

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clamelle ® 500mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Pale blue, oblong, biconvex film-coated tablets, with imprint PLIVA on one side and 500 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of confirmed asymptomatic *Chlamydia trachomatis* genital infection in individuals aged 16 years and over and the epidemiological treatment of their sexual partners.

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

4.2 Posology and method of administration

Posology

A single 1g (2 x 500mg tablets) dose.

Special populations

Renal impairment

No dose adjustment is required in patients with GFR \geq 10 ml/min. In patients with GFR <10 ml/min azithromycin should be administered with caution (see section 5.2).

Hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B) (see section 5.2). No data are available in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, azithromycin should be administered with caution in these patients (see section 4.4).

Elderly

No dose adjustment is required in elderly patients (see section 5.2). Since the elderly are more likely to experience proarrhythmic conditions, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes (see section 4.4).

Method of administration

For oral use.

Tablets should be swallowed whole as a single dose and may be taken with or without a meal. Administration immediately before a meal may enhance the gastrointestinal tolerability.

Other pharmaceutical forms are available that may be more appropriate to treat patients unable to swallow tablets as well as paediatric patients weighing less than 45 kg.

4.3 Contraindications

- Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1.
- Relative for Azithromycin sold as a Pharmacy Medicine.
- Symptomatic infection.
- Symptoms suggestive of other STIs e.g. any unusual genital or anal swellings or lesions.
- Children aged under 16 years.
- Individuals receiving terfenadine and disopyramide.
- Individuals receiving azithromycin for treatment of other infections.

4.4 Special warnings 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.

Severe skin and hypersensitivity reactions

Rare serious allergic reactions including angioedema and anaphylaxis (rarely fatal), severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with azithromycin treatment (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions. 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, azithromycin 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.

QT interval prolongation

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). 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 (see section 4.5)
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency
- Elderly patients: Elderly patients may be more susceptible to drug-associated effects on the QT interval

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. Hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have also been reported with azithromycin, some of which have resulted in death (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop azithromycin administration and to contact their physician if signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy develop. In such cases liver function tests/investigations should be performed immediately.

Clostridioides difficile associated diarrhoea (CDAD), pseudomembranous colitis CDAD and pseudomembranous colitis have been reported with azithromycin and may range in severity from mild diarrhoea to fatal colitis (see section 4.8). CDAD and pseudomembranous colitis must be considered in patients who present with diarrhoea during or subsequent to the administration of azithromycin. 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.

Vomiting: To reduce the risk of vomiting, advise the individual to take the dose before bed and at least 2hrs after food or drink. If vomiting occurs after taking the dose pharmacist advice should be sought.

Oral contraception

If vomiting or diarrhoea occurs whilst taking Clamelle 500mg tablets refer to the oral contraceptive's instructions for measures to minimise the risk of contraception failure.

Sexually transmitted infections

Neisseria gonorrhoeae is very likely to be resistant to macrolides, including the azalide azithromycin (see section 5.1). Therefore, azithromycin is not recommended for the treatment of uncomplicated gonorrhoea and pelvic inflammatory disease unless laboratory results have confirmed susceptibility of the organism to azithromycin. If left untreated or treated sub-optimally, this condition may lead to late onset complications such as infertility and ectopic pregnancy.

In addition, if single dose azithromycin is considered for the treatment of urethritis and cervicitis due to *N. gonorrhoeae* or *C. trachomatis* (see section 4.2), concomitant urogenital infection by *Mycoplasma genitalium* should be excluded due to the high risk of emergence of resistance in this organism.

Furthermore, a concomitant infection caused by *Treponema pallidum* should be excluded as symptoms of incubating syphilis could be masked delaying diagnosis.

For all patients with sexually transmitted urogenital infections, appropriate antibacterial therapy and microbiological follow-up tests should be initiated.

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).

Non-susceptible organisms

The use of azithromycin may result in the overgrowth of non-susceptible organisms. If superinfection occurs, interruption of treatment or other appropriate measures may be required.

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 may not be co-administered.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Antacids:

In individuals receiving azithromycin and antacids, azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

Nelfinavir:

Co-administration of 1200 mg azithromycin and steady state nelfinavir (750 mg 3 times daily) resulted in a mean decrease of AUC of 16% for nelfinavir, an increase of AUC of azithromycin of 113%, and an increase of C_{max} of 136%. Dose adjustment is not necessary, but the increased potential for known side-effects of azithromycin should be considered.

