SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zaraxin 500mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains azithromycin dihydrate 524.10 mg equivalent to 500 mg azithromycin base.

Excipient(s) with known effect:
Lactose monohydrate – 3.0 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

White, oblong, biconvex, film coated tablets, scored on one side.
The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

4.1 Therapeutic indications

Zaraxin 500 mg film-coated tablets is indicated for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin:

- infections of the lower respiratory tract such as acute bronchitis and mild to moderately severe community-acquired pneumonia. Clinical efficacy against respiratory infections due to *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila*, has not been observed. Zaraxin is not suitable for treatment of severe infections requiring a quick and high concentration of an antibiotic in the blood, e.g. in severe pneumonia.
- infections of the upper respiratory tract such as sinusitis, pharyngitis, tonsillitis and acute otitis media
- skin and soft tissue infections, with the exception of infected burns
- uncomplicated urethritis and cervicitis caused by *Chlamydia trachomatis*

Penicillin is usually first- line choice of treatment for pharyngitis due to *Streptococcus pyogenes* and for the prophylaxis of subsequent rheumatic fever.

Zaraxin is indicated for the prophylaxis of *Mycobacterium Avium-intracellulare Complex* (MAC) infection in patients with advanced HIV (CD4 count $\leq 100/mm^3$) (see section 5.1).

Consideration should be given to official local guidance (e.g. national recommendations) regarding the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology:
This medicine should be taken in a single daily dose.
The duration of treatment for the different types of infection are mentioned below.

Adults
The dosage for treatment of sexually transmitted diseases caused by *chlamydia trachomatis* is 1000 mg taken in a single oral dose.

The usual dosage for prophylaxis of MAC infections in patients with HIV (CD4 count $\leq 100/mm^3$) is 1200 mg once a week.
For all other indications, the total dosage is 1500 mg, to be administered as a single daily dose of 500 mg for three days. Alternatively, the same total dosage (1500 mg) can be given over a period of 5 days, starting with 500 mg on day 1 and 250 mg on day 2 to 5.

Paediatric population
Zaraxin tablets should only be given to children with a body weight above 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycin, e.g. suspensions, may be used.

Elderly
Elderly patients receive the recommended dosage for adults. Because of a tendency to exhibit irregular heartbeat and due to the risk to develop cardiac arrythmia and torsade de pointes a special caution should be paid (see sections 4.4).

Method of administration
The tablets should be swallowed whole and may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients listed in Section 6.1.

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalized exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with 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.

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 cases of signs and symptoms of liver dysfunction such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/investigations should be performed immediately.
Azithromycin administration should be stopped if liver dysfunction has emerged.

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

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides, including azithromycin (see section 4.8).
As the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with on-going proarrhythmic conditions (especially women and elderly patients) such as: - Patients with congenital or documented QT prolongation.
- Patients currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA (quinidine and procainamide) and III (dofetilide, sotalol and amiodarone), cisapride and terfenadine, antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin.
- Patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia.
- Patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

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).
As with any antibacterial agent, observation for signs of superinfections with non-susceptible organisms (e.g. fungal infections) is recommended.

Clostridioides difficile associated diarrhea (CDAD) has been reported with the 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*. Strains of *C. difficile* produces toxins A and B which contribute to the development of CDAD. Certain 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 during or subsequent to the administration of any antibiotic. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
No dosage adjustment is required in patients with mild or moderate renal function impairment (creatinine clearance > 40 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).
After the use of macrolide antibiotics, cases of pseudomembranous colitis have been reported. This diagnosis should therefore be considered for patients who suffer from diarrhea after start of the treatment with azithromycin.
There is no experience regarding the safety and efficacy of long-term use of azithromycin for the mentioned indications except for prophylaxis against MAC infections.
In case of rapid recurrent infections, treatment with another antibiotic should be considered.
After the use of Azithromycin in neonates (treatment in the first 42 days after birth), cases of hypertrophic pyloric stenosis in infants (IHPS) were reported. The parents and the nursing staff are prompted to contact their doctor if any vomiting or irritation would occur at feeding.

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

Excipients
Lactose
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
Azithromycin 500 mg film-coated tablets contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Chloroquine and hydroxychloroquine:
Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

Antacids:
When studying the effect of simultaneously administered antacids on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak serum concentrations of azithromycin were reduced by approximately 24 %. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Didanosine (Dideoxyinosine):
Co-administration of daily doses of 1200 mg azithromycin with 400 mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

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 is required.

