SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Azithromycin 250 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 250 mg of azithromycin (as monohydrate).

Excipient(s) with known effect
Each film-coated tablet contains 6.84 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, oval film-coated tablets with breaking notches on both sides and the embossment “A 250“on one side.

The film-coated tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin is indicated for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin (see section 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
- skin and soft tissue infections
- 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

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

For all other indications the dose is 1,500 mg, to be administered as 500 mg per day for three consecutive days.

Elderly people
The same dose range as in adult patients may be used in the elderly. Since older elderly people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes (see section 4.4).

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

Patients with renal impairment:
No dose adjustment is necessary 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).

Method of administration

Azithromycin 250 mg film-coated tablet should be administered as a daily single dose. Azithromycin 250mg film-coated tablet may be taken with food.

4.3 Contraindications

Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed in section 6.1 (see also section 4.4).

4.4 Special warnings and precautions for use

Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported.

Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

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

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 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.

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

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

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

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

<u>Cardiovascular events</u>
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including azithromycin (see section 4.8). Therefore as the following

situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval 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

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

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 in children have not been established.

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.

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

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

As for other macrolides, high resistance rates of Streptococcus pneumoniae (> 30 %) have been reported for azithromycin in some European countries (see section 5.1). This should be taken into account when treating infections caused by Streptococcus pneumoniae.

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

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

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

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

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

Sexually transmitted disease
In case of sexually transmitted diseases a concomitant infection by T. palladium should be excluded.

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

Azithromycin film-coated tablets contain Lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Azithromycin film-coated tablets contains 0.025 mmol (0.57 mg) sodium per dose which is less than 1 mmol sodium (23 mg), that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on azithromycin:

Antacids
In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

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

Fluconazole
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.

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 medicinal product.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see Section 4.8).

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.

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.

Effect of azithromycin on other medicinal products:

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

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

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

Cyclosporin
In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin Cmax and AUC0-5 were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

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.

Trimethoprim/sulfamethoxazole
Co-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1,200 mg on Day 7 had no significant effect on peak concentrations total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Zidovudine
Single 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

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

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

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

Carbamazepine

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

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

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.

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.

Indinavir
Co-administration of a single dose of 1,200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone
In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam
In healthy volunteers, co-administration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

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 Cmax of sildenafil or its major circulating metabolite.

Triazolam
In 14 healthy volunteers, co-administration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

Breastfeeding
Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in breastfeeding 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

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to drive or operate machinery.
Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery (section 4.8).

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and postmarketing surveillance by system organ class and frequency. 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:

System Organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis

System Organ Class	Frequency	Adverse reaction
		Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis
	Not known	Pseudomembranous colitis (see section 4.4)
Blood and lymphatic system disorders	Uncommon	Leukopenia Neutropenia Eosinophilia
	Not known	Thrombocytopenia Haemolytic anaemia
Immune system disorders	Uncommon	Angioedema Hypersensitivity
	Not known	Anaphylactic reaction (see section 4.4)
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Uncommon	Nervousness Insomnia
	Rare	Agitation Depersonalisation
	Not known	Aggression Anxiety Delirium Hallucination
Nervous system disorders	Common	Headache
	Uncommon	Dizziness Somnolence Dysgeusia Paraesthesia
	Not known	Syncope, convulsion Hypoaesthesia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4).
Eye disorders	Uncommon	Visual impairment
	Not known	Blurred vision
Ear and labyrinth disorders	Uncommon	Ear disorder Vertigo
	Not known	Hearing impairment including deafness and/or tinnitus
Cardiac disorders	Uncommon	Palpitations
	Not known	Torsades de pointes (see section 4.4)

System Organ Class	Frequency	Adverse reaction
		Arrhythmia (see section 4.4) including ventricular tachycardia electrocardiogram QT prolonged (see section 4.4)
Vascular disorders	Uncommon	Hot flush
	Not known	Hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Vomiting Abdominal pain Nausea
	Uncommon	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion
	Not known	Pancreatitis Tongue discolouration
Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Hepatic function abnormal Jaundice cholestatic
	Not known	Hepatic failure (which has rarely resulted in death) (see section 4.4)* Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders	Uncommon	Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis
	Rare	Photosensitivity reaction Acute generalised exanthematous pustulosis (AGEP)
	Not known	Steven-Johnson syndrome Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and connective tissue disorders	Uncommon	Osteoarthritis Myalgia Back pain Neck pain