CYP3A4:

Although azithromycin is a weak CYP450 inhibitor and does not interact significantly with CYP450 substrates, CYP3A4 inhibition cannot be completely ruled out.

Therefore, caution is recommended in case of co-administration with CYP3A4 substrates with narrow therapeutic index.

Azithromycin is an inhibitor of the transporter P-glycoprotein (P-gp). Co-administration of azithromycin with P-gp substrates, such as digoxin and colchicine, may increase their exposure. For narrow therapeutic index drugs, caution and clinical and/or therapeutic drug monitoring and dose adjustment as appropriate are advised. The relatively long half-life of azithromycin should be taken into account in this context (see section 5.2).

Medicinal products that are known to prolong the QT interval

Azithromycin should be used with caution in patients receiving medicinal products known to prolong the QT interval (see section 4.4), such as antiarrhythmics of Classes IA (e.g. quinidine and procainamide) and III (e.g. dofetilide, amiodarone and sotalol), antipsychotic agents (e.g. pimozide), antidepressants (e.g. citalopram), fluoroquinolones (e.g. moxifloxacin and levofloxacin), cisapride, chloroquine and hydroxychloroquine.

Drug interaction information for azithromycin with potential concomitant medicinal products is summarised in the table and text below. The drug interactions described are based on clinical drug-drug interaction studies conducted with azithromycin or, where indicated, are potential drug interactions that may occur with azithromycin.

Table 2: Clinically relevant drug interactions between azithromycin and other medicinal products

Medicinal product (therapeutic area)	Interaction Effect on exposure	Mechanism	Recommendation concerning co-administration
Atorvastatin (HMG CoA reductase inhibitor) Azithromycin 500 mg orally once daily for 3 days. Atorvastatin 10 mg orally once daily.	Azithromycin: ND Atorvastatin: ↔ AUC ↔ C _{max}	Atorvastatin is a CYP3A4 and P-gp substrate.	Caution should be exercised since post-marketing cases of rhabdomyolysis in patients receiving azithromycin concomitantly with statins have been reported.
Ciclosporin (immunosuppressant) Azithromycin 500 mg orally once daily for 3 days. Ciclosporin 10 mg/kg	Azithromycin: ND Ciclosporin: ↔ AUC ↑C _{max} 24 %	Ciclosporin is a CYP3A4 and P-gp substrate with narrow therapeutic index and/or competition for biliary excretion.	Clinical monitoring and therapeutic drug monitoring as appropriate should be performed during and after treatment with azithromycin. Ciclosporin dose should be adjusted if required.

orally single dose.			
Colchicine (gout)	Azithromycin: ND Colchicine: ↑ 57% AUC _{0-t} ↑ 22% C _{max}	Colchicine is a P-gp substrate with narrow therapeutic index.	Clinical monitoring is needed during and after treatment with azithromycin.
Dabigatran (oral anticoagulant)	ND <i>Expected:</i> ↑ Dabigatran	Dabigatran is a P-gp substrate with narrow therapeutic index.	Caution should be exercised since post-marketing data suggest an increased risk for haemorrhages in patients receiving azithromycin concomitantly with dabigatran.
Digoxin (cardiac glycosides)	ND <i>Expected:</i> ↑ Digoxin	Digoxin is a P-gp substrate with narrow therapeutic index.	Clinical monitoring, and possibly digoxin level monitoring, is needed during and after treatment with azithromycin.
Warfarin (oral anticoagulant) Azithromycin 500 mg orally once daily for 1 day and then 250 mg orally once daily for 4 days. Warfarin 15 mg orally single dose.	Azithromycin: ND Warfarin: ND No change in prothrombin time in clinical drug interaction study but post-marketing reports of potentiated anticoagulation of coumarin-type oral anticoagulants upon co-administration with azithromycin.	Not known.	A higher frequency of prothrombin time monitoring should be considered during and after treatment with azithromycin.

Note: statistically significant changes by more than 10% are indicated as “↑” or “↓”, no change as “↔”, not determined as “ND”.

No clinically relevant change in the exposure of azithromycin or the co-administered medicinal products was observed in clinical studies evaluating potential drug-drug interactions of azithromycin with oral antacids (aluminium hydroxide/magnesium hydroxide), carbamazepine, cetirizine, cimetidine, efavirenz, fluconazole, methylprednisolone, midazolam, rifabutin, sildenafil, theophylline, triazolam, trimethoprim/sulfamethoxazole and zidovudine.

Paediatric population

Interaction studies have only been performed in adults.

Due to interaction, Clamelle 500mg tablets are contraindicated if individual is concomitantly taking any of the following medications (see also section 4.3):

Disopyramide:

Some of the related macrolide antibiotics have been reported to increase serum disopyramide levels, which can result in ventricular fibrillation.

Ergot derivatives:

Because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

Terfenadine:

There is a theoretical risk of serious dysrhythmias due to prolongation of QTc interval.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of teratogenic effects was found. There are, however, no adequate and well-controlled studies in pregnant women.

There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy (more than 7000 azithromycin exposed pregnancies). Most of these studies do not suggest an increased risk of adverse foetal effects such as major congenital malformations or cardiovascular malformations.,

Epidemiological evidence related to the risk of miscarriage following azithromycin exposure in early pregnancy is inconclusive. Animal studies do not indicate reproductive toxicity (see section 5.3).

Azithromycin should only be used during pregnancy if clinically needed.

Breast-feeding

Azithromycin is excreted in human milk to substantial extent. No serious adverse effects of azithromycin on the breast-fed infants were observed, while effects such as diarrhoea, mucosal fungal infection as well as hypersensitivity can occur in breast-fed newborns/infants even at sub-therapeutic doses. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machines

Azithromycin has a moderate influence on the ability to drive and use machines. Dizziness, drowsiness and convulsions have been reported in some patients taking azithromycin and some patients experienced visual and/or auditory impairment. This should be considered when assessing a patient's ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions during treatment include diarrhoea, headache, vomiting, abdominal pain, nausea and abnormal laboratory test values. Other important adverse reactions include anaphylactic reactions, torsade de pointes, arrhythmia including ventricular tachycardia, pseudomembranous colitis and hepatic failure (see section 4.4). Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with azithromycin treatment (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions identified through clinical trial experience and post marketing surveillance are listed below, by system organ class and frequency.

Frequencies of adverse reaction occurrence 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). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Tabulated list of adverse reactions

System Organ Class	Very Common	Common	Uncommon	Rare	Unknown
	$> 1/10$	$\geq 1/100$ to $< 1/10$	$\geq 1/1,000$ to $< 1/100$	$\geq 1/10,000$ to $< 1/1,000$	
Infections and infestations			Candidia infection Oral candidiasis Vaginal infection Pneumonia, Fungal infection Bacterial infection Pharyngitis Gastroenteritis Rhinitis.		
Blood and lymphatic system disorders		Lymphocyte count decreased Eosinophil count increased Basophil count increased Monocyte count increased Neutrophil count	Leukopenia, Neutropenia, Eosinophilia Platelet count increased Haematocrit decreased		Thrombocyto penia, Haemolytic anaemia

System Organ Class	Very Common	Common	Uncommon	Rare	Unknown
	> 1/10	$\geq 1/100$ to < 1/10	$\geq 1/1,000$ to < 1/100	$\geq 1/10,000$ to < 1/1,000	
		increased			
Immune system disorders			Angioedema, Hypersensitivity (see section 4.4)		Anaphylactic reaction
Metabolism and nutrition disorder		Anorexia	Decreased appetite		
Psychiatric disorders			Nervousness, Insomnia	Agitation	Aggression Anxiety Delirium Hallucination
Nervous system disorders		Headache	Dizziness Dysgeusia Paraesthesia Somnolence		Syncope Psychomotor hyperactivity Anosmia Ageusia Hypoesthesia Parosmia Myasthenia gravis (see section 4.4) Seizure
Eye disorders			Visual impairment		
Ear and labyrinth disorders			Ear disorder Vertigo		Deafness Hypoacusis Tinnitus
Cardiac disorders			Palpitations		Torsades de pointes (see section 4.4) Arrhythmia including ventricular tachycardia (see section 4.4) Electrocardiogram QT prolonged (see section 4.4)
Vascular disorders			Hot flush		Hypotension
Respiratory, thoracic and mediastinal disorders			Dyspnoea Respiratory disorder Epistaxis		