Zidovudine:
1000 mg single doses and 1200 mg or 600 mg multiple doses of azithromycin had no effect upon 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 mononuclear cells in the peripheral circulation. The clinical significance of these findings is unclear, but 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.

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.

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 digoxin serum concentrations of the substrate should be considered. Clinical monitoring and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Ergot derivatives:
There is a theoretical possible interaction between azithromycin and ergot derivatives (see section 4.4).

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 conducted in healthy volunteers, azithromycin had no significant effect on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

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

Coumarin-Type Oral Anticoagulants:
In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15-mg dose of warfarin administered to healthy volunteers. There have been reports received in the 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.

Cyclosporin:
In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

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

Indinavir:
Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

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

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

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

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

Theophylline:

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

Triazolam:
In 14 healthy volunteers, coadministration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

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

Astemizol and Alfentanil:
No data are available on interactions with astemizol, and alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentiation of its effect during concomitant use of the macrolide antibiotic erythromycin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy:
There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period (>7,300 first trimester exposures). While most studies do not suggest an association with adverse fetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy. Therefore, azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breast-feeding:
Azithromycin is excreted in breast milk. Because of the long half-life, accumulation in the milk is possible. Information available from published literature indicates that, in short-term use, this does not lead to clinically relevant quantities in the milk. No serious side effects have been observed by azithromycin in breast-fed children.

A decision should be taken whether breastfeeding is discontinued or that treatment with azithromycin is discontinued/initiated or not, taking into

account the benefit of breastfeeding for the child and the benefit of treatment for the woman.

Fertility
In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of these results in human is not known.

4.7 Effects on ability to drive and use machines

No data is available on the influence of azithromycin on the ability to drive and to use machines.

The appearance of dizziness as a side effect should be considered when executing these above- mentioned actions.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1 000 to <1/100); Rare (≥ 1/10 000 to <1/1 000); Very Rare (< 1/10 000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1. Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

very common	common	uncommon	rare	very rare	not known
Infections and infestations					
		Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection, Pharyngitis, Gastroenteritis, Respiratory disease, Rhinitis Oral candidiasis			Pseudomembranous colitis (see 4.4)
Blood and lymphatic system disorders					
		Leukopenia			Thrombocytopenia,

very common	common	uncommon	rare	very rare	not known
		Neutropenia Eosinophilia			Haemolytic anaemia
Immune system disorders					
		Angioedema Hypersensitivity			Anaphylactic reaction (see section 4.4.)
Metabolism and nutrition disorders					
		Anorexia			
Psychiatric disorders					
		Nervousness Insomnia	Irritability		Aggression Anxiety Delirium Hallucinations
Nervous system disorders					
	Headache Paraesthesia Dysgeusia Dizziness Somnolence	Hypoesthesia			Syncope, Convulsion, Psychomotor hyperactivity, Anosmia, Ageusia, Parosmia, Myasthenia gravis (see section 4.4)
Eye disorders					
	Visual impairment				
Ear and labyrinth disorders					
	Deafness	Ear disorder, Vertigo Hearing impairment (including hearing loss) Tinnitus			
Cardiac disorders					
		Palpitations			Torsade de pointes (see section 4.4) Arrhythmia including ventricular tachycardia (see section 4.4) Electrocardiogram QT prolonged (see section 4.4)

very common	common	uncommon	rare	very rare	not known
Vascular disorders					
		Hot flashes			Hypotension
Disorders of the respiratory tract, thorax and mediastinum					
		Dyspnea Epistaxis			
Gastrointestinal disorders					
Diarrhoea Abdominal pain Nausea Flatulence	Vomiting Dyspepsia	Constipation Gastritis Dysphagia, Abdominal distension, Dry mouth, Eructation Mouth ulceration, Salivary hypersecretion			Pancreatitis, Tongue discoloration, Discoloration of teeth
Hepatobiliary disorders					
		Abnormal liver function Hepatitis	Cholestatic jaundice		Hepatic failure (see 4.4), which has rarely resulted in death Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders					
	Rash Pruritis	Urticaria Dermatitis Dry skin Hyperhidrosis Stevens-Johnson syndrome, Photosensitivity reaction	Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with eosinophilia and systemic Symptoms (DRESS)		Toxic epidermal necrolysis, Erythema multiforme
Musculoskeletal and connective tissue disorders					
	Arthralgia	Osteoarthritis Myalgia Back pain Neck pain			
Renal and urinary disorders					
		Dysuria Renal pain			Acute renal failure Interstitial nephritis
Gynaecological and breast diseases					

very common	common	uncommon	rare	very rare	not known
		Metrorrhagia, Testicular disorders			
General disorders and administration site conditions					
	Fatigue	Oedema Asthenia Malaise Face oedema Chest pain Pyrexia Pain Peripheral edema			
Investigations					
	Lymphocyte count decreased, Eosinophil count increased, Blood bicarbonate decreased, Basophil, monocytes and neutrophil count 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			
Injury and poisoning					
		Post procedural complication			

Table 2. Adverse effects caused possibly or very likely by the prophylaxis or treatment of *Mycobacterium avium*-infection. The data originate from clinical studies or surveys after market introduction. These side effects are different by nature or frequency from the side effects reported for a drug with an immediate or retarded release.

