Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Azromax 500mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg azithromycin (as 527.36 mg azithromycin monohydrate).

For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Azromax 500mg Film-Coated Tablets are white, capsule shaped tablets with ‘AZ’ ‘500’ on one side, and ‘G’ on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Azithromycin is indicated in the following infections caused by microorganisms that are sensitive to azithromycin:

- Lower respiratory tract infections, such as bronchitis and mild to moderately severe community acquired pneumonia
- Upper respiratory tract infections, such as sinusitis and pharyngitis/tonsillitis (see section 4.4)
- Acute otitis media
- Skin and soft tissue infections
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis.

When giving antibiotic treatment consideration must be taken of bacterial resistance and of the official/local regulations relating to the appropriate use of antimicrobial therapy.

4.2 Posology and method of adminstration

Azithromycin tablets should be given as a single daily dose. The tablets can be taken with or without food. The duration of treatment in each of the infectious diseases is given below.

Children and adolescents over 45 kg body weight, adults and the elderly:
The total dosage of azithromycin is 1500 mg which is spread over three days (500 mg once daily). Alternatively, the dosage can be spread over five days (500 mg as a single dose on the first day and thereafter 250 mg once daily).

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

Children and adolescents under 45 kg body weight:
Tablets are not indicated for these patients. Other pharmaceutical forms of azithromycin, e.g. suspensions may be used.

Elderly:
No dose adjustments are required for elderly patients.

Patients with Renal impairment:
No dose adjustment is necessary in patients with mild to moderate renal failure (creatinine clearance ≥ 40 ml/min) (see section 4.4, Special warnings and special precautions for use)

Patients with hepatic impairment:
A dose adjustment is not necessary for patients with mild to moderately impaired liver function (see section 4.4 Special warnings and special precautions for use).

4.3 Contraindications

The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, to one of the related macrolide antibiotics or to any of the excipients.

4.4 Special warnings and special precautions for use

Allergic reactions: In rare cases azithromycin is reported to have caused serious allergic (rarely fatal) reactions such as angioneurotic oedema and anaphylaxis. Some of these reactions have caused recurrent symptoms and have required longer observation and treatment.

Renal failure: No studies have been conducted on patients with a creatinine clearance of <40 ml/min, and consequently caution must be exercised in the use of azithromycin for these patients.

Hepatic failure: Since azithromycin is metabolised in the liver and excreted in the bile, the medicinal product should not be given to patients suffering from severe liver disease. No studies have been conducted regarding the treatment of such patients with Azromax 500 mg film-coated tablets.
When severe liver impairment occurs, the treatment with azithromycin should be ceased.

Ergot alkaloids and Azromax 500 mg film-coated tablets: The concurrent use of ergot alkaloids and macrolide antibiotics has been found to accelerate the development of ergotism. The interactions between ergot alkaloids and azithromycin have not been studied. The development of ergotism is however possible, so that Azithromycin and ergot alkaloid derivatives should not be administered simultaneously.

QT prolongation
Prolonged cardiac repolarisation and QT interval have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk of cardiac effects. Therefore:

- Azromax 500 mg film-coated tablets should not be used in patients with congenital or documented acquired QT prolongation.
- Azromax 500 mg film-coated tablets should not be used concurrently with other active substances that prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine.
- Azromax 500 mg film-coated tablets should not be used in patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia
- Azromax 500 mg film-coated tablets should not be used in patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

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

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

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

Superinfections: Attention should be paid to possible symptoms of superinfections caused by non-sensitive causal

agents such as fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.

Neurological or psychiatric diseases: Azithromycin should be administered with caution to patients suffering from neurological or psychiatric diseases.

Pseudomembranous colitis: After the use of macrolide antibiotics pseudomembranous colitis has been reported. This diagnosis should therefore be considered for patients who suffer from diarrhoea after start of the treatment with azithromycin. Should pseudomembranous colitis be induced by azithromycin, then anti-peristaltics should be contraindicated.

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.

Azithromycin tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

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 did fall by 30 %. Antacids and azithromycin should not be administered simultaneously.

Ergotamine: The combined use of ergotamine and Azithromycin may in theory cause ergotism, and consequently their combined use is not recommended (see also section 4.4).

Coumarin-like oral anticoagulants: An increased tendency towards haemorrhaging has been reported in connection with the concurrent use of azithromycin and warfarin or coumarin-like oral anticoagulants. Attention should be paid to the frequency of prothrombin time monitoring.

Digoxin: In some patients certain macrolide antibiotics have been reported to have impaired the metabolism of digoxin in the intestine. Consequently, in the case of patients receiving Azithromycin and digoxin, the possibility of a rise in the digoxin concentrations should be borne in mind.

Zidovudine: 1000 mg single doses and 1200 mg or 600 mg multiple doses of azithromycin had only a slight effect upon the pharmacokinetics of zidovudine or its glucuronide metabolite in the plasma or upon excretion in the urine. However, the administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in mononuclear cells in the peripheral circulation. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Didanosine: Daily dosages of 1200 mg azithromycin co-administered with didanosine in 6 volunteers appeared to have no effect on the pharmacokinetics of didanosine compared to placebo.

