Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zithromax 500 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Azithromycin dihydrate equivalent to 500 mg azithromycin.

Excipients with known effect:
Each tablet contains 36mg lactose
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film coated tablet.

White, capsule shaped, film-coated tablets engraved “ZTM 500”.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Azithromycin is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms (see section 5.1):

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see section 4.4 regarding streptococcal infections)
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*

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

4.2 Posology and method of administration

Posology
Zithromax should be given as a single daily dose. Zithromax tablets should be swallowed whole with water. Zithromax tablets may be taken with or without food.

Children over 45 kg body weight and adults, including elderly patients: The total dose of azithromycin is 1500 mg which should be given over three days (500 mg once daily).
In uncomplicated genital infections due to *Chlamydia trachomatis*, the dose is 1000 mg as a single oral dose. For susceptible *Neisseria gonorrhoeae* the recommended dose azithromycin 2000 mg as a single oral dose together with 500 mg ceftriaxone intramuscularly as a single dose according to local clinical treatment guidelines. For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

The 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).

Paediatric population
In children under 45 kg body weight: Zithromax tablets are not suitable for children under 45 kg.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10 - 80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10 ml/min) (see section 4.4 and section 5.2).

Hepatic impairment
Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin (see section 4.4).

Method of administration:

Zithromax tablets are for oral administration only.

4.3 Contraindications

Hypersensitivity to azithromycin or any of the macrolide or ketolide antibiotics, erythromycin or to any of the excipients (listed in section 6.1).

Zithromax is contraindicated in patients with serious impairment of hepatic function.

Because of the theoretical possibility of ergotism, Zithromax and ergot derivatives should not be co-administered.

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), and Dermatologic reactions including Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (rarely fatal), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with Zithromax 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.

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). The following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest (possibly fatal). 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 hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

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, observations 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 form 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 2 months after the administration of antibacterial agents.

Streptococcal infections
Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.

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

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).

Hepatic impairment
In patients with mild or moderate hepatic impairment, there is no evidence of marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients urinary recovery of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance. Hence no dose adjustment is recommended for patients with mild to moderate hepatic impairment. Nonetheless, since the liver is the principal route of elimination for azithromycin, the use of Zithromax should be undertaken with caution in patients with impaired liver function or concomitantly receiving potentially hepatotoxic agents.

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

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.

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

This medicinal product contains lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids: When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithromycin,

no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma fell by 24%. In patients receiving Zithromax and antacids, Zithromax should be taken at least 1 hour before or 2 hours after the antacid. Co-administration of azithromycin prolonged-release granules for oral suspension with a single dose of 20 ml co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

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.

Cimetidine: A single dose of cimetidine administered 2 hours before Zithromax had no effect on the pharmacokinetics of azithromycin.

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 coadministration of these two drugs. If coadministration is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

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

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

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

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 was required.

Terfenadine: Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other anti-infectives in conjunction with terfenadine, pharmacokinetic interaction studies have been performed. These 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. As with other macrolides, Zithromax should be administered with caution in combination with terfenadine.

Theophylline: Theophylline levels may be increased in patients taking Zithromax

Coumarin-type oral anticoagulants: In a pharmacodynamic interaction study, Zithromax did not alter the anticoagulant effect of a single dose of 15mg 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.

Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin did not affect 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.

Didanosine: Coadministration of daily doses of 1200 mg azithromycin with 400mg didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

Rifabutin: Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug. Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8).

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.

Indinavir: Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Trimethoprim/sulfamethoxazole: Coadministration of trimethoprim/sulfamethoxazole (160 mg/800 mg) for 7 days with 1200 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. 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.

Fertility
In fertility studies conducted in rats, 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 Zithromax may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Zithromax is well tolerated with a low incidence of side-effects.

The section below lists the adverse reactions identified through clinical trial experience and postmarketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥ 1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in

order of decreasing seriousness.

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

	Very Common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to < 1/100)	Rare (≥ 1/10,000 to <1/1,000)	Very Rare (<1/10,000)	Frequency Not Known
Infections and Infestations			Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis			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 Insomnia	Agitation		Aggression Anxiety Delirium Hallucination
Nervous System Disorders		Headache	Dizziness Somnolence Dysgeusia Paraesthesia			Syncope, convulsion Hypoestheia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section 4.4)
Eye Disorders			Visual impairment			
Ear and Labyrinth Disorders			Ear disorder Vertigo			Hearing impairment including deafness and/or tinnitus
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	Vomiting Abdominal pain Nausea	Constipation Flatulence Dyspepsia, Gastritis Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion			Pancreatitis Tongue discolouration
Hepatobiliary Disorders				Hepatic function abnormal Jaundice cholestatic		Hepatic failure (which has rarely resulted in death) (see section 4.4) Hepatitis fulminant Hepatic necrosis
Skin and Subcutaneous Tissue Disorders			Rash Pruritus Urticaria, Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction	DRESS	SJS, TEN Erythema multiforme
Musculoskeletal and Connective Tissue Disorders			Osteoarthritis, Myalgia Back pain Neck pain			Arthralgia
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			Oedema Asthenia Malaise Fatigue Face edema Chest pain Pyrexia Pain Peripheral oedema			
Investigations		Lymphocyte count decreased Eosinophil count increased	Aspartate aminotransferase increased Alanine aminotransferase increased			

		Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils 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			

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 (≥1/1000 to < 1/100)**
Metabolism and Nutrition Disorders		Anorexia	
Nervous System Disorders		Dizziness Headache Paraesthesia Dysgeusia	Hypoesthesia
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	SJS 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

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. ATC code: J01FA10

Mode of action:
Zithromax is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0. Azithromycin binds to the 23S rRNA of the 50S ribosomal subunit. It blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology:
QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

Mechanism of resistance:
The two most frequently encountered mechanisms of resistance to macrolides, including azithromycin, are target modification (most often by methylation of 23S rRNA) and active efflux. The occurrence of these resistance mechanisms varies from species to species and, within a species, the frequency of resistance varies by geographical location.

The most important ribosomal modification that determines reduced binding of macrolides is post−transcriptional (N_6) −dimethylation of adenine at nucleotide A2058 (*Escherichia coli* numbering system) of the 23S rRNA by methylases encoded by *erm* (*e*rythromycin *r*ibosome *m*ethylase) genes. Ribosomal modifications often determine cross resistance (MLS_B phenotype) to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different *erm* genes are present in different bacterial species, in particular streptococci and staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA, or in the

large subunit ribosomal proteins L4 and L22.

Efflux pumps occur in a number of species, including Gram-negatives, such as *Haemophilus influenzae* (where they may determine intrinsically higher minimal inhibitory concentrations [MICs]) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by *mef* (A) genes.

Methodology for determining the in vitro susceptibility of bacteria to azithromycin
Susceptibility testing should be conducted using standardized laboratory methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (MIC determination) and disk susceptibility methods. Both CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretive criteria for these methods.

Based on a number of studies, it is recommended that the in vitro activity of azithromycin be tested in ambient air, to ensure physiological pH of the growth medium. Elevated CO_2 tensions, as often used for streptococci and anaerobes, and occasionally for other species, result in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides.

The CLSI susceptibility breakpoints, based on broth microdilution or agar dilution testing, with incubation in ambient air, are given in the table below.

CLSI Dilution Susceptibility Interpretive Criteria

	Broth microdilution MIC (mg/L)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≤ 4	-	-[b]
Moraxella catarrhalis	≤ 0.25	-	-
Neisseria meningitidis	≤ 2	-	-[b]
Staphylococcus aureus	≤ 2	4	≥ 8
Streptococci [a]	≤ 0.5	1	≥ 2

[a] Includes *Streptococcus pneumoniae*, β−hemolytic streptococci and viridans streptococci.

[b] The current absence of data on resistant strains precludes defining any category other than susceptible. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.
Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration.
Source: CLSI, 2012.; CLSI, 2010

Susceptibility can also be determined by the disk diffusion method, measuring inhibition zone diameters after incubation in ambient air. Susceptibility disks contain 15 µg of azithromycin. Interpretive criteria for inhibition zones, established by the CLSI on the basis of their correlation with MIC susceptibility categories, are listed in the table below.

CLSI Disk Zone Interpretive Criteria

	Disk inhibition zone diameter (mm)		
Organism	**Susceptible**	**Intermediate**	**Resistant**
Haemophilus species	≥ 12	-	-
Moraxella catarralis	≥ 26	-	-
Neisseria meningitidis	≥ 20	-	-
Staphylococcus aureus	≥ 18	14 - 17	≤ 13
Streptococci	≥ 18	14 - 17	≤ 13

[a] Includes *Streptococcus pneumoniae*, β−hemolytic streptococci and viridans streptococci.
Incubation in ambient air.

CLSI = Clinical and Laboratory Standards Institute; mm = Millimeters.
Source: CLSI, 2012; CLSI, 2010

The validity of both the dilution and disk diffusion test methods should be verified using quality control (QC) strains, as indicated by the CLSI. Acceptable limits when testing azithromycin against these organisms are listed in the table below.

Quality Control Ranges for Azithromycin Susceptibility Tests

Broth microdilution MIC	
Organism	**Quality control range (mg/L azithromycin)**
Haemophilus influenzae ATCC 49247	1 – 4
Staphylococcus aureus ATCC 29213	0.5 – 2
Streptococcus pneumoniae ATCC 49619	0.06 – 0.25
Disk inhibition zone diameter (15 µg disk)	
Organism	**Quality control range (mm)**
Haemophilus influenzae ATCC 49247	13 – 21
Staphylococcus aureus ATCC 25923	21 – 26
Streptococcus pneumoniae ATCC 49619	19 – 25

Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration; mm = Millimeters.
Source: CLSI, 2012.

The EUCAST has also established susceptibility breakpoints for azithromycin based on MIC determination. The EUCAST susceptibility criteria are listed in the table below.

EUCAST Susceptibility Breakpoints for Azithromycin

	MIC (mg/L)	
	Susceptible	**Resistant**
Staphylococcus species	≤ 1	> 2
Streptococcus pneumoniae	≤ 0.25	> 0.5
β−hemolytic streptococci [a]	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Includes Groups A, B, C, G.
EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = Minimal inhibitory concentration.
Source: EUCAST Website.
EUCAST Clinical Breakpoint Table v. 2.0, valid from 2012-01-01www.eucast.org/.../EUCAST.../Breakpoint_table_v_2.0_120221.pdf

Antibacterial spectrum

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.

Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive isolates. As discussed above, some ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramins B (which

include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in viridans streptococci and *Streptococcus agalactiae*.

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative Gram-positive bacteria (erythromycin-susceptible isolates): *S. aureus*, *Streptococcus agalactiae**, *S. pneumoniae**, *Streptococcus pyogenes**, other β−hemolytic streptococci (Groups C, F, G), and viridans streptococci. Macrolide-resistant isolates are encountered relatively frequently among aerobic and facultative Gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP).

Aerobic and facultative Gram-negative bacteria: *Bordetella pertussis*, *Campylobacter jejuni*, *Haemophilus ducreyi**, *Haemophilus influenzae**, *Haemophilus parainfluenzae**, *Legionella pneumophila*, *Moraxella catarrhalis**, and *Neisseria gonorrhoeae**. *Pseudomonas* spp. and most *Enterobacteriaceae* are inherently resistant to azithromycin, although azithromycin has been used to treat *Salmonella enterica* infections.

Anaerobes: *Clostridium perfringens*, *Peptostreptococcus* spp. and *Prevotella bivia*.
Other bacterial species: *Borrelia burgdorferi*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae**, *Mycoplasma pneumoniae**, *Treponema pallidum*, and *Ureaplasma urealyticum*.

Opportunistic pathogens associated with HIV infection: MAC*, and the eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.
∗The efficacy of azithromycin against the indicated species has been demonstrated in clinical trials.

5.2 Pharmacokinetic properties

Absorption
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2 to 3 hours after taking the medicinal product.

Distribution
Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.

Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

Elimination
The 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. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O- demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

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 humans 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 for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core:
Pregelatinised Maize Starch
Calcium Phosphate Dibasic Anhydrous
Croscarmellose Sodium
Magnesium Stearate
Sodium lauryl sulfate

Film Coating:
Lactose Anhydrous
Hypromellose
Titanium Dioxide (E171)
Triacetin

The film coat contains titanium dioxide (E171), lactose, hypromellose and triacetin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special storage conditions required.

6.5 Nature and contents of container

Packs of 1 tablet. Aluminium/PVC blister strip, 1 tablet per strip, 1 strip in a carton box.
Packs of 2 tablets. Aluminium/PVC blister strip, 2 tablets per strip, 1 strip in a carton box.
Packs of 3 tablets. Aluminium/PVC blister strip, 3 tablets per strip, 1 strip in a carton box.

Polythene tablet container with child resistant cap, 100 tablets per container.

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

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0019/047/009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 May 1996

Date of last renewal: 08 May 2006

10 DATE OF REVISION OF THE TEXT

January 2016