Very common	Common	Rare
Metabolism and nutrition disorders		
	Anorexia	
Nervous system disorders		
	Dizziness, Headache, Paraesthesia, Dysgeusia	Hypoesthesia
Eye disorders		
	Visual impairment	
Ear and labyrinth disorders		
	Deafness	Hearing impairment, Tinnitus
Cardiac disorders		
		Palpitations
Gastrointestinal disorders		
Diarrhea, Abdominal pain, Nausea, Flatulence, Abdominal condition, Soft defecation		
Hepatobiliary disorders		
		Hepatitis
Skin and subcutaneous tissue disorders		
	Rash, Pruritis	Stevens-Johnson syndrome, Photosensitivity reaction
Musculoskeletal and connective tissue disorders		
	Arthralgia	
General disorders and administration site conditions		
	Fatigue	Malaise, Asthenia

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 www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

Pharmacodynamic properties

General properties

Pharmacotherapeutic group: macrolides
ATC code: J01FA10

Mechanism of action:
Azithromycin is an azalide, a subclass of the macrolide antibiotics. It prevents the translocation of peptide chains from one side of a ribosome to the other by binding to the ribosomal 50S subunit. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

Mechanism of resistance:
The 2 most common mechanisms of resistance against macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these mechanisms varies by species and within a certain species, the frequency of resistance varies by geographic location.

The most important ribosomal modification responsible for the reduced binding of macrolides is post-transcriptional (N_6)-methylation of adenine at nucleotide A2058 (*E. coli* numbering system) of the 23S rRNA by methylases, which are coded by *erm* (erythromycin ribosome methylase) genes. Ribosomal modifications often determine the cross-resistance (MLS_B phenotype) to other classes of antibiotics, for which the ribosomal binding sites overlap with those of the macrolides: lincosamides (e.g. clindamycin) and streptogramins of group B (e.g. the quinupristin-component of quinupristin/dalfopristin). Different *erm* genes are present in different bacterial species, namely Streptococci and staphylococci. The sensitivity of macrolides can also be influenced by less frequent mutational changes in the nucleotides A2058 and A2059, and in some other loci of 23S rRNA or in the large ribosomal subunit proteins L4 and L22.
Efflux pumps occur in a number of species, including gram-negative bacteria, e.g. *Haemophilus influenzae* (where these can determine intrinsically higher MIC's) and staphylococci. In streptococci and enterococci an efflux pump recognizing 14- and 15-membered macrolides (e.g. respectively erythromycin and azithromycin), are coded by *mef* (A) genes.

Susceptibility *Breakpoints* of tests

The EUCAST susceptibility breakpoints are presented in the table below.

EUCAST susceptibility breakpoints for azithromycin

	MIC (mg/l)	
	susceptible	resistant
Staphylococcus species	≤ 1	> 2
Streptococcus pneumoniae	≤ 0.25	> 0.5
Streptococcus A, B, C, G	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0,12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

EUCAST= European Committee on Antimicrobial Susceptibility Testing
MIC= Minimal Inhibitory Concentration

Antibacterial spectrum:
Azithromycin shows cross-resistance to erythromycin-resistant gram-positive isolates. As mentioned above, certain ribosomal modifications determine the cross-resistance with other classes of antibiotics for which the ribosomal binding sites overlap with those of the macrolides: lincosamides (e.g. clindamycin) and streptogramins of group B (including the quinupristin-component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been observed for *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed for viridans streptococci and *Streptococcus agalactiae*.

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

Susceptibility Mycobacterium Avium Complex:
The susceptibility methods and diagnostic procedures that are currently available *in vitro* to determine the mrc of *Mycobacterium Avium Complex* (MAC) organisms, are not generally accepted and not validated.
Breakpoints which show that clinically isolated species of *M. avium* or *M. intracellulare* are susceptible for azithromycin, have not yet been identified.

