SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Azithromycin Clonmel 250 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipients with known effect: Contains Soya Lecithin

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White to off-white, oblong, film-coated, plain on both sides.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azithromycin Clonmel is indicated for the treatment of the following infections, when caused by micro-organisms sensitive 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 moderate severe community acquired pneumonia
- skin and soft tissue infections
- uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

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

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

4.2 Posology and method of administration

Azithromycin Clonmel should be given as a single daily dose. The tablets may be taken with food.

Adults

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

For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1500 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 patients

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).

Children

Azithromycin Clonmel 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.

In 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).

In 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, soya, peanut or to any excipient listed in section 6.1 (List of excipients).

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

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 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.

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

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.

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.

Use in 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).

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.

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 MAC (Mycobacterium Avium Complex) in children have not been established.

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.

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.

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.

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.

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

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

It is recommended that prothrombin time be monitored in patients receiving concomitant treatment with anticoagulants (see section 4.5).

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

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.

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 antibiotics (see section 5.1).

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.

4.5 Interactions with other medicinal products and other forms of interaction

Antacids
In a pharmacokinetic study on the effect of concomitant administration of antacids and azithromycin, no effect on the total bio-availability was seen, although the peak serum levels were 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, co-administration 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)
Co-administration 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 P-glycoprotein 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. The possibility of increased digoxin levels should be borne in mind, and digoxin levels monitored.

Zidovudine
Single administrations of 1000 mg of azithromycin and multiple administrations of 600 mg or 1200 mg azithromycin had no effect on the plasma pharmacokinetics or the renal 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.

Ergotamine derivatives
In patients treated with ergotamine derivatives ergotism can be induced by the concomitant administration of some macrolide antibiotics. There is no known data about the possibility of an interaction between ergotamine derivatives and azithromycin. Because of the theoretical possibility of ergotism azithromycin and ergotamine derivatives should not be combined.

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). 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.

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 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 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 ciclosporin, the resulting cyclosporin 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 co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz: 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: Co-administration 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 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 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, 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.

Nelfinavir: Co-administration 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: 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 (500mg 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: Pharmacokinetic studies in healthy volunteers revealed no interaction between azithromycin and theophylline with concomitant administration. Since interactions of other macrolides with theophylline were reported, care should be taken of signs of increased theophylline levels.

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.

Trimethoprim/sulfamethoxazole: Co-administration of trimethoprim/sulfamethoxazole (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.

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.

Astemizole, alfentanil: There is no known data regarding interaction with astemizole or alfentanil. Caution is needed in the concomitant use of these medicinal products and azithromycin, as an increase of action with the concomitant use of the macrolide antibiotic erythromycin has been described.

Protease Inhibitors: Co-administration 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.

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. 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 characterized the pharmacokinetics of azithromycin excretion into human breast milk. Azithromycin should not be used in the treatment of a lactating woman unless the physician feels that the potential benefits justify the potential risks to the infant.

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:

System Organ Class	Very Common	Common	Uncommon	Rare	Not known
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			
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

System Organ Class	Very Common	Common	Uncommon	Rare	Not known
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, hyperhidrosis		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		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 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

Azithromycin Clonmel 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 differ 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 disorders		Rash, pruritus	Stevens-Johnson 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 preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost'. Alternatively, the traditional post-paid 'yellow card' option may also continue to be used.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O'Malley House
Earlsfort Centre
Earlsfort Terrace
Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. Characteristic symptoms of an overdose of macrolide antibiotics were: reversible hearing loss, severe nausea, vomiting and diarrhoea. In case of an overdose lavage and general supporting measures are indicated.

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*.

Breakpoints:
According to the NCCLS (National Committee on Clinical Laboratory Standards) in 2001 the following breakpoints have been defined for azithromycin:

- 2 μg/ml susceptible; 4 μg/ml intermediate; ≥ 8 μg/ml resistant
- *Haemophilus* spp.: ≤ 4 μg/ml susceptible
- *Streptococcus pneumoniae* and *Streptococcus pyogenes*: ≤ 0.5 μg/ml susceptible; 1 μg/ml intermediate; ≥ 2 μg/ml resistant

There are currently no recommended NCCLS breakpoints for enterobacteriaceae, *Neisseria gonorrhoeae*, *Moraxella catarrhalis* and *Mycobacterium avium* complex.

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.

Species	**Range of acquired resistance (%)**
Commonly susceptible species	
Aerobic Gram-positive	
Corynebacterium diphteriae	-
Listeria spp.	-
Staphylococcus aureus - Methicillin-susceptible	 0-19
Coagulase-neg. Staphylococci - Methicillin-susceptible	 -
Streptococcus pneumonia - Erythromycin-sensitive - Penicillin-sensitive	5-37 - 3-23
Streptococcus pyogenes - Erythromycin-sensitive	0-43 21
Streptococci viridans group	20-32
Aerobic Gram-negative	
Bordetella pertussis	-
Haemophilus influenzae	0-2
Haemophilus ducreyi	-
Legionella spp.	-
Moraxella catarrhalis - Erythromycin-sensitive - Erythromycin-intermediate	0-2 - -
Pasteurella multocida	-
Anaerobic	
Clostridium perfringens	-
Fusobacterium spp.	-
Prevotella spp.	-

Porphyromonas spp.	-
Propionibacterium spp.	-
Other microorganisms	
Borrelia burgdorferi	-
Chlamydia pneumoniae	-
Chlamydia trachomatis	-
Helicobacter pylori	-
Mycobacterium avium complex	-
Mycoplasma pneumoniae	-
Ureaplasma urelyticum	-
Species for which acquired resistance may be a problem	
Aerobic Gram-positive	
Streptococcus pneumonia - Penicillin-intermediate - Penicillin-resistant - Erythromycin-intermediate	 20-62 23-78 -
Streptococcus pyogenes - Erythromycin-intermediate	 -
Streptococci viridans group Penicillin-intermediate	 -
Aerobic Gram-negative	
Moraxella catarrhalis - Erythromycin-resistant	 -
Anaerobic	
Peptostreptococcus spp.	-
Inherently resistant organisms	
Aerobic Gram-positive	
Corynebacterium spp.	-
Enterococcus spp.	-
Staphylococci MRSA, MRSE	Resistant
Streptococcus pneumonia - Erythromycin-resistant - Penicillin & Erythromycin resistant	 - -
Streptococcus pyogenes - Erythromycin-resistant	 -
Streptococci viridans group - Penicillin-resistant - Erythromycin-resistant	 - -
Aerobic Gram-negative	
Pseudomonas aeruginosa	-
Anaerobic	
Bacteroides fragilis group	-

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.

Excretion
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 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 high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

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

Mutagenic potential:
Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

Reproductive toxicity:
No teratogenic effects were observed in animal studies of embryotoxicity 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-/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

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

Coating:
Polyvinyl alcohol
Titanium dioxide (E171)
Talc
Soya Lecithin
Xanthan Gum

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/Alu blister
Pack sizes: 4, 6, 12, 24, 50, and 100 film-coated tablets
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd.
Waterford Road
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 126/150/1

9 DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

Date of first authorisation: 18th November 2005
Date of last renewal: 25th January 2010

10 DATE OF REVISION OF THE TEXT

October 2013