# ZITHROMAX®
## (Azithromycin)

### 1. NAME OF THE MEDICINAL PRODUCT

ZITHROMAX® 250 mg Capsules

ZITHROMAX® 250 mg, 500 mg Tablets

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Capsules:** Azithromycin dihydrate 262.05 mg equivalent to 250 mg azithromycin base.

**Film-coated Tablets 250 mg:** Azithromycin dihydrate 262.05 mg equivalent to 250 mg azithromycin base.

**Film-coated Tablets 500 mg:** Azithromycin dihydrate 524.10 mg equivalent to 500 mg azithromycin base.

### 3. PHARMACEUTICAL FORM

**Capsules**: Azithromycin capsules for oral administration are available as plain white No. 0 hard gelatin capsules containing azithromycin dihydrate equivalent to 250 mg azithromycin.

**Film-coated Tablets:** Azithromycin film-coated tablets are capsular shaped and contain azithromycin dihydrate equivalent to 250 mg or 500 mg azithromycin.

### 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. Pharmacodynamic Properties**):
- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis (see section **4.4. Special Warnings and Precautions for Use** 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® Capsules or Tablets should be given as a single daily dose.

In common with many other antibiotics ZITHROMAX® Capsules or Tablets should be taken at least 1 hour before or 2 hours after 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 is 1000 mg or 2000 mg of azithromycin in combination with 250 mg or 500 mg ceftriaxone according to local clinical treatment guidelines. For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

**Paediatric population:**
**In children under 45 kg body weight**: ZITHROMAX® Capsules or 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. Special Warnings and Precautions for Use** and section **5.2. Pharmacokinetic Properties**).

**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. Special Warnings and Precautions for Use**).

Method of administration
ZITHROMAX® Capsules or Tablets are for oral administration only.

## 4.3. CONTRAINDICATIONS

ZITHROMAX® is contra-indicated in patients with a known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients (listed in section **6.1. List of Excipients**).

## 4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity
As with erythromycin and other macrolides, serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), Acute Generalized Exanthematous Pustulosis (AGEP) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

Hepatotoxicity
Since the liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section **4.8 Undesirable**

**Effects**). 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.

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-administrated.

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. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation (see section **4.8 Undesirable Effects**); therefore caution is required when treating patients:

- With congenital or documented QT prolongation
    - Currently receiving treatment with other active substance known to prolong QT interval such as antiarrhythmics of Classes Ia and III, cisapride and terfenadine
- With electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Superinfection

As with any antibiotic preparation, observation 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 from mild diarrhoea to fatal colitis. Strains of *C. difficile* producing hypertoxin A and B 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. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific trea®ent for *C. difficile* should be considered.

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 GFR <10 ml/min a 33% increase in systemic exposure to azithromycin was observed (see section **5.2. Pharmacokinetic Properties**).

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. Undesirable Effects**).

Hydroxychloroquine or chloroquine
Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section **4.5. Interaction with other medical products and other forms of interaction**).

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

This medicinal product contains sulfur dioxide which may rarely cause severe hypersensitivity reactions and bronchospasm.

This medicinal product contains less than 1 mmol sodium (23 mg) per Capsules or Tablets, that is to say essentially 'sodium-free'.

ZITHROMAX® Capsules or Tablets are for oral administration only.

## 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 24%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

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

**Didanosine *(Dideoxyinosine)*:**
Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

**Digoxin and colchicine:**
Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, 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 digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

**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 derivatives:**
Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section **4.4. Special Warnings and Precautions for Use**).

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

**Atorvastatin:**
Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

**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 dose of 15 mg warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

**Ciclosporin:**
In a pharmacokinetic study with healthy volunteers 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 concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

**Efavirenz:**
Co-administration of a single dose of 600 mg azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

**Fluconazole:**
Co-administration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole; however, a clinically insignificant decrease in $C_{max}$ (18%) of azithromycin was observed.

