

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azithromycin 250 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Azithromycin 250 mg Film-coated Tablets contain 250 mg azithromycin (as dihydrate).

Excipients with known effect:

Each tablet contains 60 mg lactose anhydrous

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

White to off-white oval, 6.7 x 13.5 mm, biconvex film-coated tablets marked "250" on one side and plain on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Azithromycin is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin (see sections 4.4 and 5.1):

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

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

4.2 Posology and method of administration

Posology

Azithromycin should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below.

Adults, Children and adolescents with a body weight above 45 kg, adults and the elderly:

The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5.

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

Children and adolescents with a body weight below 45 kg:

Azithromycin tablets are not suitable for patients under 45 kg body weight. Other dosage forms are available for this group of patients.

Elderly patients

For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes (see section 4.4).

Patients with renal impairment:

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min) (see section 4.4).

Patients with hepatic impairment:

Dose adjustment is not required for patients with mild to moderate hepatic dysfunction (see section 4.4).

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

Method of administration

The tablets can be taken with or without food.

The tablets should be taken with ½ glass of water.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity

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

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

Hepatotoxicity

Since 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.

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.

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 serious liver dysfunction has emerged.

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered (see section 4.5).

Superinfection

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

Clostridium difficile-associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

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 antibacterial agents.

Renal impairment

In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Prolongation of the QT interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides, including azithromycin (see section 4.8). The following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest (possibly fatal). Azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of Class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin.
- 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.

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

Streptococcal infections

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

Paediatric population

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

The following should be considered before prescribing azithromycin:

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

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

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

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

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

Skin and soft tissue infections

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

Infected burn wounds

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

Sexually transmitted disease

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

Neurological or psychiatric diseases

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

*Excipients**Lactose*

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

Sodium

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

4.5 Interaction with other medicinal products and other forms of interactions**Antacids**

When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma fell by 24%. In patients receiving Azithromycin and antacids, Azithromycin should be taken at least 1 hour before or 2 hours after the antacid. Co- administration of azithromycin prolonged - release granules for oral suspension with a single dose of 20ml co - magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Cetirizine

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

Didanosine (Dideoxyinosine)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine (P-glycoprotein 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 substrates should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Zidovudine

Single 1000 mg doses and multiple doses of 600 mg or 1200 mg azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergot derivatives

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

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolide antibiotic erythromycin.

Atorvastatin

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.

Cimetidine

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

Coumarin-Type Oral Anticoagulants:

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

Cyclosporin

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

Efavirenz

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

Fluconazole

Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in 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.

Nelfinavir

Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.

Rifabutin

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

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (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, 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.

Hydroxychloroquine and chloroquine:

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.

4.6 Fertility, pregnancy and lactationPregnancy

There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed (see section 5.3). The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore Azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery. However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

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. 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 ($< 1/10,000$); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

very common $\geq 1/10$	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 frequency cannot be estimated from available data
Infections and infestations					
		Candidiasis, oral candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorders, rhinitis			Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders					
		Leukopenia, neutropenia, eosinophilia			Thrombocytopenia, haemolytic anaemia
Immune system disorders					
		Angioedema, hypersensitivity			Anaphylactic reaction (see section 4.4.)
Metabolism and nutrition disorders					
	Anorexia				
Psychiatric disorders					
		Nervousness, insomnia	Agitation, depersonalisation		Aggression, anxiety, delirium hallucination
Nervous system disorders					
	Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia, somnolence			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis, hypoesthesia (see section 4.4)
Eye disorders					
	Visual				

