SUMMARY OF PRODUCT CHARACTERISTICS POCCOZITH 250MG AND 500MG TABLET

1. NAME OF THE MEDICINAL PRODUCT

POCCOZITH 250 mg film-coated tablets
POCCOZITH 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

250 mg film-coated tablets:
1 film-coated tablet contains azithromycin monohydrate equivalent to 250 mg azithromycin

500 mg film-coated tablets:
1 film-coated tablet contains azithromycin monohydrate equivalent to 500 mg azithromycin

Excipient with known effect
Each film-coated tablet contains 0.04 mg lecithin (soya).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

250 mg film-coated tablets: white to off-white, oblong, film-coated, plain on both sides

500 mg film-coated tablets: white to off-white, oblong, film-coated, deep score line on one side and score line on other side.
The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

POCCOZITH is indicated for the treatment of infections caused by organisms susceptible to azithromycin (see 4.4 and 5.1):

- upper respiratory tract infections: sinusitis, pharyngitis, tonsillitis (see section 4.4)
- acute otitis media
- lower respiratory tract infections: acute bacterial exacerbation of chronic bronchitis and mild to moderately severe community acquired pneumonia
- skin and soft tissue infections
- uncomplicated *Chlamydia trachomatis* urethritis and cervicitis (see section 4.4)

Considerations 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. As an alternative the same total dose (1,500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Elderly
The same dosage as in adult patients is used in the elderly. 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).

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min) (see section 4.4).

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

Paediatric population
POCCOZITH 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.

Method of administration
For oral use.
POCCOZITH should be given as a single daily dose. The tablets may be taken with food.

4.3 Contraindications

Hypersensitivity to the active substance, to erythromycin, any macrolide or ketolide antibiotic, soya or peanut or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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

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

Hepatotoxicity
Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

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

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

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

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Pseudomembranous colitis
Pseudomembranous colitis has been reported with the use of macrolide antibiotics. This diagnosis should therefore be considered in patients who get diarrhoea after starting the treatment with azithromycin. Should pseudomembranous colitis be induced by azithromycin, then anti-peristaltics should be contraindicated.

There is no experience regarding the safety and efficacy of the long-term application of azithromycin for the above mentioned indications. In case of quickly recurring infections, treatment with another antibacterial agent should be considered.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10–80 ml/min). 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).

Prolongation of the QT interval
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides including azithromycin (see section 4.8). 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.
- 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.

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

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

Pneumonia
Due to the emerging resistance of *Streptococcus pneumoniae* towards macrolides azithromycin is not the drug of first choice in community acquired pneumonia. In hospital acquired pneumonia azithromycin should only be used in combination with further appropriate antibiotics.

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

Pharyngitis and 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.

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.

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

Neurological or psychiatric disorders
Azithromycin should be administered with caution to patients with neurological or psychiatric disorders.

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

Further information
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.

Excipients
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interactions with other medicinal products and other forms of interaction

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 24 %. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

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

Didanosine (dideoxyinosine)
Co-administration of 1,200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

Digoxin and colchicine
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-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

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.

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

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

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).

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.

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 dose of 15 mg 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.

Ciclosporin
In a pharmacokinetic study with healthy volunteers who 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 ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated (by 24 % and 21 % respectively), however no significant changes were seen in $AUC_{0-\infty}$. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

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

Fluconazole
Co-administration of a single dose of 1,200 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 co-administration of fluconazole, however, a clinically insignificant decrease in C_{max} (18 %) of azithromycin was observed.

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 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg midazolam.

Nelfinavir
Co-administration of azithromycin (1,200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.

Rifabutin
Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either active substance. 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, co-administration of 500 mg azithromycin 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
Co-administration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with 1,200 mg azithromycin 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 the use of azithromycin in pregnant women. In reproduction toxicity studies in animals azithromycin was shown to pass the placenta, but no teratogenic effects were observed (see section 5.3). The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breast-feeding
Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterised 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.

4.8 Undesirable effects

Azithromycin is well tolerated with a low incidence of side 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 as follows: 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 (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	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 (cannot be estimated from the available data)
Infection 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,* *anxiety,* *delirium,* *hallucination*
Nervous system disorders		Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia, somnolence, insomnia			*Syncope,* *convulsion,* *psychomotor hyperactivity,* *anosmia,* *ageusia,* *parosmia,* *myasthenia gravis (see section 4.4)*
Eye disorders		Visual impairment				

System Organ Class	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 (cannot be estimated from the available data)
Ear and labyrinth disorders		Deafness	Hearing impaired, tinnitus, vertigo, ear disorder			
Cardiac disorders			Palpitations			*Torsades de pointes (see section 4.4),* *arrhythmia (see section 4.4) including ventricular tachycardia, Electrocardiogram 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 discolouration*
Hepatobiliary disorders			Hepatitis	Hepatic function abnormal, jaundice cholestatic		*Hepatic failure (see section 4.4)**,* *hepatitis fulminant,* *hepatic necrosis*
Skin and subcutaneous tissue disorders		Rash, pruritus	Stevens-Johnson syndrome, photosensitivity reaction, urticaria, dermatitis, dry skin,	Acute generalised exanthematous pustulosis (AGEP)	DRESS	*Toxic epidermal necrolysis,* *erythema multiforme*

System Organ Class	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 (cannot be estimated from the available data)
			hyperhidrosis			
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		Injection site pain,* injection site inflammation,* fatigue	Chest pain, oedema, malaise, asthenia, face oedema, pyrexia, pain, peripheral oedema			
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			

System Organ Class	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 (cannot be estimated from the available data)
			increased, hematocrit decreased, bicarbonate increased, abnormal sodium			
Injury and poisoning			Post procedural complication			

* ***for powder for solution for infusion only***

** ***which has rarely resulted in death***

POCCOZITH film-coated tablets contain soya lecithin, which can very rarely cause allergic reactions.