Data from clinical research:
Patients who received azithromycin in a placebo-controlled study, were less than one-half as likely to develop MAC bacteremia as those on placebo. They showed a 1-year cumulative incidence of disseminated MAC disorder of 8.24% compared to 20.22% in patients who received placebo.

For patients with CD4-count < 10/mm^3, combination therapy with another suited drug is to be considered, as the benefits of this combination outweigh the potential risks.

A comparative study showed a reduced risk to develop MAC-bacteremia in patients who were treated with azithromycin when compared to patients who received rifabutin. Patients who received both azithromycin and rifabutin, had 1/3 less chance on developing MAC-bacteremia in comparison with patients who were given solely 1 of these drugs.

The 1-year cumulative incidence of disseminated MAC disorder was 7.62% with azithromycin, 15.25% with rifabutin and 2.75% with a combination therapy of azithromycin and rifabutin. However, discontinuation in the patient group that received this combination therapy, was larger due to a lower tolerance.

In studies evaluating the prophylaxis of MAC infections, the occurrence of other bacterial infections was also reduced due to treatment with azithromycin.

In clinical studies comparing the 2 doses for treatment of *Streptococcus pharyngitis* in children (a single dose of 10 mg/kg or 20 mg/kg for 3 days), efficacy was comparable for both doses, but the bacterial eradication was higher for the 20 mg/kg/day dose.

Paediatric population:
After evaluation of studies conducted on children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy or combined with chloroquine or artemisinin-based drugs, because the non-inferiority compared to antimalaria drugs recommended for the treatment of uncomplicated malaria was not observed.

5.2 Pharmacokinetic properties

Absorption
Bioavailability after oral administration of azithromycin is approximately 37%. Peak concentrations in the plasma are attained 2-3 hours after taking the medicinal product.

Distribution
Orally administered azithromycin is widely distributed throughout the body. Pharmacokinetic studies have shown significant higher azithromycin levels in tissues (up to 50 times the maximum concentration observed in plasma) compared to the levels in plasma. This shows that the substance is significantly bounded in the tissues (steady-state distribution volume approximately 31 l/kg). The mean maximum observed serum concentration (C_{max}) after a single dose of 500 mg azithromycin is approximately 0.4 mg/ml, 2-3h after administration. There is no accumulation in the serum with the recommended dose. There is accumulation in the tissues where the levels are much higher than those in serum. Three days after administration of 500 mg as

single dose or divided into multiple doses, concentrations of 1.3-4.8 mg/g, 0.6-2.3 mg/g, 2.0-2.8 mg/g and 0-0.3 mg/ml were found in lungs, prostate, tonsils and serum, respectively.

Mean peak concentrations measured in peripheral leukocytes, where the MAC infection is active, was 140 µg/ml. The concentration remained above 32 µg/ml during approximately 60 hours after a single oral administration of 1200 mg. These concentrations were higher than the mrc_{90} of the most common pathogens.

In experimental *in vitro* and *in vivo* research, azithromycin accumulated in phagocytes. Release is facilitated by active phagocytosis. In animal models, this process seems to contribute to the accumulation of azithromycin in tissues.

The protein binding of azithromycin in serum is variable and varies between 52% at 0.005 mg/ml and 18% at 0.5 mg/ml, depending on the serum level.

Elimination
Terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

In elderly volunteers (>65 years), higher (29 %) AUC values were observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.
After intravenous administration, approximately 12% of unchanged azithromycin is excreted in urine over a period of 3 days; the largest part within the first 24 hours.

Concentrations up to 237 mg/ml azithromycin, 2 days after a 5-day treatment, are being found in human bile, together with 10 metabolites (formed through N- and O-demethylation, hydroxylation of the desosamine and aglycone rings, and degradation of cladinose conjugate). A comparison of HPLC and microbiological analyses suggests that the metabolites don’t play any part in the microbiological activity of azithromycin.

5.3 Preclinical safety data

No details

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Pregelatinized starch
- Crospovidone
- Calcium hydrogen phosphate, anhydrous

- Sodium laurylsulfate
- Magnesium stearate

Coating:
- hypromellose,
- titanium dioxide (E171)
- lactose monohydrate
- triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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: PVC/Aluminum
Pack sizes: 3 film-coated tablets.

6.6 Special precautions for disposal

No special requirements for disposal

7. MARKETING AUTHORISATION HOLDER

Maddox Pharma Swiss B.V.
Sylviusweg 74
2333 BE Leiden

The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PL 49430/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/08/2025

10 DATE OF REVISION OF THE TEXT

06/06/2025