	impairment				
Ear and labyrinth disorders					
	Deafness	Ear disorder, hearing impaired, tinnitus, vertigo			
Cardiac disorders					
		Palpitations			Torsades de pointes (see section 4.4), arrhythmia (see section 4.4) including ventricular tachycardia. Electrodiogram QT prolonged (see section 4.4)
Vascular disorders					
		Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders					
		Dyspnoea, epistaxis			
Gastrointestinal disorders					
Diarrhoea, abdominal pain, nausea, flatulence	Vomiting, dyspepsia	Gastritis, constipation, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion			Pancreatitis, tongue and teeth discoloration
Hepatobiliary disorders					
		Hepatitis	Hepatic function abnormal, jaundice cholestatic		Hepatic failure (which has rarely resulted in death) (see section 4.4), hepatitis fulminant, hepatic necrosis
Skin and subcutaneous tissue disorders					
	Rash, pruritis	Stevens-Johnson syndrome, photosensitivity reaction, urticaria, dermatitis, dry skin, hyperhidrosis	Allergic reactions including angioneurotic oedema, Acute generalised exanthematous pustulosis (AGEP)		Toxic epidermal necrolysis, erythema multiforme DRESS (Drug reaction with eosinophilia and systemic symptoms)
Musculoskeletal and connective tissue disorders					
	Arthralgia	Osteoarthritis, myalgia, back pain, neck pain			

Renal and urinary disorders					
		Dysuria, renal pain	Renal failure acute, nephritis interstitial		
Reproductive system and breast disorders					
		Metrorrhagia, testicular disorders			
General disorders and administration site conditions					
	Fatigue	Chest pain, face oedema, pyrexia, peripheral pain, oedema, malaise, asthenia			
Investigations					
	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophils increased, monocytes increased, neutrophils increased	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal, blood alkaline phosphatase increased, chloride increased, glucose increased, platelets increased, hematocrit decreased, bicarbonate increased, abnormal sodium			
Injury and poisoning					
		Post procedural complications			

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	Adverse reaction	Frequency
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Metabolism and Nutrition Disorders	Anorexia	Common
Nervous System Disorders	Dizziness, headache, paraesthesia, dysgeusia	Common
	Hypoesthesia	Uncommon
Eye Disorders	Visual impairment	Common
Ear and Labyrinth Disorders	Deafness	Common
	Hearing impaired, tinnitus	Uncommon
Cardiac Disorders	Palpitations	Uncommon
Gastrointestinal Disorders	Diarrhoea, abdominal pain, nausea, flatulence, abdominal discomfort, loose stools	Very common
Hepatobiliary Disorders	Hepatitis	Uncommon
Skin and Subcutaneous Tissue Disorders	Rash, pruritus	Common
	Steven-Johnson syndrome, photosensitivity reaction	Uncommon
Musculoskeletal and Connective Tissue Disorders	Arthralgia	Common
General Disorders and Administration Site Conditions	Fatigue	Common
	Asthenia, malaise	Uncommon

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

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, general symptomatic and supportive measures are indicated as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Azithromycin is a macrolide antibiotic belonging to the azalide group.

The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0.

Mechanism of action

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

Pharmacokinetic/pharmacodynamics relationship

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

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). Co-administration 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.

Mechanism of resistance

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

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N 6)-dimethylation of adenine at nucleotide A2058 (Escherichia coli numbering system) of the 23S rRNA by methylases encoded by erm (erythromycin ribosome methylase) genes. Ribosomal modifications often determine cross resistance (MLS^B phenotype)

to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different erm genes are present in different bacterial species, in particular streptococci and staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA, or in the large subunit ribosomal proteins L4 and L22.

Efflux pumps occur in a number of species, including Gram-negatives, such as Haemophilus influenzae (where they may determine intrinsically higher minimal inhibitory concentrations [MICs]) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by mef (A) genes.

Methodology for determining the in vitro susceptibility of bacteria to azithromycin

Susceptibility testing should be conducted using standardized laboratory methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (MIC determination) and disk susceptibility methods. Both CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretive criteria for these methods.

Based on a number of studies, it is recommended that the in vitro activity of azithromycin be tested in ambient air, to ensure physiological pH of the growth medium. Elevated CO₂ tensions, as often used for streptococci and anaerobes, and occasionally for other species, result in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides.

The CLSI susceptibility breakpoints, based on broth microdilution or agar dilution testing, with incubation in ambient air, are given in the table below.

