SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Azithromycin 500mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, oval shaped film-coated tablets debossed with '5' and breakline on one side and plain on the other side.

The tablet dimensions are 17mm x 8.5 mm.

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

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) In adults and children weighing at least 45kg:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, acute streptococcal tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia (CAP)
- Acute bacterial skin and skin structure infections (ABSSSI)
- Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas.
- Uncomplicated Chlamydia trachomatis urethritis and cervicitis.
- Chronic prostatitis caused by Chlamydia trachomatis
- Erythema migrans (early localised Lyme disease)
- Periodontal abscesses and periodontitis
- Urethritis and cervicitis caused by *Chlamydia trachomatis*

- Urethritis and cervicitis caused by Neisseria gonorrhoeae, in combination with another appropriate
  antibacterial agent (e.g. ceftriaxone)
- Chancroid
- Disseminated Mycobacterium avium complex (DMAC) infection in people living with advanced HIV infection, in combination with ethambutol.
- The prophylaxis of Mycobacterium avium complex (MAC) infection in people living with HIV with inadequate immune restoration.
- The treatment of adult patients with acute exacerbation of chronic bronchitis or with pelvic inflammatory disease, the latter always in combination with other appropriate antibacterial agent(s) (e.g. metronidazole).

Azithromycin is also indicated for the prophylaxis of Mycobacterium avium complex (MAC) infection in people living with HIV with inadequate immune restoration.

Azithromycin is indicated for the treatment of adult patients with acute exacerbation of chronic bronchitis or with pelvic inflammatory disease, the latter always in combination with other appropriate antibacterial agent(s) (e.g. metronidazole).

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

4.2 Posology and method of administration

For oral use.

Posology:

Adults, elderly, children and adolescents over 45 kg body weight:

Azithromycin tablets should be given as a single daily dose. The duration of treatment in each of the infectious diseases is given below.

Method of Administration

For oral use.

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

The tablets should be taken with ½ glass of water.

Table 1: Dosing recommendations for adults and adolescents weighing at least 45 kg

Indication	Azithromycin dosing regimen

Acute streptococcal tonsillitis and pharyngitis Acute bacterial sinusitis Acute bacterial otitis media Acute exacerbation of chronic bronchitis* Community-acquired pneumonia[#] Acute bacterial skin and skin structure infections Periodontal abscesses and periodontitis	500 mg/day for 3 days or 500 mg on day 1, followed by 250 mg/day on days 2-5
Erythema migrans (early localised Lyme disease)	1000 mg on day 1, followed by 500 mg/day on days 2-10
Urethritis and cervicitis caused by Chlamydia trachomatis	1000 mg as a single dose
Urethritis and cervicitis caused by Neisseria gonorrhoeae, in combination with another appropriate antibacterial agent (e.g. ceftriaxone)	1000 mg or 2000 mg* as a single dose
Pelvic inflammatory disease, in combination with other appropriate agent(s) (e.g. metronidazole)[*+]	Only as an oral switch after intravenous administration if clinically indicated: 250 mg once daily to complete a 7- day course of treatment
Chronic prostatitis caused by Chlamydia trachomatis	500 mg/day on 3 consecutive days per week for 3 weeks (total dose: 4500 mg)
Chancroid	1000 mg as a single dose
Treatment of disseminated *Mycobacterium avium* complex (DMAC) infection in people living with advanced HIV infection (in combination with ethambutol)	<500 mg> or <600 mg> once daily
Prophylaxis of Mycobacterium avium complex (MAC) infections in people living with HIV with inadequate immune restoration	<1200 mg> or <1250 mg> once a week
* for treatment of adults only # in adults, oral treatment may also follow intravenous treatment, if clinically indicated to complete a 7- to 10-day total course of treatment (for details refer to the Summary of Product Characteristics of azithromycin IV formulations). + oral azithromycin should not be used for the initial treatment of pelvic inflammatory disease (for details refer to the Summary of Product Characteristics of azithromycin IV formulations). Consideration should be given to the treatment regimens, doses and duration of treatment as recommended in updated treatment guidelines for each indication.	

Missed dose

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

If more than 12 hours have passed since the time the dose is usually taken, the patient should be advised to wait until the next scheduled dose.

Special Populations

Children and adolescents 45 kg and under body weight:

Azithromycin tablets are not suitable for these patients. Other dosage forms are available for this group of patients. e.g. suspensions may be used.

Elderly patients:

No dose adjustments are required for elderly patients. 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). In patients with GFR <10 ml/min azithromycin should be administered with caution (see section 5.2).

Patients with 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).
Paediatric population

The safety and efficacy of Azithromycin for the treatment of adolescent girls with pelvic inflammatory disease has not been established.

There is no relevant use of Azithromycin for the treatment of acute exacerbations of chronic bronchitis in paediatric patients.

The safety and efficacy of Azithromycin in prevention or treatment of Mycobacterium avium complex infections in paediatric patients < 12 years has not been established. Other pharmaceutical forms are available that may be more appropriate to treat patients unable to swallow capsules as well as paediatric patients weighing less than 45 kg.

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 excipient listed in section 6.1.

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

Renal impairment:

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 30-80 ml/min/1.73m$_2$). Caution is advised in patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Hepatic impairment:

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.

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

Ergot alkaloids and azithromycin:

The concurrent use of ergot alkaloids and macrolide antibiotics has been found to accelerate the development of ergotism. The interactions between ergot alkaloids and azithromycin have not been studied. The development of ergotism is however

possible, so that azithromycin and ergot alkaloid derivatives should not be administered simultaneously.
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.

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 acquired QT prolongation.
- concurrently with other active substances that 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 (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

Myasthenia gravis and azithromycin:

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).

Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex (MAC) in children have not been established.
Non-susceptible organisms :

As with any antibiotic preparation, observation for signs of superinfection with nonsusceptible organisms, including fungi is recommended. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.

Clostridium difficile associated diarrhoea (CDAD), pseudomembranous colitis:

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including 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. 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.

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.

Hydroxychloroquine or chloroquine:

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).

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.

The following should be considered before prescribing azithromycin:

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.

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.*

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.

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.

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.

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 administered with caution to patients suffering from neurological or psychiatric diseases.

Long-term use:

There is no experience regarding the safety and efficacy of long-term use of azithromycin for the mentioned indications. In case of rapid recurrent infections, treatment with another antibiotic should be considered.

Due to cross-resistance existing among macrolides, in areas with a high incidence of erythromycin resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other macrolides (see section 5.1).

Azithromycin is not the first choice for the empirical treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1).

Paediatric population:

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

4.5 Interaction with other medicinal products and other forms of interaction

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 ↔ Cmax	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 orally single dose.	Azithromycin: ND Ciclosporin: ↔ AUC ↑Cmax 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.
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 *Expected:* ↑ 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 *Expected:* ↑ 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.

<u>Paediatric population</u>

Interaction studies have only been performed in adults.

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 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.

Breastfeeding:

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. 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 (≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

Table 3: Tabulated list of adverse reactions

very common ≥ 1/10	**common** ≥ 1/100 to < 1/10	**uncommon** ≥ 1/1,000 to < 1/100	**rare** ≥ 1/10,000 to <1/1,000	**very rare** < 1/10,000	**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 disorder, rhinitis.			Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders					
	Lymphocyte count decreased Eosinophil count increased Basophil count increased Monocyte	Leukopenia, neutropenia, eosinophilia Platelet count increased Haematocrit decreased			Thrombocytopenia, haemolytic anaemia

	count increased Neutrophil count increased				
Immune system disorders					
		Angioedema Hypersensitivity (see section 4.4)			Anaphylactic reaction
Metabolism and nutrition disorders					
		Decreased appetite[#2]			
Psychiatric disorders					
		Nervousness, insomnia	Agitation,		Aggression anxiety, delirium, hallucination
Nervous system disorders					
	headache,	Dizziness[#2] paraesthesia[#2], somnolence dysgeusia[#2]			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis, seizure, parosmia Hypoaesthesia[#3] (see section 4.4)
Eye disorders					
		Visual impairment[#2]			
Ear and labyrinth disorders					
		Ear disorder, vertigo, hearing impaired,			Deafness[#2] Hypoacusis[#3] Tinnitus[#3]
Cardiac disorders					
		Palpitations			Torsades de pointes (see section 4.4) arrhythmia (see section 4.4) including ventricular tachycardia.(see

					section 4.4) Electrodiogram QT prolonged (see section 4.4)
Vascular disorders					
		Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders					
		Dyspnoea, epistaxis , Respiratory disorder			
Gastrointestinal disorders					
Diarrhoea, abdominal discomfort,	Vomiting, dyspepsia, nausea[#1], Abdominal pain[#1]	Gastritis, constipation, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion Flatulence			Pancreatitis, tongue and teeth discoloration Pseudomembranous colitis (see section 4.4)
Hepatobiliary disorders					
		Hepatitis, Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubin increased Blood alkaline phosphatase increased	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					
		, , urticaria, Dermatitis, dry skin, hyperhidrosis , Rash[#2], pruritus[#2]	Allergic reactions including angioneurotic oedema, photosensitivity reaction, Acute generalised exanthematous		Toxic epidermal necrolysis, erythema multiforme, Stevens-Johnson syndrome[#3]

			pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS)		
Musculoskeletal and connective tissue disorders					
		Osteoarthritis, Myalgia, back pain, neck pain			Arthralgia[#2]
Renal and urinary disorders					
		Dysuria, renal pain , Blood urea increased Blood creatinine increased			Acute kidney injury Tubulointerstitial nephritis
Reproductive system and breast disorders					
		Intermenstrual bleeding Testicular Disorder			
General disorders and administration site conditions					
		Chest pain, face oedema, pyrexia, peripharal pain, oedema malaise , Fatigue[#2] asthenia			
Investigations					
	Blood bicarbonate Decreased	blood potassium abnormal, blood alkaline phosphatase increased, chloride increased, glucose increased, platelets increased, hematocrit decreased, bicarbonate increased, abnormal sodium			
Injury poisoning and procedural complications					
		Post procedural			

		complications			

* These ADRs were only seen during azithromycin administration for MAC prophylaxis and/or therapy
#1 In MAC the frequency of these ADRs was Very Common (>1/10).
#2 In MAC the frequency of these ADRs was Common (>1/100 to <1/10).
#3 In MAC the frequency of these ADRs was Uncommon (>1/1 000 to <1/100).

