For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days.

**Elderly patients**
The same dose range as in younger patients may be used in the elderly.

**Children**
Azithromycin 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.

**Patients with 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).

**Patients with hepatic impairment:**
A dose adjustment is not necessary for patients with mild to moderately impaired liver function. Since azithromycin is metabolised in the liver and excreted in bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of the use of azithromycin (see section 4.4).

**Method of Administration:**
&lt;Azithromycin 250 mg film-coated tablet&gt; should be administered as a daily single dose. &lt;Azithromycin 250 mg film-coated tablet&gt; may be taken with meals.

**4.3 Contraindications**
The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, to other macrolide or ketolide antibiotics, or to any of the excipients (see section 4.4 and 6.1).

**4.4 Special warnings and precautions for use**
As with erythromycin and other macrolides, serious allergic reactions including angioeurotic oedema and anaphylaxis (rarely fatal), have been reported.
Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy. Neurological or psychiatric diseases: Azithromycin should be administered with caution to patients suffering from neurological or psychiatric diseases. Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Superinfections: As with any antibacterial agent, observation for signs of superinfection with non-susceptible organisms, including fungi, is recommended. 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.

Streptococcal infections: Penicillin is usually the first choice for treatment of streptococcus pyogenes-pharyngitis/tonsillitis and comprises prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in oropharynx, but no data is available that shows efficacy of azithromycin in preventing acute rheumatic fever. These medicinal products contain lactose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Antacids: When studying the effect of simultane-
ously administered antacids 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 approximately 25%. <Azithromycin 250 mg film-coated tablet> should be taken at least 1 hour before or 2 hours after the antacid.

**Astemizol, Alfentanil:**
No data are available on interactions with Astemizol 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.

**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:** Coadministration of daily doses of 1200 mg azithromycin with didanosine in 6 HIV-positive subjects did not appear to affect the pharmacokinetics of didanosine as compared with placebo.

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

**Zidovudine:** 1000 mg single doses and 1200 mg or 600 mg multiple doses of azithromycin had little effect upon the pharmacokinetics of zidovudine or its glucuronide metabolite in the plasma or upon excretion in urine. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in mononuclear cells in the peripheral circulation. The clinical significance of these findings is unclear, but 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.

**Cisapride:** Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because other macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsade de pointes.

**Ergotamine derivatives:** Due to the theoretical possibility of ergotism, the concurrent use of azithromycin and ergot derivatives is not recommended (see section 4.4).

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

**Atorvastatin:** 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).

**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.
Ciclosporin: In a pharmacokinetic study with healthy volunteers that were administered 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. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, ciclosporin 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 conducted 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: Concomitant administration of 1200 mg azithromycin and steady state nelfinavir (750 mg 3 times daily) resulted in an average 16% decrease of nelfinavir AUC, an increase of azithromycin AUC and C_{max} with 113% and 136% respectively. No dose adjustment is necessary but patients should be monitored for known side effects of azithromycin.

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).

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: Azithromycin has not affected the pharmacokinetics of theophylline when healthy volunteers received Azithromycin and theophylline simultaneously. The combined use of Theophyllin and other macrolide antibiotics sometimes led to an increasing serum level of theophylline.

Triazolam: In 14 healthy volunteers, coadministration 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: Coadministration of trimethoprim/sulfamethoxazole DS (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 Pregnancy and lactation
Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human
response, azithromycin should be used during pregnancy only if clearly needed.

There are no data on secretion in breast milk. As many drugs are excreted in human 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.

### 4.7 Effects on ability to drive and use machines

Experience to date indicates that, in general, azithromycin has no effect on ability to concentrate and react. However, undesirable effects of treatment, such as dizziness, somnolence and convulsions (see section 4.8), can influence the ability to drive and operate machinery.

### 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)
- **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:

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse reaction</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>Candidiasis, oral candidiasis, vaginal infection</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Pseudomembranous collitis (see section 4.4)</td>
<td>Not known</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Leukopenia, neutropenia</td>
<td>Uncommon</td>
</tr>
<tr>
<td></td>
<td>Thrombocytopenia, haemolytic anaemia</td>
<td>Not known</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Hypersensitivity, angioedema</td>
<td>Not known</td>
</tr>
<tr>
<td></td>
<td>Anaphylactic reaction (see section 4.4)</td>
<td>Not known</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Anorexia</td>
<td>Common</td>
</tr>
</tbody>
</table>

### Psychiatric Disorders

- **Nervousness**: Uncommon
- **Agitation**: Rare
- **Aggression, anxiety**: Not known

### Nervous System Disorders

- **Dizziness, headache, paresthesia, dysgeusia**: Common
- **Hypoesthesia, somnolence, insomnia**: Uncommon
- **Syncope, convulsion, psychomotoric hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (see Section 4.4)**: Not known

### Eye Disorders

- **Visual impairment**: Common

### Ear and Labyrinth Disorders

- **Deafness**: Common
- **Hearing impaired, tinnitus**: Uncommon
- **Vertigo**: Rare

### Cardiac Disorders

- **Palpitations**: Uncommon
- **Torsades de pointes (see section 4.4), arrhythmia (see section 4.4) including ventricular tachycardia**: Not known

### Vascular Disorders

- **Hypotension**: Not known

### Gastrointestinal Disorders

- **Diarrhea, abdominal pain, nausea, flatulence**: Very common
- **Vomiting, dyspepsia**: Common
- **Gastritis, constipation**: Uncommon
- **Pancreatitis, tongue discoloration**: Not known