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 <u>differ</u> from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
Metabolism and nutrition disorders		Anorexia	
Nervous system disorders		Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia
Eye disorders		Visual impairment	
Ear and labyrinth disorders		Deafness	Hearing impaired, tinnitus
Cardiac disorders			Palpitations
Gastrointestinal disorders	Diarrhoea abdominal pain, nausea, flatulence, abdominal discomfort, loose stools		
Hepatobiliary disorders			Hepatitis
Skin and subcutaneous tissue		Rash,	Stevens-Johnson

	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
disorders		pruritus	syndrome, photosensitivity reaction
Musculoskeletal and connective tissue disorders		Arthralgia	
General disorders and administration site conditions		Fatigue	Asthenia, malaise

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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Management
In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment 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 an azalide, derived from the macrolide class of antibiotics. The mode of action of azithromycin is inhibition of protein synthesis in bacteria by binding to the 50s ribosomal subunit and preventing translocation of peptides. Azithromycin is usually bacteriostatic. However, in high concentrations, azithromycin may be bactericidal against selected microorganisms. Azithromycin is active against many Gram-positive and Gram-negative aerobic and anaerobic bacteria and bacterial pathogens such as *Mycobacterium avium* complex, *Mycoplasma* spp., *Borrelia burgdorferi, Chlamydia* spp. and *Campylobacter* spp. In addition, azithromycin has activity against protozoan microorganisms such as *Toxoplasma gondii*.

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

Breakpoints
EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens	susceptible	resistant

Staphylococcus spp. [1)]	≤ 1 mg/l	> 2 mg/l
Streptococcus spp. (Groups A, B, C, G) [1)]	≤ 0.25 mg/l	> 0.5 mg/l
Streptococcus pneumoniae [1)]	≤ 0.25 mg/l	> 0.5 mg/l
Haemophilus influenzae [1)]	≤ 0.125 mg/l	> 4 mg/l
Moraxella catarrhalis [1)]	≤ 0.25 mg/l	> 0.5 mg/l
Neisseria gonorrhoeae [2)]	≤ 0.25 mg/l	> 0.5 mg/l

[1)] Erythromycin can be used to determine susceptibility to azithromycin.
[2)] Breakpoints are based on a 2 g-single dose in monotherapy.

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.

Commonly susceptible species
Aerobic Gram-positive microorganisms
Mycobacterium avium°
Streptococcus pyogenes [1]
Aerobic Gram-negative microorganisms
Haemophilus influenzae[$]
Moraxella catarrhalis°
Neisseria gonorrhoeae
Other microorganisms
Chlamydophila trachomatis°
Chlamydophila pneumoniae°
Legionella pneumophila°
Mycoplasma pneumoniae°
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus (Methicillin-susceptible)
Staphylococcus aureus (Methicillin-resistant)[+]
Streptococcus agalactiae
Streptococcus pneumoniae
Inherently resistant organisms
Aerobic Gram-negative microorganisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa

° No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.
[$] Inherent susceptibility of most of the isolates shows intermediate resistance.
[+] At least one region shows resistance rates higher than 50 %.
[1] The resistance rates are in some studies ≥ 10 %.

Other information
The diagnostic procedures available *in vitro* at this moment to determine the susceptibility of *Mycobacterium avium complex* (MAC) organisms are not generally accepted and validated.

Streptococci and staphylococci that are resistant to erythromycin are also resistant to azithromycin. Cross-resistance to *Mycobacterium avium* complex organisms occurs between clarithromycin and azithromycin.

5.2 Pharmacokinetic properties

Absorption
After oral administration the bioavailability of azithromycin is approximately 37 %. Peak plasma levels are reached after 2-3 hours (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
Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12 % of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination. The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

After a 5 day treatment slightly higher (29 %) AUC values were seen in the elderly volunteers (> 65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

Pharmacokinetics in special populations

Renal insufficiency
Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1 % and 4.2 % respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61 % and 35 % respectively compared to normal.

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

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

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 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 $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) 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 the finding for animals and for humans is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

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

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

Reproductive toxicity
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 led to mild retardation of foetal ossification and maternal weight gain.
In peri- and post-natal studies in rats, mild retardation was observed following treatment with 50 mg/kg/day azithromycin and above.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Microcrystalline cellulose
Pregelatinised maize starch
Sodium starch glycolate
Colloidal anhydrous silica
Sodium laurilsulfate
Magnesium stearate

Coating:
Polyvinyl alcohol
Titanium dioxide (E 171)
Talc
Soya lecithin
Xanthan gum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30 degrees Centigrade, away from Sunlight.

6.5 Nature and contents of container

Alu/ Alu blister

Pack sizes/ Presentation
250 mg: 6 film-coated tablets in Alu-Alu blister pack
500 mg: 10 film-coated tablets in Alu-Alu blister pack

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

First J Pocco Pharmaceutial Limited
89 Dennis Osadebe Way, Asaba, Delta State.
Manufactured By:
Scott Edil Pharmacia Limited.
56, E.P.I.P. Phase 1, Jmarmajri, Baddi, Dist Solan, H. P.
India.