Rifabutin: The concurrent administration of azithromycin and rifabutin may affect the serum levels of both active substances. Neutropenia was observed in patients who were being treated concurrently with azithromycin and rifabutin.

Theophylline: Azithromycin has not affected the pharmacokinetics of theophylline when healthy volunteers received Azithromycin and theophylline simultaneously. Theophylline levels may be increased in patients taking azithromycin.

Even though azithromycin does not appear to inhibit the enzyme CYP3A4, caution is advised when combining the medicinal product with quinidine, cyclosporine, cisapride, astemizole, terfenadine, ergot alkaloids, pimozide or other medicinal products with a narrow therapeutic index predominantly metabolised by CYP3A4.

Cyclosporin: Since pharmacokinetic and clinical studies on the possible combined effects of azithromycin and cyclosporin have not been carried out, the therapeutic situation should be carefully considered before these active substances are administered simultaneously. If combination treatment is considered justifiable, the cyclosporin levels

should be carefully monitored and the dosage should be adjusted accordingly.

Terfenadine: In pharmacokinetic studies there are no reports of interactions 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. Azithromycin should be administered with caution in combination with terfenadine.

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 torsade de pointes.

Astemizol, Triazolam, Midazolam, Alfentanil:
No data are available on interactions with Astemizol, Triazolam, Midazolam and Alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentiation of its effect during concomitant use of the macrolide antibiotic erythromycin.

4.6 Pregnancy and lactation

There are no adequate and well controlled studies in pregnant women. Animal reproduction studies show passage across the placenta. No teratogenic effects were observed in rat reproduction studies (see further section 5.3). Since animal studies are not always predictive of human response, azithromycin should be used with caution during pregnancy and only if adequate alternatives are not available.

Limited data indicate that azithromycin is excreted in breast milk. A decision should be made whether to discontinue breastfeeding or discontinue azithromycin taking into account the importance of treatment to the nursing mother.

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

About 13% of patients included in clinical trials reported adverse events most commonly gastro-intestinal disorders.

System organ class	**Common >1/100, <1/10**	**Uncommon >1/1000, <1/100**	**Rare >1/10000, <1/1000**
Blood and lymphatic - system disorders			• thrombocytopenia • haemolytic anaemia • transient mild reductions in neutrophil counts have occasionally been observed in clinical trials for which a causal relationship with Azithromycin treatment has not been confirmed
Psychiatric disorders			• aggression • agitation • anxiety • nervousness • depersonalisation, in elderly patients delirium may occur.
Nervous system disorders		• dizziness/vertigo • somnolence • headache • convulsions • disruption to the patient's sense of smell	• paraesthesia, syncope and asthenia • insomnia • hyperactivity

		and taste	
Ear and labyrinth disorders			• macrolide antibiotics have been reported to have caused hearing damage. In some patients receiving azithromycin, impaired hearing, deafness and ringing in the ears have been reported. Many of these cases relate to experimental studies in which Azithromycin was used in large doses over prolonged periods. According to available follow-up reports, the majority of these problems, however, were reversible
Cardiac disorders			• palpitations • arrhythmia including associated ventricular tachycardia. • there is a potential risk of QT prolongation and torsade de pointes, particularly in patients who are susceptible to these conditions
Gastrointestinal disorders	• nausea/vomiting • diarrhoea • abdominal discomfort (pain/cramps)	• loose stools (as a result of infrequent dehydration) • flatulence • anorexia • digestive disorders	• constipation • tongue discolouration • pancreatitis • discolouration of the teeth • pseudomembranous colitis
Hepatobiliary disorders			• abnormal liver function test values • hepatitis • cholestatic jaundice • rare cases of hepatic necrosis and hepatic failure which have rarely resulted in death
Skin and subcutaneous tissue disorders		• allergic reactions including pruritus and rash	• allergic reactions including angioneurotic oedema, urticaria and photosensitivity; serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders		• arthralgia	
Renal and urinary tract disorders			• interstitial nephritis • acute renal failure
Reproductive system and breast disorders		• vaginitis	
General disorders and administration site conditions			• anaphylaxis including oedema (rarely fatal) • asthenia • candidiasis

4.9 Overdose

The undesirable effects at dosages in excess of the recommended dosages were similar to those after normal dosages. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. In cases of overdose the administration of medicinal charcoal and general symptomatic treatment and measures to support vital functions are indicated where necessary.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.
ATC code: J01FA10

Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the 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.

The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the ribosomal 50S sub-unit and thus inhibiting the translocation of peptides.

Breakpoints
Azithromycin susceptibility breakpoints for typical bacterial pathogens:

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

Note that national breakpoints may differ from those recommended by NCCLS

There are currently no recommended NCCLS breakpoints to azithromycin for *Neisseria gonorrhoeae* and *Moraxella catarrhalis*.

There are no currently recommended NCCLS breakpoints for the atypical pathogens against which azithromycin has demonstrated clinically significant activity, such as *Chlamydia* spp., *Mycobacterium avium* Complex, *Mycoplasma* spp., *Borrelia* spp. and *Helicobacter pylori.*

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information provides only an approximate guidance on the probability of an organism being susceptible to azithromycin.

Table: Antibacterial spectrum of azithromycin

Species	**Range of acquired resistance (%)**
Commonly susceptible species.	
Aerobic Gram-positive	
Corynebacterium diphteriae	-
Staphylococcus aureus – *methicillin susceptible*	0-19
Coagulase-neg. staphylococci- *methicillin susceptible*	-
Streptococcus pneumoniae	5-37
Erythromycin-sensitive	-
Penicillin-sensitive	3-23
Streptococcus pyogenes	0-43
Erythromycin-sensitive	21
Streptococci viridans group	20-32
Aerobic Gram-negative	
Bordetella pertussis	-
***Escherichia coli* – ETEC**	-
***Escherichia coli* – EAEC**	-
Haemophilus influenzae	0-2
Haemophilus ducreyi	-
Legionella spp.	-
Moraxella catarrhalis	0-2
Erythromycin-sensitive	-
Erythromycin-intermediate	-
Neisseria gonorrhoeae	0
Pasteurella mutocida	-
Anaerobic	
Clostridium perfringens	-
Fusobacterium nucleatum ***Fusobacterium necrophorum***	-
Prevotella spp.	-
Porphyromonas spp.	-
Propionibacterium spp.	-
Other microorganisms	
Borrelia burgdorferi	-
Chlamydia pneumoniae	-
Chlamydia trachomatis	-
Helicobacter pylori	-
Listeria spp.	-
Mycobacterium avium Complex	
Mycoplasma pneumoniae	-
Ureaplasma urelyticum	-

Species for which acquired resistance may be a problem.	
Aerobic Gram-positive	
Streptococcus pneumoniae	
Penicillin-intermediate	20-62
Penicillin-resistant	23-78
Erythromycin-intermediate	-
Streptococcus pyogenes	
Erythromycin-intermediate	-
Streptococci viridans group	
Penicillin-intermediate	-
Aerobic Gram-negative	
Moraxella catarrhalis - *erythromycin-resistant*	
Anaerobic	
Peptostreptococcus spp.	-
resistant Inherently resistant organisms	
Aerobic Gram-positive	
Corynebacterium spp.	-
Enterococcus spp.	-
Staphylococci MRSA, MRSE	Resistant
Streptococcus pneumoniae	
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
(Cross) resistance

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

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

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

5.2 Pharmacokinetic properties

Absorption:
Following oral administration, the bioavailability of azithromycin is approximately 37 %. Peak plasma levels are reached after 2-3 hours.

Distribution:
Orally administered azithromycin is widely distributed over the whole body. Pharmacokinetic studies have shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma) than in the plasma. This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 µg/ml, 2-3 hours after administration. With the recommended dosage no accumulation in the serum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than in the serum/plasma. Three days after administration of 500 mg as a single dose or in divided doses, concentrations of 1.3-4.8 µg/g, 0.6-2.3 µg/g, 2.0-2.8 µg/g and 0-0.3 µg/ml are found in lung, prostate, tonsil and serum respectively. Mean peak concentration measured in peripheral leucocytes, are higher than the MIC_{90} of the most common pathogens.

In experimental *in-vitro* and *in-vivo* studies, azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appeared to contribute to the accumulation of azithromycin in tissue. The binding of azithromycin to plasma proteins is variable, and varies from 52 % at 0.05 µg/ml to 18 % at 0.5 µg/ml, depending on the serum concentration.

Metabolism and Excretion:
The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 4 days. In elderly volunteers (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended. Approximately 12 % of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile, together with
10 metabolites (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). A comparison of HPLC and microbiological methods of determination suggests that the metabolites do not play a role in the microbiological activity of azithromycin.

Pharmacokinetics in Special populations
Renal Insufficiency:
Following a single oral dose of azithromycin 1g, 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>80ml/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 Cmax achieved is slightly lower than adults with 224µg/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 36h in the older children was within the expected range for adults.

5.3 Preclinical safety data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets:
Pregelatinised maize starch,
anhydrous calcium hydrogen phosphate,
croscarmellose sodium,
magnesium stearate
sodium laurilsulfate

Coating:
hypromellose,
ethylcellulose,
diethyl phthalate
titanium dioxide (E171).

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Store in the original package, keep blisters in outer carton in order to protect from light and moisture.

6.5 Nature and contents of container

1, 2, 3, 4, 6, 30, 100 tablets in a PVdC/PVC-Alu blister

Not all pack sizes may be marketed.

6.6 Instructions for use and handling

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Limited
T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13,
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8 MARKETING AUTHORISATION NUMBER

PA 577/66/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th May 2005

10 DATE OF REVISION OF THE TEXT

May 2005