

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MACROLYN®

Azithromycin 500 mg Film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg azithromycin (as azithromycin dihydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, oblong, film-coated tablets with 'AZITRO' engraved on one side and scored on the other side.

The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Macrolyn tablets are indicated for the treatment of the following bacterial infections, when caused by microorganisms sensitive to azithromycin:

- acute bacterial sinusitis (adequately diagnosed),
- acute bacterial otitis media (adequately diagnosed),
- pharyngitis, tonsillitis,
- acute exacerbation of chronic bronchitis (adequately diagnosed),
- acute bacterial bronchitis
- mild to moderately severe community acquired pneumonia,
- non complicated skin and soft tissue infections,
- uncomplicated urethritis and cervicitis due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae*.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. Posology and mode of administration

Posology

Adults, adolescents and children with a body weight above 45 kg

- For most of the indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days.
- In uncomplicated urethritis and cervicitis due to *Chlamydia trachomatis*, the dose is 1000 mg as a single oral dose.
- For susceptible *Neisseria gonorrhoeae* the recommended dose is 1000 mg or 2000 mg of azithromycin in combination with 250 mg or 500 mg ceftriaxone according to local clinical treatment guidelines. For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

Missed Dose

If 12 hours or less have passed since the missed dose, the patient should be advised to take it as soon as possible and then take the next dose at the regularly scheduled time. If more than 12 hours have passed since the time the dose is usually taken, the patient should be advised to wait until the next scheduled dose.

Special populations

Elderly patients

The same dosage as in adult patients is used for elderly patients. Since older people 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).

Renal impairment

No dose adjustment is necessary 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).

Hepatic impairment

A dose adjustment is not necessary for patients with mild to moderately impaired liver function. Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin (see section 4.4).

Pediatric population

Macrolyn tablets should not be administered to children with a body weight less than 45 kg. Other dosage forms of azithromycin are available for this group of patients.

Method of administration

Macrolyn tablets are for oral use, and should be taken as a single daily dose. Macrolyn tablets can be taken with or without food. The tablets should be ingested with a half glass of water.

4.3. Contraindications

The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1.

4.4. Special warning and precautions for use

Potential for Resistance

Azithromycin could favour the development of resistance due to the associated long-lasting and decreasing levels in plasma and tissues after the end of treatment (see section 5.2). Treatment with azithromycin should only be initiated after a careful assessment of the benefit and the risks, considering the local prevalence of resistance, and when preferred treatment regimens are not indicated.

Hypersensitivity

As with erythromycin and other macrolides, serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal) and dermatological reactions including acute Generalized Exanthematous Pustulosis (AGEP), Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported (see section 4.8). 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 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.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by co-administration 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 co-administrated (see section 4.5).

Prolongation of the QT interval

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 sections 4.8 and 5.1). 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 patient with ongoing proarrhythmic conditions (especially women and elderly) such as patients:

- with congenital or documented QT prolongation,
- currently receiving treatment with other active substance known to prolong QT interval such as antiarrhythmics of Classes IA (quinidine and procainamide) and class III (dofetilide, amiodarone, sotalol) , cisapride and terfenadine, antipsychotic agents such as pimozide; antidepressants such as citalopram and fluoroquinolones such as moxifloxacin and levofloxacin (see section 4.5).
- with electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesaemia,
- with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Superinfection

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

Clostridium difficile associated diarrhoea (CDAD)

Clostridium difficile associated diarrhoea (CDAD) has been reported with the 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*.

Strains of *C. difficile* producing hypertoxin A and B 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. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the use of supportive measures together with the administration of specific treatment for *C. difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Sexually Transmitted Infections

Neisseria gonorrhoeae is very likely to be resistant to macrolides, including the azalide azithromycin (see section 5.1).

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.

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).

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).

Sodium

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

Pediatric population

Macrolyn tablets should not be administered to children with a body weight less than 45 kg.

4.5. Interactions with other medicinal products and other forms of interactions**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 24%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine

In healthy volunteers, co-administration of a 5-day regimen of azithromycin with 20 mg cetirizine 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 six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

Digoxin and colchicine (*P-gp* substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-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.

Ergotamine derivatives

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 4.4)

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.

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 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 macrolide antibiotic erythromycin.

Atorvastatin

Co-administration 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.

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.

Cisapride

Cisapride is metabolised in the liver by the enzyme CYP3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause prolongation of QT interval, ventricular arrhythmias and torsades de pointes.

Coumarin-type oral anticoagulants

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

Ciclosporin

In a pharmacokinetic study with healthy volunteers who were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC₀₋₅ were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in AUC_{0-∞}. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz

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

Fluconazole

Co-administration 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 co-

administration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Indinavir

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

Nelfinavir

Co-administration 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 was required.

Phenytoin

Macrolides may cause an increase in serum phenytoin levels, so caution should be exercised before any concomitant administration of these substances.

Rifabutin

Co-administration 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 (500 mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its major circulating metabolite.

Terfenadine

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

Theophylline

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

Triazolam

In 14 healthy volunteers, co-administration of 500mg azithromycin 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

Co-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with 1200 mg azithromycin 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.

4.6. Fertility, pregnancy and lactation**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 (see section 5.3).

Pregnancy

No adequate data on the use of azithromycin in pregnant women are available. Reproductive toxicity studies in animals have shown that azithromycin crosses the placental barrier, 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

The limited information available in the published literature indicates that azithromycin is present in human breast milk at an estimated maximum median daily intake of 0.1 to 0.7 mg/kg/day. No serious adverse reactions of azithromycin have been observed in breastfed infants. A decision should be made whether to discontinue breastfeeding or to discontinue/withhold treatment with azithromycin, taking into account the benefit of breastfeeding for the child versus the benefit of treatment for the woman.

4.7. Effects on the 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.

4.8. Undesirable effects

Summary of the safety profile

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

The frequencies of adverse reactions reported with azithromycin are defined as:

- very common ($\geq 1/10$)
- common ($\geq 1/100$ to $< 1/10$)
- uncommon ($\geq 1/1,000$ to $< 1/100$)
- rare ($\geq 1/10,000$ to $< 1/1,000$)
- very rare ($< 1/10,000$)
- not known (cannot be estimated from the available data)

Tabulated summary of adverse reaction

System Organ Class /Frequency/Effect	
<i>Infections and infestations</i>	
uncommon	Candidiasis, Vaginal infection, Pneumonia, Fungal infection, Bacterial infection, Pharyngitis, Gastroenteritis, Respiratory disorder, Rhinitis Oral candidiasis
not known	Pseudomembranous colitis
<i>Blood and lymphatic system disorders</i>	
uncommon	Leukopenia, Neutropenia, Eosinophilia
not known	Thrombocytopenia, Hemolytic anemia
<i>Immune system disorders</i>	
uncommon	Angioedema, Hypersensitivity
not known	Anaphylactic reaction
<i>Metabolism and nutrition disorders</i>	
uncommon	Anorexia
<i>Psychiatric disorders</i>	

System Organ Class /Frequency/Effect	
uncommon	Nervousness, Insomnia
rare	Agitation, Depersonalization
not known	Aggression, Anxiety, Delirium, Hallucination
<i>Nervous system disorders</i>	
common	Headache
uncommon	Dizziness, Somnolence, Dysgeusia, Parosmia
not known	Syncope, convulsion, Hypoesthesia, Psychomotor hyperactivity Anosmia, Ageusia, Parosmia, Myasthenia gravis
<i>Eye disorders</i>	
uncommon	Visual impairment
<i>Ear and labyrinth disorders</i>	
uncommon	Ear disorder, Vertigo
not known	Hearing impairment including deafness and/or tinnitus
<i>Cardiac disorders</i>	
uncommon	Palpitations
not known	Torsades de pointes, Arrhythmia including ventricular tachycardia, ECG QT prolonged
<i>Vascular disorders</i>	
uncommon	Hot flushes
not known	Hypotension
<i>Respiratory, thoracic and mediastinal disorders</i>	
uncommon	Dyspnea, Epistaxis
<i>Gastrointestinal disorders</i>	
very common	Diarrhea
common	Vomiting, Abdominal pain, Nausea
uncommon	Constipation, Flatulence, Dyspepsia, Gastritis, Dysphagia, Abdominal distension, Dry mouth, Eructation, Mouth ulceration Salivary hypersecretion
not known	Pancreatitis, Tongue discoloration
<i>Hepatobiliary disorders</i>	
uncommon	Hepatitis
rare	Abnormal hepatic function, Cholestatic Jaundice
not known	Hepatic failure (which has rarely resulted in death) (see section 4.4), Fulminant hepatitis, Hepatic necrosis
<i>Skin and subcutaneous tissue disorders</i>	
uncommon	Rash, Pruritus, Urticaria, Dermatitis, Dry skin, Hyperhidrosis
rare	Photosensitivity reaction, DRESS syndrome, Acute generalized exanthematous pustulosis (AGEP)
not known	Steven-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
<i>Musculoskeletal and connective tissue disorders</i>	
uncommon	Osteoarthritis, Myalgia, Back pain, Neck pain
not known	Arthralgia
<i>Renal and urinary disorders</i>	

System Organ Class /Frequency/Effect	
uncommon	Dysuria, Renal pain
not known	Acute renal failure, Interstitial nephritis
<i>Reproductive system and breast disorders</i>	
uncommon	Metrorrhagia, Testicular disorder
<i>General disorders and administration site disorders</i>	
uncommon	Edema, Asthenia, Malaise, Fatigue, Face edema, Chest pain, Pyrexia, Pain, Peripheral edema
<i>Investigations</i>	
common	Lymphocyte count decreased, Eosinophil count increased, Blood bicarbonate decreased, Basophils increased, Monocytes increased, Neutrophils increased
uncommon	Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood bilirubin increased, Blood urea increased, Blood creatinine increased, Blood potassium abnormal, Blood alkaline phosphatase increased, Chloride increased, Glucose increased, Platelets increased, Hematocrit decreased, Bicarbonate increased, Abnormal sodium
<i>Injury and poisoning</i>	
uncommon	Post procedural complication

Reporting of suspected adverse reactions

Reporting of suspected adverse reaction to the Authorities by Health Care Professionals is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

4.9. Overdose

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.

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group and ATC code: antibacterial for systemic use. ATC code: J01FA10

Azithromycin is an azalide, a sub-class of the macrolide antibiotics.

Mode of action

By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

PK/PD relationship

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

Mechanism of resistance

Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Azithromycin demonstrates cross resistance with erythromycin resistant gram-positive isolates.

A decrease in macrolide susceptibility over time has been noted particularly in *Streptococcus pneumoniae* and *Staphylococcus aureus*. Similarly, decreased susceptibility has been observed among *Streptococcus viridans* and *Streptococcus agalactiae* (Group B) streptococcus against other macrolides and lincosamides.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

organism	susceptibility breakpoints (mg/ml)	
	susceptible	resistant
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (Group A, B, C, G)	≤ 0.25	> 0.5
<i>Streptococcus pneumoniae</i>	≤ 0.25	> 0.5
<i>Haemophilus influenzae</i>	≤ 0.125	> 4
<i>Moraxella catarrhalis</i>	≤ 0.25	> 0.5
<i>Neisseria gonorrhoeae</i>	≤ 0.25	> 0.5

Commonly susceptible species

- Aerobic Gram-positive micro-organisms
 - *Staphylococcus aureus* (methicillin-susceptible)
 - *Streptococcus pneumoniae* (methicillin-susceptible)
 - *Streptococcus pyogenes* (group A)
 - Aerobic Gram-negative micro-organisms
 - *Haemophilus influenzae*
-

- *Haemophilus parainfluenzae*
- *Moraxella catarrhalis*
- *Pasteurella multocida*
- *Legionella pneumophila*
- *Neisseria gonorrhoeae*
- Anaerobic micro-organisms
 - *Clostridium perfringens*
 - *Fusobacterium* spp.
 - *Porphyromonas* spp.
 - *Prevotella* spp.
- Other micro-organisms
 - *Chlamydia trachomatis*

Species for which acquired resistance may be a problem

- Aerobic Gram-positive micro-organisms
 - *Streptococcus pneumoniae*
 - Penicillin intermediate
 - Penicillin resistant

Inherently resistant organisms

- Aerobic Gram-positive micro-organisms
 - *Enterococcus faecalis*
 - Staphylococci MRSA, MRSE
- Anaerobic micro-organisms
 - Bacteroides fragilis group

5.2. Pharmacokinetic properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours.

Distribution

Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.

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

Elimination

The 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. Also in bile, ten metabolites without microbiologic activity were detected.

Pharmacokinetics in special populations

- ***Renal insufficiency***

Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC₀₋₁₂₀ 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 AUC₀₋₁₂₀ increased 61% and 33% respectively compared to normal.

- ***Hepatic insufficiency***

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

- ***Elderly***

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

- ***Pediatric population***

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 µg/l in children aged 0.6-5 years and after 3 days dosing and 383 µg/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

5.3. Preclinical safety data

Phospholipidosis

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and humans is unknown.

Carcinogenic and mutagenic 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. Azithromycin has shown no mutagenic potential in standard laboratory tests.

Reproductive toxicity

In animal studies 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 led to mild retardation of 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

Core tablet: Calcium hydrogen phosphate

Carmellose sodium

Microcrystalline cellulose

Sodium laurilsulfate

Magnesium stearate

Film coating Opadry OY-D-7233

Hypromellose

Talc

Sodium laurilsulfate

Macrogol

Titanium dioxide (E171).

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

36 months (3 years).

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

PVC/PVDC/Aluminium blister.

Box with one blister containing 3 tablets and a patient leaflet.

6.6. Special precautions for disposal and other handlings

No special requirements. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

Manufacturer

Deva Holding A.Ş. Çerkezköy Organize Sanayi Bölgesi, Karaağaç Mah, Atatürk Cad., No: 32 Kapaklı-Tekirdağ, Turkey.

8. MARKETING AUHORISATION NUMBER

H2026/CTD8269/15234

9. DATE OF FIRST REGISTRATION

22 July 2026

10. DATE OF REVISION OF TEXT

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