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

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

**Midazolam:**
In healthy volunteers, co-administration of 500 mg/day azithromycin for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15 mg midazolam.

**Nelfinavir:**
Co-administration of azithromycin (1200 mg) and nelfinavir at steady-state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was required.

**Rifabutin:**
Co-administration 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 Undesirable Effects**).

**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, co-administration of 500 mg azithromycin on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

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

**Hydroxychloroquine or chloroquine:**
Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

**Medicinal products which are known to prolong the QT interval (see section 4.4. Special Warnings and Precautions for Use):**
Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine.

## 4.6. FERTILITY, PREGNANCY AND LACTATION

Pregnancy
Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the foetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women.

There is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period (> 7,300 first trimester exposures). While most studies do not suggest an association with adverse foetal effects such as major congenital malformations or cardiovascular malformations, there is limited epidemiological evidence of an increased risk of miscarriage following azithromycin exposure in early pregnancy. Therefore, azithromycin should only be used during pregnancy if clinically needed and the benefit of treatment is expected to outweigh any small increased risks which may exist.

Breast-feeding
Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/kg/day.

No serious adverse effects of azithromycin on the breast-fed infants were observed.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

## 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:**

**Infections and Infestations**
***Uncommon*** *(≥ 1/1,000 to < 1/100)*
Candidiasis, oral candidiasis, vaginal infection
***Not known*** *(cannot be estimated from available data)*
Pseudomembranous colitis (see section **4.4. Special Warnings and Precautions for Use**)

**Blood and Lymphatic System Disorders**
***Uncommon*** *(≥ 1/1,000 to < 1/100)*
Leukopenia, neutropenia
***Not known*** *(cannot be estimated from available data)*
Thrombocytopenia, haemolytic anaemia

**Immune System Disorders**
***Uncommon*** *(≥ 1/1,000 to < 1/100)*
Angioedema, hypersensitivity
***Not known*** *(cannot be estimated from available data)*
Anaphylactic reaction (see section **4.4. Special Warnings and Precautions for Use**)

**Metabolism and Nutrition Disorders**
***Common*** *(> 1/100, < 1/10)*
Anorexia

**Psychiatric Disorders**
***Uncommon*** *(≥ 1/1,000 to < 1/100)*
Nervousness
***Rare*** *(> 1/10,000, < 1/1,000)*
Agitation
***Not known*** *(cannot be estimated from available data)*
Aggression, anxiety

**Nervous System Disorders**
***Common*** *(> 1/100, < 1/10)*
Dizziness, headache, paraesthesia, dysgeusia
***Uncommon*** *(≥ 1/1,000 to < 1/100)*
Hypoaesethesia, somnolence, insomnia
***Not known*** *(cannot be estimated from available data)*
Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis (see section **4.4. Special Warnings and Precautions for Use**).

**Eye Disorders**
***Common*** *(> 1/100, < 1/10)*
Visual impairment

**Ear and Labyrinth Disorders**
***Common*** *(> 1/100, < 1/10)*
Deafness
***Uncommon*** *(≥ 1/1,000 to < 1/100)*
Hearing impaired, tinnitus
***Rare*** *(> 1/10,000, < 1/1,000)*
Vertigo

**Cardiac Disorders**
***Uncommon*** *(≥ 1/1,000 to < 1/100)*
Palpitations
***Not known*** *(cannot be estimated from available data)*
Torsades de pointes (see section **4.4. Special Warnings and Precautions for Use**), arrhythmia (see section **4.4. Special Warnings and Precautions for Use**) including ventricular tachycardia

**Vascular Disorders**
***Not known*** *(cannot be estimated from available data)*
Hypotension

**Gastrointestinal Disorders**
***Very common*** *(≥ 1/10)*
Diarrhoea, abdominal pain, nausea, flatulence
***Common*** *(> 1/100, < 1/10)*
Vomiting, dyspepsia
***Uncommon*** *(> 1/1,000, < 1/100)*
Gastritis, constipation
***Not known*** *(cannot be estimated from available data)*
Pancreatitis, tongue discolouration

