

Summary of Product Characteristics

1) Name of the medicinal product :

Aziflam-500 (Azithromycin Tablets USP 500 mg)

2) Qualitative and Quantitative composition:

Each film coated tablet contains:

Azithromycin (As Dihydrate) USP

Eq. to Anhydrous Azithromycin.....500mg

For full list of excipients, see section 6.1

3) Pharmaceutical Form: Tablets

Yellow coloured, circular, biconvex, film coated tablets

4) Clinical Particulars

4.1) Therapeutic indication

Azithromycin tablets can be applied for the treatment of the following 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)
- mild to moderately severe community acquired pneumonia
- skin and soft tissue infections
- uncomplicated Chlamydia trachomatis urethritis and cervicitis

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

4.2) Posology and method of administration:

Posology

Adults

In uncomplicated Chlamydia trachomatis urethritis and cervicitis the dose is 1,000 mg as a single oral dose.

For all other indications the dose is 1,500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1,500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Elderly people

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

Paediatric population

Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycine, e.g. suspensions, may be used.

Renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min).

Hepatic impairment: No dose adjustment is necessary for patients with mild to moderately impaired liver function.

Method of administration

Azithromycin Tablets should be given as a single daily dose. The tablets may be taken with food.

4.3) Contraindications

Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotics, lactose or to any of the excipients.

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 medicinal product should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

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. 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.

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

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.

Pseudomembranous colitis

Pseudomembranous colitis has been reported with the use of macrolide antibiotics. This diagnosis should therefore be considered in patients who get diarrhoea after starting treatment with azithromycin.

Ergot derivatives

In patients receiving ergotamine derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

Cross resistance

Cross-resistance exists between azithromycin and other macrolides (erythromycin, clarithromycin, roxithromycin), lincosamides and streptogramin B (MLSB phenotype). Concomitant use of several medicinal products from the same or related group of antibacterial agents is not recommended.

Cardiovascular events

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin. Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

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

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

Clostridoides difficile associated diarrhoea

Clostridoides 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.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Paediatric population

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

The following should be considered before prescribing azithromycin:

Serious infections

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

Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more.

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

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* (> 30 %) have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

Pharyngitis/ tonsillitis

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

Sinusitis

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

Acute otitis media

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

Skin and soft tissue infections

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

Infected burn wounds

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

Sexually transmitted disease

In case of sexually transmitted diseases a concomitant infection by *T. pallidum* should be excluded.

Neurological or psychiatric diseases

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

Superinfection

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

Renal impairment

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

4.5) Interactions with other medicinal products and other forms of interaction

Effects of other medicinal products on azithromycin:

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids and azithromycin, no effect on overall bioavailability was seen, although the peak serum concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously, but with an interval of about 2 hours.

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.

Cetirizine

In healthy volunteers, co-administration 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.

Didanosins (Dideoxyinosine)

Co-administration of 1,200 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 (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-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Ergot derivatives

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

Zidovudine

Single 1,000 mg doses and multiple 1,200 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 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

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.

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

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

Co-administration of a single dose of 1,200 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 1,200 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 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

Co-administration of azithromycin (1,200 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

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

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

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. 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, co-administration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole

Co-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1,200 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.

Hydroxychloroquine

Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine.

Medicinal products known to prolong the QT interval

Azithromycin should not be used co-administered with other medicinal products, known to prolong the QT interval.

Protease inhibitors

No data are available yet on possible interaction with protease inhibitors.

4.6) Pregnancy and lactation

Pregnancy

In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed. 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. 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. 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 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. When performing these functions, the occurrence of the

adverse reaction of dizziness, visual impairment and vision blurred should be taken into account.

4.8) Undesirable Effects:

The table below lists the adverse reactions identified through clinical experience and post-marketing 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 ($\geq 1/10$); 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). 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:

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Candidiasis Oral candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis
	Not known	Pseudomembranous colitis
Blood and lymphatic system disorders	Uncommon	Leukopenia Neutropenia Eosinophilia
	Not known	Thrombocytopenia Haemolytic anaemia
Immune system disorders	Uncommon	Angioedema Hypersensitivity
	Not known	Severe (partly fatal) anaphylactic reaction e.g. anaphylactic shock.
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Uncommon	Nervousness Insomnia
	Rare	Agitation Irritability
	Not known	Aggression Anxiety Delirium Hallucination
Nervous system disorders	Common	Headache Dizziness Somnolence Dysgeusia Paraesthesia
	Uncommon	Hypoaesthesia
	Not known	Syncope