### Hepatobiliary Disorders

- **Hepatitis**: Uncommon
- **Hepatic function abnormal**: Rare
- **Hepatic failure**, **hepatitis fulminant, hepatic necrosis, jaundice cholestatic (see section 4.4)**: Not known

### Skin and Subcutaneous Tissue Disorders

- **Rash, pruritus**: Common
- **Stevens-Johnson syndrome, photosensitivity reaction, urticaria**: Uncommon
- **Toxic epidermal necrolysis, erythema multiforme**: Not known

### Musculoskeletal and Connective Tissue Disorders

- **Arthralgia**: Common

### Renal and Urinary Disorders

- **Renal failure acute, nephritis interstitial**: Not known

### General Disorders and Administration Site Conditions

- **Fatigue**: Common
- **Chest pain, oedema, malaise, asthenia**: Uncommon

### Investigations

- **Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased**: Common
- **Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal**: Uncommon
- **Electrocardiogram QT prolonged (see section 4.4)**: Not known

**Which has rarely resulted in death**
4.9 Overdose
The adverse events experienced in higher than recommended dosages 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, macrolides, azithromycin, ATC code: J01FA10

Mode of action:
The mechanism of action of azithromycin is based on the suppression of bacterial protein synthesis, that is to say that it binds to the ribosomal 50s sub-unit and inhibits the translocation of peptides. Azithromycin acts bacteriostatic.

PK/PD Relationship:
The efficacy of azithromycin is best described by the relationship AUC/MIC, where AUC describes the area under the curve and MIC represents the mean inhibitory concentration of the microbe concerned.

Mechanism of resistance:
Resistance to azithromycin may be natural or acquired. There are 3 main mechanisms of resistance affecting azithromycin:
- Efflux: resistance may be due to an increase in the number of efflux pumps on the cell membrane. In particular, 14- and 15-link macrolides are affected. (M-phenotype)
- Alterations of the cell structure: methylisation of the 23s rRNS may reduce the affinity of the ribosomal binding sites, which can result in microbial resistance to macrolides, lincosamides and group B streptogramins (S₈) (MLSB-phenotype).
- enzymatic deactivation of macrolides is only of limited clinical significance.

In the presence of the M-phenotype, complete cross resistance exists between azithromycin and clarithromycin, erythromycin and roxithromycin. With the MLSB-phenotype, additional cross resistance exists with clindamycin and streptogramin B. A partial cross resistance exists with spiramycin.

### Breakpoints
According to EUCAST (European Committee on Antimicrobial Susceptibility Testing) the following breakpoints have been defined for azithromycin (2009-06-01):

<table>
<thead>
<tr>
<th>Species</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus spp.</td>
<td>≤1 mg/l</td>
<td>&gt;2 mg/l</td>
</tr>
<tr>
<td>Streptococcus A,B,C,G:</td>
<td>≤0,25 mg/l</td>
<td>&gt;0,5 mg/l</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>≤0,25 mg/l</td>
<td>&gt;0,5 mg/l</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>≤0,12 mg/l</td>
<td>&gt;4 mg/l</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>≤0,5 mg/l</td>
<td>&gt;0,5 mg/l</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>≤0,25 mg/l</td>
<td>&gt;0,5 mg/l</td>
</tr>
</tbody>
</table>

### 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 10% in at least one country in the European Union.

<table>
<thead>
<tr>
<th>Table of Susceptibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commonly susceptible species</td>
</tr>
<tr>
<td><strong>Aerobic Gram-negative microorganisms</strong></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
</tr>
<tr>
<td><strong>Other microorganisms</strong></td>
</tr>
<tr>
<td>Chlamydomphila pneumoniae</td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
</tr>
<tr>
<td>Legionella pneumonia</td>
</tr>
<tr>
<td>Mycobacterium avium</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
</tr>
<tr>
<td><strong>Species for which acquired resistance may be a problem</strong></td>
</tr>
<tr>
<td><strong>Aerobic Gram-positive microorganisms</strong></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td><strong>Other microorganisms</strong></td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
</tr>
</tbody>
</table>
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 than are released from inactive phagocytes. In animal models the azithromycin concentrations measured in inflammation foci were high.

Pharmacokinetics in Special Populations

Renal insufficiency
Following a single oral dose of azithromycin 1g, mean $C_{\text{max}}$ 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 $C_{\text{max}}$ and $AUC_{0-120}$ increased 61% and 33% 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 $C_{\text{max}}$ 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 animal tests in which the dosages used amount-
ed 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**
Lactose, maize starch, magnesium stearate, sodium lauryl Sulphate, Talc & EGC size 0

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
4 years

**6.4 Special precautions for storage**
Store below 30°C.
Store in the original package

**6.5 Nature and contents of container**
How supplied
Azomax capsules 250 mg, 6 capsules per pack.

### 6.6 Special precautions for disposal and other handling
No special requirements.

### 7. Marketing Authorization Holder
SAJA Pharmaceuticals
Saudi Arabian Japanese pharmaceutical company limited
Jeddah – Saudi Arabia

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Tel: + 966 2 645 0303
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### 8. Marketing Authorization Number
19/370/05

### 9. Date of First Authorization /Renewal of The Authorization
02/04/1426

### 10. DATE OF REVISION OF THE TEXT
June 2013