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 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

For oral use.

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

The tablets can be taken with or without food.

The tablets should be taken with ½ glass of water.

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

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.

For susceptible Neisseria gonorrhoeae the recommended dose is 1000 mg or 2000 mg of azithromycin in combination with 250 or 500 mg of ceftriaxone according to local clinical treatment guidelines. For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

For sinusitis, treatment is indicated for adults and adolescents 16 years of age and over.

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).

Patients with hepatic impairment:

A dose adjustment is not necessary for patients with mild to moderately impaired liver function (see section 4.4).

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

Allergic reactions:

As with erythromycin and other macrolides, rare serious allergic reactions (rarely fatal) including angioneurotic oedema and anaphylaxis (rarely fatal) have been reported.

Some of these reactions with azithromycin have caused recurrent symptoms and have required longer observation and treatment.

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 (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 astheni 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.

QT 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.

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.

Superinfections:

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:

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. 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.

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).

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

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 reduced by approximately 25 %. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

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(P-gp substrates):

Concomitant administration of macrolide antibiotics , including azithromycin, with Pglycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

Zidovudine:

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

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

Ergot:

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 and alfentanil:

No data are available on interactions with astemizole and alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentation of its effect during concomitant use of 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.

Ciclosporin:

In a pharmacokinetic study with healthy volunteers that were administered a 500mg/day oral dose of azithromycin for 3 days and were then administered a single 10mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, ciclosporin 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, aclinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Hydroxychloroquine and chloroquine:

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

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 is 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no adequate data from 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. 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.

Breastfeeding:

Azithromycin passes into human breast milk, but there are no adequate and wellcontrolled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

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 studies on the effects on the ability to drive and use machines have been performed.

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 (≥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:

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					
		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,	Agitation,		Aggression

		insomnia	depersonalisation		anxiety, delirium, hallucination
Nervous system disorders					
	Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia somnolence			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (see section 4.4)
Eye disorders					
	Visual impairment				
Ear and labyrinth disorders					
	Deafness	Ear disorder, vertigo, hearing impaired, tinnitus			
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, pruritus	Stevens-Johnson syndrome, photosensitivity reaction, urticaria, Dermatitis, dry skin, hyperhidrosis	Allergic reactions including angioneurotic oedema		Toxic epidermal necrolysis, erythema multiforme,
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 disorder			
General disorders and administration site conditions					
	Fatigue	Chest pain, face oedema, pyrexia, peripharal 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
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:

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 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. By binding to the 50Sribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side ofthe ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

Mechanism of resistance:

Generally, the resistance of different bacterial species to macrolides has been reported to occur by three mechanisms associated with target site alteration, antibiotic modification, or altered antibiotic transport (efflux). The efflux in streptococci is conferred by the *mef* genes and results in a macrolide-restricted resistance (M phenotype). Target modification is controlled by *erm* encoded methylases.

A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, beta-haemolytic streptococci of group A, *Enterococcus* spp. and *Staphylococcus aureus*, including methicillin-resistant S. *aureus* (MRSA).

A decrease in macrolide susceptibility over time has been noted particularly in Streptococcus pneumoniae and Staphylococcus aureus. Similarly, decreased susceptibility has been observed among Streptococcus viridans and Streptococcus agalactiae (Group B) streptococcus against other macrolides and lincosamides.

Penicillin-sensitive S. *pneumoniae* are more likely to be susceptible to azithromycin than are penicillin-resistant strains of S. *pneumoniae*. Methicillin-resistant S. *aureus* (MRSA) is less likely to be susceptible to azithromycin than methicillin-sensitive S. *aureus* (MSSA).

The induction of significant resistance in both *in vitro* and *in vivo* models is <1dilution rise in MICs for *S. pyogenes*, *H. influenzae* and *Enterobacterciae* after nine sub-lethal passages of active substance and three dilution increase for *S. aureus* and development of in vitro resistance due to mutation is rare.

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:

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

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

Antibacterial spectrum of Azithromycin

Commonly susceptible species.
Aerobic Gram-negative microorganisms
*Haemophilus influenzae**
*Moraxella catarrhalis**
Other microorganisms
Chlamydophila pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycobacterium avium
*Mycoplasma pneumonia**
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
*Staphylococcus aureus**
Streptococcus agalactiae
*Streptococcus pneumoniae**
*Streptococcus pyogenes**
Other microorganisms
Ureaplasma urealyticum
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Staphylococcus aureus – methicillin resistant and erythromycin resistant strains
Streptococcus pneumoniae – penicillin resistant strains

Aerobic Gram-negative microorganisms
Escherichia coli
Pseudomonas aeruginosa
Klebsiella spp.
Anaerobic Gram-negative microorganisms
Bacteroides fragilis-group

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

5.2 Pharmacokinetic properties

Absorption:

Following oral administration the bio-availability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours. The mean maximum concentration observed (Cmax) 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 shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma). This indicates that the substance is extensively bound in the tissues

(steady-state volume of distribution approximately 31 l/kg). With the recommended dosage no accumulation in the serum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than in the serum/plasma. Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 μg/g, 0,6-2,3 μg/g, 2,0-2,8 μg/g and 0-0,3 μg/ml have been measured in resp. lung, prostate, tonsil and serum.Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

In experimental *in vitro* and *in vivo* studies, azithromycin accumulates in phagocytes;release is promoted by active phagocytosis. In animal models this process appears to contribute to the accumulation of azithromycin in tissue.

The binding of azithromycin to plasma proteins is variable and varies from 52% at 0.005 μg/ml to 18% at 0.5 μg/ml.

Biotransformation and Excretion:

The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 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, together with 10 metabolites (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggests that the metabolites do not play a role in the micro-biological activity of azithromycin.

Pharmacokinetics in special populations:

Renal impairment:

Following a single oral dose of azithromycin 1g, mean Cmax and AUC0-120 increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 30-80 ml/min) compared with normal renal function (GFR > 80 ml/min/1.73m2). In subjects with severe renal impairment (GFR < 30 ml/min/1.73m2), the mean Cmax and AUC0-120 increased 61% and 35% respectively compared to normal.

Hepatic impairment:

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.There are no data on azithromycin use in cases of more severe hepatic impairment.

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 were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

Paediatric population:

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the Cmax achieved is slightly lower than 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 t1/2 of 36h 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 invivo and in vitro test models.

Reproductive toxicity:

No teratogenic effects were observed in embryotoxicity studies in rats after oral administration of azithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/day led to mild retardations in fetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

36 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

Strandhaven Ltd t/a Somex Pharma

Ilford, Essex

IG3 8BS .UK

8 MARKETING AUTHORISATION NUMBER(S)

PL15764/0118

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24/10/2017

10 DATE OF REVISION OF THE TEXT

04/01/2022