		Convulsion Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis
Eye disorders	Common	Visual impairment
	Not known	Blurred vision
Ear and labyrinth disorders	Common	Deafness
	Uncommon	Ear disorder Vertigo Hearing impairment including deafness and/or tinnitus
Cardiac disorders	Uncommon	Palpitations
	Not known	Torsades de pointes Arrhythmia including ventricular tachycardia Electrocardiogram QT prolonged
Vascular disorders	Uncommon	Hot flush
	Not known	Hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea Abdominal pain Nausea Flatulence
	Common	Vomiting Dyspepsia
	Uncommon	Constipation Gastritis Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion
	Not known	Pancreatitis Tongue discolouration Discolouration of teeth
Hepatobiliary disorders	Uncommon	Hepatitis Hepatic function abnormal
	Rare	Jaundice cholestatic
	Not known	Hepatic failure (which has rarely resulted in death) Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders	Common	Skin rash Pruritus
	Uncommon	Urticaria Dermatitis Dry skin Hyperhidrosis Steven-Johnson syndrome

		Photosensitivity reaction
	Rare	Acute generalised exanthematous pustulosis (AGEP) DRESS syndrome (drug reaction with eosinophilia and systemic symptoms)
	Not known	Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and connective tissue disorders	Uncommon	Osteoarthritis Myalgia Back pain Neck pain
	Common	Arthralgia
Renal and urinary disorders	Uncommon	Dysuria Kidney pain
	Not known	renal failure acute Nephritis
Reproductive system and breast disorders	Uncommon	Metrorrhagia Testicular disorder
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Oedema Asthenia Malaise Face oedema Chest pain Pyrexia Pain Peripheral oedema
Investigations	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
Injury and poisoning	Uncommon	Post procedural complication
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:

System Organ Class	Frequency	Adverse reaction
Metabolism and nutrition disorders	Common	Anorexia
Nervous system disorders	Common	Dizziness Headache Paraesthesia Dysgeusia
	Uncommon	Hypoaesthesia
Eye disorders	Common	Visual impairment
Ear and labyrinth disorders	Common	Deafness
	Uncommon	Hearing impaired Tinnitus
Cardiac disorders	Uncommon	Palpitations
Gastrointestinal disorders	Very common	Diarrhoea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools
Hepatobiliary disorders	Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash Pruritus
	Uncommon	Steven-Johnson syndrome Photosensitivity reaction
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Asthenia Malaise

Reporting of suspected adverse reactions: 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.

Symptoms

The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment

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) Pharmacodynamics properties

Pharmacotherapeutic group: Antibacterials for systemic use; Macrolids; Azithromycin

ATC code: J01FA10

Mode of action:

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

Cardiac electrophysiology:

Extension of the QTc interval was studied in a randomised, placebo-controlled parallel trial in 116 healthy subjects who received chloroquine (1 000 mg), alone or in combination with azithromycin (500 mg, 1 000 mg, and 1 500 mg once a day). Concomitant administration of azithromycin increased the QTc interval in a dose and concentration-dependent manner. Compared to chloroquine alone, the maximum average (95% upper confidence limit) increases in the QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the concomitant administration of 500 mg, 1 000 mg and 1 500 mg of azithromycin, respectively.

PK/PD relationship

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

Mechanism of resistance:

The two most frequently occurring mechanisms of resistance against macrolides, including azithromycin, are target modification (most often due to methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies by species and within a species, the frequency of resistance varies by geographical location.

The main ribosomal modification that determines the reduced binding of macrolides is posttranscriptional (N6)-dimethylation of adenine in nucleotide A2058 (E. coli numbering system) of the 23S rRNA encoded by methylases by erm (erythromycin ribosome methylase) genes. Ribosomal modifications often determine cross-resistance (MLSB phenotype) against other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin) and streptogramins B (including, for example, the quinupristin component of quinupristin/dalfopristin). Different erm genes are present in different bacterial species, in particular streptococci and staphylococci. Sensitivity to macrolides may also be affected by less frequently occurring mutational changes in the nucleotides A2058 and A2059 and in several other loci of 23S rRNA, or in the large subunit ribosomal proteins L4 and L22.

Efflux pumps occur in several types, including gram negatives, such as Haemophilus influenzae (where they can determine intrinsically higher MICs) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-pronged macrolides (including erythromycin and azithromycin respectively) is encoded by mef (A) genes

Breakpoints

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for Azithromycin and are listed here:

Antibacterial spectrum:

Azithromycin exhibits cross resistance with erythromycin-resistant Gram-positive isolates. As discussed above, several ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin) and streptogramins B (including, for example, the

quinupristin component of quinupristin/dalfopristin). A decrease in macrolide sensitivity over time has been noted in *Streptococcus pneumoniae* and *Staphylococcus aureus* and has also been observed in viridans streptococci and *Streptococcus agalactiae*.

Mycobacterium avium complex sensitivity:

The sensitivity methods and diagnostic procedures currently available in vitro to determine the MRC of *Mycobacterium avium* complex (MAC) organisms have not been generally accepted and validated.

Breaking points to show that clinically isolated strains of *M. avium* or *M. intracellulare* are sensitive to azithromycin have not yet been established.

Susceptibility:

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

Pathogens for which resistance may be a problem: prevalence of resistance is equal to or greater than 10% in at least one country in the European Union.

Table of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms
<i>Haemophilus influenzae</i> *
<i>Moraxella catarrhalis</i> *
Other microorganisms
<i>Chlamydia pneumoniae</i>
<i>Chlamydia trachomatis</i>
<i>Legionella pneumophila</i>
<i>Mycobacterium avium</i>
<i>Mycoplasma pneumoniae</i> *
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
<i>Staphylococcus aureus</i> *
<i>Streptococcus agalactiae</i>
<i>Streptococcus pneumoniae</i> *
<i>Streptococcus pyogenes</i> *
Other microorganisms
<i>Ureaplasma urealyticum</i>
Inherently resistant organisms
Aerobic Gram-positive microorganisms
<i>Staphylococcus aureus</i> – methicillin resistant and erythromycin resistant strains
<i>Streptococcus pneumoniae</i> – penicillin resistant strains
Aerobic Gram-negative microorganisms
<i>Escherichia coli</i>
<i>Pseudomonas aeruginosa</i>
<i>Klebsiella</i> spp.
Anaerobic Gram-negative microorganisms
<i>Bacteroides fragilis</i> group

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

Clinical trial data:

Patients receiving azithromycin in a placebo-controlled study had a one-year cumulative incidence of disseminated MAC disease of 8.24% compared to 20.22% in patients receiving placebo.

In a group of patients with a CD4 count $<10/\text{mm}^3$ combination therapy with another suitable medicine can be considered, as the benefits of the combination outweigh potential disadvantages.

In a comparative study, a lower risk of developing MAC bacteraemia was seen in patients treated with azithromycin than in patients treated with rifabutin. Patients treated with a combination of azithromycin and rifabutin were one-third less likely to develop a MAC bacteraemia than those treated with one of these medicines.

The one-year cumulative incidence of disseminated MAC disease was 7.62% with azithromycin, 15.25% with rifabutin and 2.75% with combination therapy of azithromycin and rifabutin. However, discontinuation in patients receiving combination therapy was greater due to poorer tolerance.

Studies on prophylaxis against MAC infections indicated that due to treatment with azithromycin, the occurrence of other bacterial infections were also reduced.

In clinical trials comparing the two doses of Streptococcal pharyngitis in children (a single dose of 10 mg/kg or 20 mg/kg for 3 days), the efficacy was similar, but bacterial eradication was higher at the 20 mg/kg/day dose.

Paediatric population

After the assessment of studies carried out in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin-based medicines, as the non-inferiority towards antimalarial medicines recommended in the treatment of uncomplicated malaria was not established.

5.2) Pharmacokinetics properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution

Azithromycin penetrates throughout the body. Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). The average maximum observed serum level (C_{max}) after a single dose of 500 mg is approximately 0.4 mg/mL, 2-3 hours after administration. No accumulation occurs in the serum at the recommended dosage. Accumulation occurs in the tissues where the levels are much higher than in the serum. Three days after administration of 500 mg as a single dose, or in divided 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 are found in the lung, prostate, tonsil and serum respectively. Average peak concentrations measured in peripheral leukocytes, where the MAC infection was active, were 140 $\mu\text{g/mL}$. The concentration remained above 32 $\mu\text{g/mL}$ for approximately 60 hours after a single oral administration of 1,200 mg. These concentrations are higher than the mrc_{90} of the most common pathogens.

In experimental in vitro and in vivo studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.

In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 52% in 0.095 mg/l to 182% in 0.5 mg/l.

Elimination

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination.

The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

Pharmacokinetics in special populations

Renal insufficiency

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 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.

Infants, toddlers, children and adolescents

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 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/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

In high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Mutagenic potential:

Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Reproductive toxicity:

No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6) PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Lauryl Sulphate, Dibasic Calcium Phospahte, Maize Starch, P.V.P.K 30 , Purified Talc, Magnesium Stearate, Sodium Lauryl Sulphate, Sodium Starch Glycolate, Croscarmellose Sodium, Methylene Chloride, H.PM.C.E 15CPS, Titanium Dioxide, Purified Talc, P.E.G 4000, Propylene Glycol, Isopropyl Alcohol, Color Tartrazine yellow Lake.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3years

6.4 Special precautions for storage

Store in a cool and dry place below 30°C

6.5 Nature and contents of container

Alu-Pvc Blister of 3 tablets (1X3's)

6.6 Special precautions for disposal

No special requirements.

7. Marketing Authorisation Holder

Harley's Limited
63 westlands road

Manufactured by

Medico Remedies Pvt Ltd
8 Dewan & Sons Udhyog Nagar,Palghar(West) Dist.Palghar Maharashtra -401404, India

8. Marketing Authorisation Number

H2007/383/R1

9. Date of First Authorisation/Renewal of the Authorisation

2026 July 14

10. Date of Revision of the Text

2026 July 14