CLSI Dilution Susceptibility Interpretive Criteria			
	Broth microdilution MIC (mg/L)		
	Susceptible	Intermediate	Resistant
Organism			
CLSI dilution susceptibility interpretive criteria			
	Broth microdilution MIC (mg/L)		
Organism	Susceptible	Intermediate	Resistant
<i>Haemophilus</i> species	≤4	-	≥ ^b
<i>Moraxella catarrhalis</i>	≤0.25	-	-
<i>Neisseria meningitidis</i>	≤2	-	≥ ^b
<i>Staphylococcus aureus</i>	≤2	4	≥8
<i>Streptococci</i> ^a	≤0.5	1	≥2
^a Includes Streptococcus pneumoniae, b-hemolytic streptococci and viridans streptococci. ^b The current absence of data on resistant strains precludes defining any category other than susceptible. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing. Incubation in ambient air. CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal			

inhibitory concentration. Source: CLSI, 2012; CLSI, 2010			

Susceptibility can also be determined by the disk diffusion method, measuring inhibition zone diameters after incubation in ambient air. Susceptibility disks contain 15 micrograms of azithromycin. Interpretive criteria for inhibition zones, established by the CLSI on the basis of their correlation with MIC susceptibility categories, are listed in the table below.

CLSI Disk Zone Interpretive Criteria			
	Disk inhibition zone diameter (mm)		
Organism	Susceptible	Intermediate	Resistant
<i>Haemophilus</i> species	≥12	-	-
<i>Moraxella catarrhalis</i>	≥26	-	-
<i>Neisseria meningitidis</i>	≥20	-	-
<i>Staphylococcus aureus</i>	≥18	14- 17	£ 13
<i>Streptococci</i> ^a	≥18	14- 17	£ 13
^a Includes <i>Streptococcus pneumoniae</i> , b-hemolytic streptococci and viridans streptococci. Incubation in ambient air. CLSI = Clinical and Laboratory Standards Institute; mm = Millimeters. Source: CLSI, 2012; CLSI, 2010			

The validity of both the dilution and disk diffusion test methods should be verified using quality control (QC) strains, as indicated by the CLSI. Acceptable limits when testing azithromycin against these organisms are listed in the table below.

Quality Control Ranges for Azithromycin Susceptibility Tests (CLSI)	
Broth microdilution MIC	
Organism	Quality control range (mg/L azithromycin)
<i>Haemophilus influenza</i> ATCC 49247	1 - 4
<i>Staphylococcus aureus</i> ATCC 29213	0.5 - 2
<i>Streptococcus pneumoniae</i> ATCC 49619	0.06 - 0.25
Disk inhibition zone diameter (15 microgram disk)	
Organism	Quality control range (mm)
<i>Haemophilus influenza</i> ATCC 49247	13 - 21
<i>Staphylococcus aureus</i> ATCC 29213	21 - 26
<i>Streptococcus pneumoniae</i> ATCC 49619	19 - 25
Quality control ranges for azithromycin susceptibility tests (CLSI)	
Broth microdilution MIC	
Organism	Quality control range (mg/L azithromycin)
Incubation in ambient air. CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration; mm = Millimeters. Source: CLSI, 2012.	

The EUCAST (European Committee on Antimicrobial Susceptibility Testing) has also established susceptibility breakpoints for azithromycin based on MIC determination. The EUCAST susceptibility criteria are listed in the table below.

EUCAST Susceptibility Breakpoints for Azithromycin		
	MIC breakpoint (mg/L)	
Pathogens	Susceptible (mg/L)	Resistant (mg/L)
<i>Staphylococcus</i> spp.	≤ 1	> 2
<i>Streptococcus</i> spp. (Group A, B, C, G)	≤ 0.25	> 0.5
<i>Streptococcus pneumoniae</i>	≤ 0.25	> 0.5
<i>Haemophilus influenzae</i>	≤ 0.125	> 4

<i>Moraxella catarrhalis</i>	≤ 0.25	> 0.5
<i>Neisseria gonorrhoeae</i>	≤ 0.25	> 0.5
Includes Groups A, B, C, G. EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = Minimal inhibitory concentration. Source: EUCAST Website. EUCAST Clinical Breakpoint Table v. 2.0, valid from 2012-01-01 www.eucast.org/.../EUCAST.../Breakpoint_table_v_2.0_120221.pdf		

Antibacterial Spectrum

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.

Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive isolates. As discussed above, some ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramins B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in viridans streptococci and *Streptococcus agalactiae*.

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible isolates): *S. aureus*, *Streptococcus agalactiae**, *S. pneumoniae**, *Streptococcus pyogenes**, other b-hemolytic streptococci (Groups C, F, G), and *viridans streptococci*. Macrolide-resistant isolates are encountered relatively frequently among aerobic and facultative Gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP).

Aerobic and facultative Gram-negative bacteria: *Bordetella pertussis*, *Campylobacter jejuni*, *Haemophilus ducreyi**, *Haemophilus influenzae**, *Haemophilus parainfluenzae**, *Legionella pneumophila*, *Moraxella catarrhalis**, and *Neisseria gonorrhoeae**. *Pseudomonas* spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* infections.

Anaerobes: *Clostridium perfringens*, *Peptostreptococcus* spp. and *Prevotella bivia*.

Other bacterial species: *Borrelia burgdorferi*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae**, *Mycoplasma pneumoniae**, *Treponema pallidum*, and *Ureaplasma urealyticum*.

Opportunistic pathogens associated with HIV infection: MAC* and the eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.

*The efficacy of azithromycin against the indicated species has been demonstrated in clinical trials.

Paediatric population

Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

5.2 Pharmacokinetic properties

Absorption

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

Distribution

Orally administered azithromycin is widely distributed throughout the body.

Pharmacokinetic studies have demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (up to 50 times the maximum observed concentration in plasma) than those measured in plasma. This indicates that the agent strongly binds to tissues (steady-state distribution volume approx. 31 l/kg).

At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial 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 have been measured in resp. lung, prostate, tonsil and serum.

In experimental *in vitro* and *in vivo* studies azithromycin accumulates in phagocytes. Release is stimulated by active phagocytosis. In animal models this process contributes to the accumulation of azithromycin in tissue. Binding of azithromycin to serum proteins is variable and varies from 52% at 0,05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration.

Elimination

The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

Approximately 12% of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile. Ten metabolites have been identified (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggest that the metabolites do not play a role in the microbiological activity of azithromycin.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

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 35% respectively compared to normal.

Hepatic insufficiency

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

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred. In elderly volunteers (> 65 years) higher (29%) AUC values have been measured after a 5 day treatment than in younger volunteers (< 45 years). These differences are not regarded as clinically relevant; dose adjustment is therefore not recommended.

Infants, toddlers, children and adolescents

Pharmacokinetics has 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 in adults, with 224 µg/l in children aged 0.6-5 years and after 3 days dosing, and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Carcinogenic potential

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

Mutagenic potential

There was no evidence of a potential for genetic and chromosome mutations in *in-vivo* and *in-vitro* test models.

Reproductive toxicity

Teratogenic effects were not observed in rat reproductive toxicity studies. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Croscarmellose sodium (E468)
Magnesium stearate (E572)
Microcrystalline cellulose (E460)
Silicon dioxide (E551)
Poloxamer
Povidone (E1201)
Talc
lactose

Coating:

Hypromellose (E464)
Hydroxypropylcellulose
Macrogol
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

PVC/Alu blisters: Do not store above 25°C. Store in the original packaging to protect from moisture.
OPA-PVC-Alu/Alu blisters: This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Alu blister with 4 or 6 tablets of 250 mg.
OPA-PVC-Alu/Alu blister with 4 or 6 tablets of 250 mg

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Not Applicable

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/142/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 16th November 2012
Date of Last Renewal: 5th July 2017

10 DATE OF REVISION OF THE TEXT

May 2022