System Organ Class	Frequency	Adverse reaction
	Not known	Arthralgia
Renal and urinary disorders	Uncommon	Dysuria Renal pain
	Not known	Renal failure acute Nephritis interstitial
Reproductive system and breast disorders	Uncommon	Metrorrhagia Testicular disorder
General disorders and administration site conditions	Uncommon	Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema
Investigations	Common	Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased
	Uncommon	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubine increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline phosphatase increased Chloride increased Glucose increased Platelets increased Hematocrit decreased Bicarbonate increased Abnormal sodium
Injury and poisoning	Uncommon	Post procedural complication

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 (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties
Pharmacotherapeutic group: antibacterials for systemic use, macrolides, azithromycin
ATC code: J01FA10

Mode of action
Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

PK/PD Relationship
The efficacy of azithromycin is best described by the relationship AUC/MIC, where AUC describes the area under the curve and MIC represents the mean inhibitory concentration of the microbe concerned.

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.

Mechanism of resistance
Resistance to azithromycin may be inherent or acquired. There are 3 main mechanisms of resistance affecting azithromycin:

- Efflux: resistance may be due to an increase in the number of efflux pumps on the cell membrane. In particular, 14- and 15-link macrolides are affected. (M-phenotype)
- Alterations of the cell structure: methylisation of the 23s rRNS may reduce the affinity of the ribosomal binding sites, which can result in microbial resistance to macrolides, lincosamides and group B streptogramins (SB) (MLSB-phenotype).
- Enzymatic deactivation of macrolides is only of limited clinical significance.

In the presence of the M-phenotype, complete cross resistance exists between azithromycin and clarithomycin, erythromycin and roxithromycin. With the MLSB-phenotype, additional cross resistance exists with clindamycin and streptogramin B. A partial cross resistance exists with spiramycin.

Breakpoints

According to EUCAST (European Committee on Antimicrobial Susceptibility Testing) the following breakpoints have been defined for azithromycin (2009-06-01):

Species	**Susceptible**	**Resistant**
Staphylococcus spp.	≤ 1 mg/l	> 2 mg/l
Streptococcus (Group A,B,C,G)	≤ 0,25 mg/l	> 0,5 mg/l
Streptococcus pneumoniae	≤ 0,25 mg/l	> 0,5 mg/l
Haemophilus influenzae	≤ 0,12 mg/l	> 4 mg/l
Moraxella catarrhalis	≤ 0,5 mg/l	> 0,5 mg/l
Neisseria gonorrhoeae	≤ 0,25 mg/l	> 0,5 mg/l

Susceptibility

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

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

Table of Susceptibility

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

5.2 Pharmacokinetic properties

Absorption
Bioavailability after oral administration is approximately 37%. Peak concentrations in the plasma are attained 2-3 hours after taking the medicinal product. (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution
Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg.

In experimental in vitro and in vivo studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.
In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Elimination
Terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days.

Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination. In the same source, 10 metabolites were also detected, which were formed through N- and O-demethylation, hydroxylation of desosamine- and aglycone rings and degradation of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

Pharmacokinetics in Special Populations

Renal insufficiency
Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 33% respectively compared to normal.

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

Elderly
The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents
Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety data

In animal tests in which the dosages used amounted to 40 times the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule, no true toxicological consequences were observed which were associated with this. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Carcinogenic potential:
Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only, and there were no signs indicative of carcinogenic activity.

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

Reproductive toxicity:
In animal studies of the embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation in physical development and delay in reflex development following treatment with 50 mg/kg/day azithromycin and above were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Tablet core</u>

Microcrystalline cellulose
Maize starch
Sodium starch glycolate
Silicium dioxide
Magnesium stearate
Sodium laurylsulphate

Film-coating
Lactose monohydrate
Hypromellose
Macrogol 4000
Titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

The film-coated tablets are packed in aluminium/polyvinylchloride blisters.

Packs containing 2, 3, 4, 6, 9, 12 and 24 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Sandoz Ltd
Frimley Business Park
Frimley
Camberley
Surrey

GU16 7SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04416/1235

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28/05/2008

10 DATE OF REVISION OF THE TEXT

01/08/2019