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
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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

Symptoms:

Adverse reactions experienced with 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 an 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.

5.1 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 Iactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homo-erythromycin A. The molecular weight is 749.0.

Mechanism of action:

Azithromycin is an azalide, a sub-class of the macrolide antibiotics. The mechanism of action of azithromycin is based on the inhibition of the bacterial protein synthesis by binding to the 50Sribosomal 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.

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.

Pharmacokinetic/pharmacodynamics (PK/PD) relationship:

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

Breakpoints:

Azithromycin susceptibility breakpoints for typical bacterial pathogens s published by EUCAST are: (Clinical breakpoint table v.6.0, valid from 01/01/2016):

Organism	**MIC breakpoints (mg/L)**	
	Susceptible (S≤)	**Resistant (R>)**
Staphylococcus spp.	1[1]	2[1]
Streptococcus groups A, B, C and G	0.25[1]	0.5[1]
Streptococcus pneumoniae	0.25[1]	0.5[1]
Haemophilus influenzae	0.125[2]	4[2]
Moraxella catarrhalis	0.25[1]	0.5[1]
Neisseria gonorrhoeae	0.25	0.5

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.

Antibacterial spectrum of Azithromycin

Commonly susceptible species.
Aerobic Gram-negative microorganisms
Haemophilus influenzae
Moraxella catarrhalis
Haemophilus ducreyi
Legionella pneumophila°
Aerobic Gram-positive microorganisms
Mycobacterium avium complex°
Streptococcus pyogenes
Anaerobic microorganisms
Peptostreptococcus spp.
Porphyromonas gingivalis
Tannerella forsythia
Treponema denticola
Other microorganisms
Aggregatibacter actinomycetemcomitans (formerly Actinobacillus actinomycetemcomitans)
Borrelia burgdorferi
Chlamydia trachomatis°
Chlamydophila pneumoniae°
Chlamydophila psittaci
Mycoplasma pneumoniae°
Prevotella intermedia
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus+
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus agalactiae
Streptococcus pneumoniae++
Streptococcus pyogenes
Viridans streptococci
Aerobic Gram-negative microorganisms
Neisseria gonorrhoeae
Anaerobic microorganisms
Fusobacterium spp.

Prevotella spp
Inherently resistant organisms
Aerobic Gram-negative microorganisms
Escherichia coli
Pseudomonas aeruginosa
Klebsiella spp
Anaerobic Gram-negative microorganisms
Bacteroides spp.

°No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.
+At least one region shows resistance rates higher than 50% for methicillin-resistant Staphylococcus aureus.
++Penicillin susceptible strains of Streptococcus pneumoniae are more likely to be susceptible to azithromycin than are penicillin resistant strains of Streptococcus pneumoniae.

5.2 Pharmacokinetic properties

Absorption:

The peak serum concentrations (Cmax) 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 (Tmax) 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 Cmax and AUC0-24 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: AUC0-24 and Cmax of azithromycin for the 3-day and 5-day regimen at last day of dosing

Dose regimen, formulation	**AUC_{0-24} (µg•h/ml)**	**C_{max} (µg/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 cladinosa 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 AUC0-24 and Cmax was shown in the range of 250 mg to 1000 mg.

Pharmacokinetics in 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 Cmax and AUC0-120 increased by 5.1% and 4.2%, respectively compared to subjects with GFR >80 ml/min). The mean Cmax and AUC0-120 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 AUC0-inf and 34% and 72% higher on Cmax, 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 AUC0-24 on Days 1 and 5 were 3.0 and 2.7 μg•h/ml, respectively. A 29% higher AUC0-24, a 8% higher Cmax and a 37.5% higher Tmax 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 to15 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 AUC0-24 values were 3.1 μg•h/ml and 1.8 μg•h/ml, respectively. The mean Cmax value was 0.38 μg/ml and the corresponding mean Tmax value was 2.4 hours in children aged 6 to 15 years and 0.22 μg/ml and 1.9 hours for children 1 to 5 years of age. The mean Cmax and AUC0-24 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 AUC0-24 for 7 children aged 2 to 4 years was 2.90 μg•h/ml while for the 8 children aged 5 to 10 years the value was 2.08 μg•h/ml. A low AUC0-24 value of 0.74 μg•h/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

Dibasic calcium phosphate(anhydrous granular)(E341)

Sodium lauryl sulfate

Croscarmellose sodium (E468)

Pregelatinised starch (Lycatab-C)

Magnesium stearate (E470b)

Tablet film-coating:

Hypromellose (E464)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months

6.4 Special precautions for storage

Store in the original package.

6.5 Nature and contents of container

PVC/PVDC/aluminium blister pack. Pack sizes: Blister with 2, 3, 4 or 6 film-coated tablets in a carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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