System Organ Class	Very Common	Common	Uncommon	Rare	Unknown
	> 1/10	≥ 1/100 to < 1/10	≥ 1/1,000 to < 1/100	≥ 1/10,000 to < 1/1,000	
Gastrointestinal disorders	Diarrhoea	Vomiting Abdominal pain Nausea	Constipation Gastritis Dyspepsia Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion Flatulence		Pancreatitis Pseudomembranous colitis (see section 4.4) Tongue discolouration
Hepatobiliary disorders			Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood alkaline phosphatase increase	Hepatic function abnormal Jaundice cholestatic	Hepatic failure (see section 4.4) Hepatitis fulminant Hepatic necrosis,
Skin and subcutaneous tissue disorders			Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Acute generalised exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS) Photosensitivity reaction	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme
Musculoskeletal and connective tissue disorders			Osteoarthritis Myalgia Back pain Neck pain		Arthralgia
Renal and urinary disorders			Dysuria Renal pain Blood urea		Acute kidney injury

System Organ Class	Very Common	Common	Uncommon	Rare	Unknown
	> 1/10	$\geq 1/100$ to < 1/10	$\geq 1/1,000$ to < 1/100	$\geq 1/10,000$ to < 1/1,000	
			increased Blood creatinine increased		Tubulointerstitial nephritis
Reproductive system and breast disorders			Intermenstrual bleeding Testicular disorder		
General disorders and administration site conditions			Oedema Face oedema Chest pain Pyrexia Pain Peripheral oedema Malaise Fatigue Asthenia		
Investigations		Blood bicarbonate decreased	Blood potassium abnormal Blood chloride increased Blood glucose increased Blood bicarbonate increased Blood sodium abnormal		
Injury, poisoning and procedural complications			Post procedural complications		

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 the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for **MHRA Yellow Card** in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses (see section 4.8). The typical symptoms of an overdose with azithromycin include gastrointestinal symptoms, i.e. vomiting, diarrhoea, abdominal pain and nausea.

Treatment

In the event of overdose, general symptomatic treatment and support of vital functions are indicated and, if required, administration of medicinal charcoal or gastric lavage.

There are no data on the effects of dialysis on the elimination of azithromycin. However, due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use.

ATC code: J01FA10

Mechanism of Action:

The mechanism of action of azithromycin is based on the inhibition of the bacterial protein synthesis by binding to the ribosomal 50 S subunit and inhibiting translocation of the peptides.

Pharmacokinetic/pharmacodynamic relation

The efficacy depends mainly on the ratio between AUC (area under the curve) and MIC (minimum inhibitory concentration) of the causative organism.

Mechanism of resistance:

Resistance against azithromycin can be based on the following mechanisms:

- Efflux: Resistance can be caused by an increase in the number of efflux pumps in the cytoplasmic membrane. Only 14- and 15-ring-membered macrolides are concerned (so called M-phenotype).
- Change of target structure: Affinity to ribosomal binding sites is lowered by methylation of the 23S rRNA causing a resistance against macrolides (M), lincosamides (L) and streptogramins of the B-group (SB) (so called MLSB-phenotype). Resistance-conferring methylases are encoded by *erm* genes. Affinity to ribosomal binding sites is also lowered by mutations in the 23S rRNA target structure or by mutations in the large subunit ribosomal proteins.
- Enzymatic inactivation of macrolides is only of minor clinical interest.

With the M-phenotype a complete cross-resistance between azithromycin, clarithromycin, erythromycin and roxithromycin is observed. The MLSB-phenotype shows an additional cross-resistance with clindamycin and streptogramin B. With the 16-ring-membered macrolide spiramycin a partial cross-resistance is exerted.

Due to low permeability of the outer membrane, most Gram-negative species are inherently resistant to macrolides.

Susceptibility testing interpretive criteria

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:

https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Prevalence of acquired resistance

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. Particularly in the case of severe infections or therapeutic failure, a microbiological diagnosis with identification of the pathogen and determination of its susceptibility to azithromycin should be sought.

Table 4: Prevalence of acquired resistance

Commonly susceptible species
<i>Other microorganisms</i>
<i>Chlamydia trachomatis</i> ^o

^oNo updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.

5.2 Pharmacokinetic properties

Absorption

The peak serum concentrations (C_{max}) of azithromycin after 500 mg oral suspension (40 mg/ml), 1000 mg powder for oral suspension, 500 mg (2 x 250 mg) tablets and 1000 mg (4 x 250 mg) capsules in healthy volunteers under fasted conditions were 0.29, 0.75, 0.34, and 1.07 mg/L respectively. The time-to-peak plasma (T_{max}) concentrations of azithromycin after oral administration ranges from 2 to 3 hours. The mean absolute bioavailability in healthy volunteers after 500 mg oral suspension and 1000 mg powder for oral suspension in sachet was 37% and 44% in fasted conditions, respectively.

The effect of food on the relative oral bioavailability of azithromycin is formulation dependent. After the administration of 500 mg of an oral suspension (40 mg/ml), 1000 mg as powder for oral suspension and 500 mg oral dose of azithromycin tablets (2 x 250 mg), similar exposure was obtained with high-fat meal vs fasted conditions. Following the administration of a single dose of 500 mg (2 x 250 mg) capsule formulation with a high-fat meal vs fasted conditions, the mean ratio of C_{max} and AUC_{0-24} was 52% and 43% lower.

Table 5 shows mean (SD) pharmacokinetic parameters in adult healthy volunteers after standard dosing regimens with tablets and capsules.

Table 5: AUC_{0-24} and C_{max} of azithromycin for the 3-day and 5-day regimen at last day of dosing

Dose regimen, formulation	AUC_{0-24} ($\mu\text{g}\cdot\text{h/ml}$)	C_{max} ($\mu\text{g/ml}$)
3-day regimen (500 mg daily), tablet	1.88 (0.96)	0.42 (0.21)

5-day regimen (500 mg D1, 250 mg D2 to D5), tablet	0.80 (0.42)	0.18 (0.10)
5-day regimen (500 mg D1, 250 mg D2 to D5), capsule	2.1 (0.6)	0.24 (0.08)

Distribution

Azithromycin is widely and rapidly distributed from plasma to the extravascular compartment, including tissues such as tonsil, lung and gynaecological tissues as well as the intracellular compartment, in particular to polymorphonuclear leukocytes, macrophages, and monocytes. Pharmacokinetic studies have shown considerably higher azithromycin concentrations in certain tissues (up to 50 times the maximum concentration observed in the plasma). This indicates an extensive binding to these tissues with a steady-state volume of distribution ranging from 23 to 31 L/kg. The redistribution phase from the intracellular to the extracellular compartment and to the plasma may result in prolonged low concentrations after treatment cessation.

Azithromycin shows low plasma protein binding, mainly to alpha 1-acid glycoprotein, and it decreases with increasing concentrations of antibiotic: 50%, 23% and 7% protein binding at concentrations of 0.05, 0.1 and 1 mg/L, respectively.

Biotransformation

Azithromycin is minimally metabolised in the liver. The primary route of biotransformation is N-demethylation of the desosamine sugar. Other pathways include O-demethylation, hydrolysis of cladinose (deconjugation of the cladinose sugar), and hydroxylation of desosamine sugar and macrolide ring.

There is no evidence of clinically relevant hepatic cytochrome CYP 3A4 induction or inhibition via the formation of a cytochrome-metabolite complex. Also, auto-induced metabolism of azithromycin by this pathway has not been detected.

Elimination

Azithromycin is mainly eliminated by (active) biliary excretion mostly as unchanged drug, but also as metabolites which are devoid of antibacterial activity. Urinary excretion represents a minor route of elimination with less than 6% of an oral dose and around 20% of the drug that reaches the systemic circulation excreted in urine. More than 50% of faecal, and 12% or urinary excretion is in the form of unchanged compound.

Following the administration of a single 500 mg azithromycin dose, a plasma clearance of 630 ml/min was estimated with a terminal half-life of approximately 68 hours. Renal clearance is generally in the range of 100-189 ml/min, substantially smaller than plasma clearance as expected due to the relatively poor contribution of the renal route to elimination.

Linearity/non-linearity

Following oral administration of an immediate release formulation, dose proportionality on AUC_{0-24} and C_{max} was shown in the range of 250 mg to 1000 mg.

Special populations

Renal Impairment

Azithromycin pharmacokinetics was investigated in 43 adults (21 to 85 years of age) following the oral administration of a single 1.0 g dose of azithromycin (4 x 250 mg

capsules) to subjects with GFR >80 ml/min (n =12), subjects with GFR between 10 and 80 ml/min (n = 12) and subjects with GFR <10 ml/min (n = 19).

The pharmacokinetics of azithromycin in subjects with GFR between 10 and 80 ml/min were not affected (mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2%, respectively compared to subjects with GFR >80 ml/min). The mean C_{max} and AUC_{0-120} increased 61% and 35%, respectively, in subjects with GFR <10 ml compared to subjects with GFR >80 ml/min.

No data are available for subjects undergoing dialysis, but due to the elimination mechanism of azithromycin, dialysis is unlikely to result in significant removal of the active substance.

Hepatic Impairment

Azithromycin pharmacokinetics was investigated in 22 adults following the oral administration of a single 500 mg dose of azithromycin (2 x 250 mg capsules) to subjects with normal hepatic function (n = 6), Child-Pugh A (n = 10) and Child-Pugh B (n = 6). The pharmacokinetics of azithromycin in subjects with Child-Pugh A and B were 3% and 19% lower on AUC_{0-inf} and 34% and 72% higher on C_{max} , respectively, compared to subjects with normal hepatic function.

Elderly

In elderly volunteers (> 65 years) given azithromycin 500 mg (2 x 250 mg capsules) on day 1 followed by 250 mg from days 2 to 5 in the fasted state the AUC_{0-24} on Days 1 and 5 were 3.0 and 2.7 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively. A 29% higher AUC_{0-24} , a 8% higher C_{max} and a 37.5% higher T_{max} than in younger volunteers (<40 years) were observed at day 5. Since these differences are not considered clinically significant, no dose adjustment is required for elderly subjects with normal renal and hepatic function.

Paediatric population

The pharmacokinetics of azithromycin oral suspension have been characterised in 14 children aged 6 to 15 years with pharyngitis and in 7 children aged 1 year to 5 years with otitis media. In these two studies, azithromycin oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5. Following 5 days of treatment, mean AUC_{0-24} values were 3.1 $\mu\text{g}\cdot\text{h}/\text{ml}$ and 1.8 $\mu\text{g}\cdot\text{h}/\text{ml}$, respectively. The mean C_{max} value was 0.38 $\mu\text{g}/\text{ml}$ and the corresponding mean T_{max} value was 2.4 hours in children aged 6 to 15 years and 0.22 $\mu\text{g}/\text{ml}$ and 1.9 hours for children 1 to 5 years of age. The mean C_{max} and AUC_{0-24} values are 1.7 times greater in children 6 to 15 years of age than in children 1 to 4 years of age.

The PK of a 3-day course of azithromycin oral suspension at a dose of 10 mg/kg daily was also assessed in 16 children 6 months to 10 years with bacterial infections. The mean AUC_{0-24} for 7 children aged 2 to 4 years was 2.90 $\mu\text{g}\cdot\text{h}/\text{ml}$ while for the 8 children aged 5 to 10 years the value was 2.08 $\mu\text{g}\cdot\text{h}/\text{ml}$. A low AUC_{0-24} value of 0.74 $\mu\text{g}\cdot\text{h}/\text{ml}$ was recorded for a single child in the 6 months to 2-year-old group. Single dose pharmacokinetics of azithromycin in paediatric patients with given doses of 30 mg/kg have not been studied.

5.3 Preclinical safety data

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity did not indicate adverse reactions clearly relevant to humans not already considered in other sections of the SmPC.

However, phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues 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 this finding for humans is in general unknown.

In animal studies for embryotoxic effects performed up to moderately maternal toxic doses (2 to 3 times the maximum recommended adult daily dose of (500 mg based on body surface area), no teratogenic effect was observed in mice and rats. Azithromycin was shown to cross the placenta. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day (2 to 3 times the maximum recommended adult daily dose of 500 mg based on body surface area) led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with azithromycin doses of 200 mg/kg/day (3 times the maximum recommended adult daily dose of 500 mg based on body surface area) was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Calcium hydrogen phosphate
Hypromellose
Maize starch
Pregelatinised starch
Microcrystalline cellulose
Sodium laurylsulfate
Magnesium stearate

Film-coating:

Hypromellose
Colour Indigotin (E132)
Titanium dioxide (E171)
Polysorbate 80
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25 °C in a dry place, in original packaging.

6.5 Nature and contents of container

Blisters (PVC/Al foil) packed in a carton box containing 2 tablets.

6.6 Special precautions for disposal

There are no special instructions for disposal.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Limited
Sage House
319 Pinner Road
North Harrow
Middlesex
HA1 4HF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20075/0554

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/2024

10 DATE OF REVISION OF THE TEXT

07/05/2026