**Hepatobiliary Disorders**
***Uncommon*** *(> 1/1,000, < 1/100)*
Hepatitis
***Rare*** *(> 1/10,000, < 1/1,000)*
Hepatic function abnormal
***Not known*** *(cannot be estimated from available data)*

Hepatic failure (see section **4.4. Special Warnings and Precautions for Use**), which has rarely resulted in death, hepatitis fulminant, hepatic necrosis, jaundice cholestatic

**Skin and Subcutaneous Tissue Disorders**
***Common*** *(> 1/100, < 1/10)*
Pruritus and rash
***Uncommon*** *(> 1/1,000, < 1/100)*
SJS, photosensitivity reaction, urticaria
***Rare*** *(≥ 1/10,000 to < 1/1,000)*
Acute Generalized Exanthematous Pustulosis (AGEP)*§
Drug reaction with eosinophilia and systemic symptoms (DRESS)*§
***Not known*** *(cannot be estimated from available data)*
TEN*, erythema multiforme*

**Musculoskeletal, Connective Tissue Disorders**
**Common** (> 1/100, < 1/10)
Arthralgia

**Renal and Urinary Disorders**
***Not known*** *(cannot be estimated from available data)*
Renal failure acute, nephritis interstitial

**General Disorders and Administration Site Conditions**
**Common** (> 1/100, < 1/10)
Fatigue
***Uncommon*** *(> 1/1000, < 1/100)*
Chest pain, oedema, malaise, asthenia

**Investigations**
**Common** (> 1/100, < 1/10)
Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased
***Uncommon*** *(> 1/1,000, < 1/100)*
Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal
***Not known*** *(cannot be estimated from available data)*
Electrocardiogram QT prolonged (see section **4.4. Special Warnings and Precautions for Use**)

*ADR identified post-marketing
§ADR frequency represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3".

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.

## 4.9. OVERDOSE

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe

nausea, vomiting and diarrhoea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment 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. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

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.

Azithromycin demonstrates cross resistance with erythromycin resistant gram positive isolates. A decrease in macrolide susceptibility over time has been noted particularly in *Streptococcus pneumoniae* and *Staphylococcus aureus*. Similarly, decreased susceptibility has been observed among *Streptococcus viridans* and *Streptococcus agalactiae* (Group B) streptococcus against other macrolides and lincosamides.

***Breakpoints***
Azithromycin susceptibility breakpoints for typical bacterial pathogens, as published by EUCAST are:

| **Organism** | **MIC breakpoints (mg/L)** | |
|---|---|---|
| | **Susceptible (S≤)** | **Resistant (R>)** |
| *Staphylococcus* spp. | 1 | 2 |
| *Streptococcus* groups A, B, C and G | 0.25 | 0.5 |
| *Streptococcus pneumoniae* | 0.25 | 0.5 |
| *Haemophilus influenzae* | 0.12 | 4 |
| *Moraxella catarrhalis* | 0.25 | 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.

Table: Antibacterial spectrum of Azithromycin

| **Commonly susceptible species** |
|---|
| **Aerobic Gram-positive microorganisms** |

| |
|---|
| *Staphylococcus aureus*<br>Methycillin-susceptible |
| *Streptococcus pneumoniae*<br>Penicillin-susceptible |
| *Streptococcus pyogenes* **(Group A)** |
| **Aerobic Gram-negative microorganisms** |
| *Haemophilus influenzae*<br>*Haemophilus parainfluenzae* |
| *Legionella pneumophila* |
| *Moraxella catarrhalis* |
| *Neisseria gonorrhoeae* |
| *Pasteurella multocida* |
| **Anaerobic microorganisms** |
| *Clostridium perfringens* |
| *Fusobacterium spp.* |
| *Prevotella spp.* |
| *Porphyromonas spp.* |
| **Other microorganisms** |
| *Chlamydia trachomatis* |
| **Species for which acquired resistance may be a problem** |
| **Aerobic Gram-positive microorganisms** |
| *Streptococcus pneumoniae*<br>Penicillin-intermediate<br>Penicillin-resistant |
| **Inherently resistant organisms** |
| **Aerobic Gram-positive microorganisms** |
| *Enterococcus faecalis* |
| Staphylococci **MRSA, MRSE*** |
| **Anaerobic microorganisms** |
| Bacteroides fragilis group |

* Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

Paediatric population

Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

## 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

- **Capsules:** The capsules contain lactose anhydrous, corn starch, magnesium stearate, and sodium lauryl sulphate as excipients. The capsule shell contains gelatin, titanium dioxide (E171) and up to 1000 ppm sulfur dioxide.

- **Film-coated Tablets:** The film-coated tablets contain pregelatinized corn starch, calcium phosphate dibasic anhydrous, croscarmellose sodium, magnesium stearate and sodium lauryl sulphate. The film coating contains Opadry Blue YS1-4254 and carnauba wax No. 120 powder.

### 6.2. INCOMPATIBILITIES

Not available

### 6.3. SHELF LIFE

| Pack (Nature & Content of Container) | Shelf-life | Storage Conditions |
|---|---|---|
| The 6 capsules are packed in one blister pack. | 24 months | Store below 30°C.<br>Avoid exposure to heat & sunlight. |
| The 6 film-coated tablets are packed in one blister pack. | 24 months | Store below 30°C.<br>Avoid exposure to heat & sunlight. |

### 6.4. SPECIAL PRECAUTIONS FOR STORAGE

None.

### 6.5. NATURE AND CONTENT OF CONTAINER

**ZITHROMAX® 250 mg capsules:**
Each blister pack contains 6 hard capsules.
**ZITHROMAX® 500 mg film-coated tablets:**
Each blister pack contains 6 film-coated tablets.
**ZITHROMAX® 250 mg film-coated tablets:**
Each blister pack contains 6 film-coated tablets.

Not all pack sizes may be marketed.

### 6.6. SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

**Capsules:** The capsules should be swallowed whole.

**Film-coated Tablets:** The film-coated tablets should be swallowed whole.

## 6.7. DRUG PRODUCT SPECIFICATIONS

**ZITHROMAX® 250 mg capsules:** USP Specs.
**ZITHROMAX® 500 mg film-coated tablets:** USP Specs.
**ZITHROMAX® 250 mg film-coated tablets:** USP Specs.

## 7. REGISTRATION HOLDER / MARKETING AUTHORIZATION HOLDER

**Marketed by**
Pfizer Pakistan Limited
B-2, S.I.T.E., Karachi, Pakistan

| Name of Manufacturing site | Address of site | Manufacturing step |
|---|---|---|
| Pfizer Pakistan Limited | B-2, S.I.T.E., Karachi, Pakistan | Production, Packaging, Testing & Batch Release |

## 8. REGISTRATION / MARKETING AUTHORIZATION NUMBER

**ZITHROMAX® 250 mg capsules:** 014471
**ZITHROMAX® 500 mg tablets:** 076685
**ZITHROMAX® 250 mg tablets:** 076686

## 9. DATE FROM WHICH MARKETING IS AUTHORIZED

**ZITHROMAX® 250 mg capsules:**
Date of first Registration/ Market Authorization: i.e., 17-Oct-1993
Date of latest renewal: i.e., 27-May-2021
**ZITHROMAX® 500 mg tablets:**
Date of first Registration/ Market Authorization: i.e., 23-Jan-2015
Date of latest renewal: i.e., 15-Jan-2020
**ZITHROMAX® 250 mg tablets:**
Date of first Registration/ Market Authorization: i.e., 23-Jan-2015
Date of latest renewal: i.e., 15-Jan-2020

## 10. DATE OF REVISION OF THE TEXT

21-October-2022

**Zithromax Oral/LPD/PK-03**
**According to UK Approved SPC dated: 23/08/2023 & approved information in Pakistan**

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet*