1.3.1 PRESCRIBING INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fazimax Capsules (AZITHROMYCIN Capsules 500mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each film coated Capsules contains:
Azithromycin USP 500mg As
Azithromycin dihydrate
Colour : Approved colour used

a3. PHARMACEUTICAL FORM

Capsules for Oral administration

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Azithromycin Capsules can be applied for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin:

− acute bacterial sinusitis (adequately diagnosed)
− acute bacterial otitis media (adequately diagnosed)
− pharyngitis, tonsillitis
− acute exacerbation of chronic bronchitis (adequately diagnosed)
− mild to moderately severe community acquired pneumonia
− skin and soft tissue infections
− uncomplicated Chlamydia trachomatis urethritis and cervicitis

4.2 Dosage and administration:

Posology

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 500mg on the second to the fifth day.

Older people

The same dosage as in adult patients is used for older people. Since older people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

Paediatric population

Azithromycin Capsules 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 azithromycine, 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). In patients with hepatic impairment: A dose adjustment is not necessary for patients with mild to moderately impaired liver function.

Method of administration

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

4.3 Contraindications:

The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the 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 lifethreatening liver failure have been reported with azithromycin. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests / investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

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

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. 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 older people) such as patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as

citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

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

4.5 Interaction with other Medicinal products and other forms of Interaction

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine

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

Didanosine (Dideoxyinosine)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

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. *Zidovudine*

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

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

Ergot

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Pharmacokineticstudieshavebeenconductedbetweenazithromycinandthefollowingdrugsknown to undergosignificantcytochromeP450mediatedmetabolism.

Atorvastatin

Coadministration 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 coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Cyclosporin

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of cyclosporin, the resulting cyclosporin 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 coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz

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

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.

Methylprednisolone

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

Midazolam

In healthy volunteers, coadministration 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

Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either 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.

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and C_{max} of sildenafil or its major circulating metabolite.

Terfenadine

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin

and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred. *Theophylline*

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam

In 14 healthy volunteers, coadministration of azithromycin 500 mg on Day 1 and 500mg 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

Coadministration 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.

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.

Lactation

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.

Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

4.7 Effects on Ability to Drive and Use Machines:

There is no evidence to suggest that azithromycin may have an effect: on a patient's ability to drive or operate machinery.

4.8 Undesirable Effects

The table below lists the adverse reactions identified through clinical 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); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

System Organ Class	***Frequency***	***Adverse reaction***
Infections and infestations	Infections and infestations infection	Candidiasis Vaginal Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder

		Rhinitis Oral candidiasis
	Infections and infestations	Pseudomembranous colitis
Blood and lymphatic system disorders	disorders	Leukopenia Neutropenia Eosinophilia
	Not known	Thrombocytopenia Haemolytic anaemia
Immune system disorders	Uncommon	Angioedema Hypersensitivity
	Not known	Anaphylactic reaction
Metabolism and nutrition disorders	Uncommon	Anorexia
	Uncommon	Nervousness Insomnia
	Rare	Agitation Depersonalisation
	Not known	Aggression Anxiety Delirium Hallucination
Nervous system disorders	Common	Headache
	Uncommon	Dizziness Somnolence Dysgeusia Paraesthesia
	Not known	Syncope, convulsion Hypoaesthesia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Ear disorder Vertigo
	Not known	Hearing impairment including deafness and/or tinnitus
Cardiac disorders	Uncommon	Palpitations
	Not known	*Torsades de pointes*

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

disorders		Back pain Neck pain
	Not known	Arthralgia
Renal and urinary disorders	Uncommon	Dysuria Renal pain
	Not known	Renal failure acute Nephritis interstitial
Reproductive system and breast disorder0073	Uncommon	Metrorrhagia Testicular disorder
General disorders and administration site conditions	Uncommon	Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema
Investigations	Common	Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased
	Uncommon	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubine increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline phosphatase increased Chloride increased Glucose increased Platelets increased Hematocrit decreased Bicarbonate increased Abnormal sodium
Injury and poisoning	Uncommon	Post procedural complication

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 general supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

ATCclassification
Pharmacotherapeutic group: Antibacterials for systemic use; macrolids.
ATC code: J01FA10.

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

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

Mechanism of resistance:
Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic. Complete cross resistance exists among Streptococcus pneumoniae, betahaemolytic streptococcus of group A, Enterococcus faecalis and Staphylococcus aureus, including methicillin resistant S. aureus (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Breakpoints
EUCAST (European Committee on Antimicrobial Susceptibility Testing)

Pathogens (mg/l)	**Susceptible (mg/l)**	**Resistant**
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (Group A, B, C, G)	≤ 0.25	> 0.5
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis		≤ 0.5 > 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

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

Table of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms
*Haemophilus influenzae**
*Moraxella catarrhalis**
Other microorganisms
Chlamydophila pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycobacterium avium
*Mycoplasma pneumonia**
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
*Staphylococcus aureus**
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Staphylococcus aureus – methicillin resistant and erythromycin resistant strains
Streptococcus pneumoniae – penicillin resistant strains
Streptococcus agalactiae
*Streptococcus pneumoniae**
*Streptococcus pyogenes**
Other microorganisms
Ureaplasma urealyticum
Aerobic Gram-negative microorganisms
Escherichia coli
Pseudomonas aeruginosa
Klebsiella spp.
Anaerobic Gram-negative microorganisms
Bacteroides fragilis group

* Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indications.

5.2. Pharmacokinetic properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (Cmax 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 MIC90 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.

5.3 Preclinical safety data
In animal tests in which the dosages used amounted to 40 times the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule, no true toxicological consequences were observed which were associated with this. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown. *Carcinogenic potential:*
Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only, and there were no signs indicative of carcinogenic activity.
Mutagenic potential:
There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.
Reproductive toxicity:
In animal studies of the embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation in physical development and delay in reflex development following treatment with
50 mg/kg/day azithromycin and above were observed.

6. PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS:
Azithromycin USP (As azithromycin dihydrate)
Lactose BP
Colloidal Anhydrous Silica BP
Microcrystalline Cellulose BP
Povidone BP
Isopropyl Alcohol BP

Purified Talc BP Stearic Acid BP Croscarmellose sodium BP Magnesium Stearate BP Hypromellose (15 cps) BP
Dichloromethane BP
Titanium Dioxide BP
Macrogol (6000) BP
Polysorbate 80 BP

6.2 Shelf Life

36 Months

6.3 Special Precautions for Storage

Store at temperature below 30°C.
Protect from light and moisture.

6.4 Nature and Contents of Container

Azithromycin Capsules 500mg is packed in a clear Alu-PVC blister pack.

6.5 Special Precautions for Disposal and Other Handling

Keep out of reach of children.

7. MARKETING AUTHORISATION HOLDER

AZMU PHARMACEUTICALS LIMITED.
MANGAL PLAZA, AREA 11, GARKI FCT. AQBUJA FCT

8. MARKETING AUTHORISATION NUMBER(S)

B4-3112

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION