Zithromax*

Azithromycin dihydrate

250 mg Capsule

Reference market:
Italy

AfME markets using this LPD:
Egypt

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

ZITHROMAX 250 mg hard-gelatin capsules

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 250 mg hard-gelatin capsule contains:

Active substance:
Azithromycin dihydrate 262.05 mg
equivalent to Azithromycin base 250 mg

Excipients with known effects: lactose.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Hard gelatin capsules: White cap and body containing white to off white powder imprinted with black ink "Pfizer ZTM 250".

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Treatment of infections caused by azithromycin-susceptible bacteria.
- infections of the upper respiratory tract (sinusitis, tonsillitis, and pharyngitis),
- infections of the lower respiratory tract (including bronchitis and pneumonia);
- middle ear infections (acute otitis media),
- odontostomatological infections,
- skin and soft tissue infections,
- non-gonococcal urethritis (caused by *Chlamydia trachomatis*),
- soft chancres (caused by *Haemophilus ducreyi).*

### 4.2 Posology and method of administration

Adults
For the treatment of upper and lower respiratory tract infections, skin and soft tissues infections and odontostomatological infections: 500 mg per day taken once daily, for 3 consecutive days.
For the treatment of sexually transmitted diseases caused by susceptible strains of *Chlamydia trachomatis* and *Haemophilus ducreyi*: 1,000 mg taken only once in a single oral administration.

Elderly
The same dosage regimen can be applied to elderly patients. Since elderly patients are more susceptible to developing cardiac arrhythmia, particular caution is recommended due to the risk of developing cardiac arrhythmia and torsade de pointes (see Section 4.4).

Administration after a large meal reduces the bioavailability of ZITHROMAX (azithromycin) capsule by 50%. For this reason, every dose should be administered at least 1 hour before or 2 hours after meals.
Capsules must be taken whole.

Renal Impairment
No dose adjustment is required for patients with mild to moderate renal impairment (GFR 10 - 80 mL/min); however, caution is necessary in those seriously compromised (GFR < 10 mL/min) (see Sections 4.4 and 5.2).

Hepatic Impairment
No dose adjustment is required for patients with mild to moderate hepatic impairment (see Sections 4.4 and 5.2).

## 4.3 Contraindications

Hypersensitivity to the active ingredient, to erythromycin, any other macrolide or ketolide antibiotics, or any other excipients listed in section 6.1.

Zithromax is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of Zithromax.

## 4.4 Special warnings and precautions for use

Hypersensitivity
As for erythromycin and other macrolides serious rare allergic reactions have been reported, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatological reactions including acute generalized exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and rash with eosinophilia and systemic symptoms (DRESS). Some of these reactions associated with Zithromax have caused recurring symptoms and have required an observation period and prolonged treatment.

If there is an allergic reaction, the administration of the medicinal product must be discontinued and adequate therapy started. Physicians should be aware of the fact that when the symptomatic therapy is suspended allergic symptoms may occur.

Hepatotoxicity
Azithromycin must be used with caution in patients with serious liver disease since its primary route of elimination is the liver. With azithromycin, there have been reports of hepatic impairment, hepatitis, cholestatic jaundice, hepatic necrosis and fulminant hepatic failure, potentially caused by hepatic impairment, some of which had fatal results (see Section 4.8). A few patients may have had previous hepatic diseases or may have taken other hepatotoxic medicinal products. If signs and symptoms of hepatic dysfunction develop, such as rapid appearance of asthaenia associated with jaundice, dark urine, bleeding or hepatic encephalopathy, diagnostic analysis/exams must be run on hepatic function immediately. Immediately suspend treatment with azithromycin if any signs of hepatic dysfunction develop.

Infantile hypertrophic pyloric stenosis (IHPS)
As a result of the use of azithromycin in infants (treatment up to 42nd day of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and health operators must be told to contact their physician if vomiting or irritability occurs after eating.

Ergotamine Derivatives
Co-administration of macrolide antibiotics in patients being treated with ergotamine derivatives has precipitated convulsive ergotism. There are no data currently available on the possibility of interaction between ergotamine and azithromycin. However, due to the theoretical possibility of ergotism, azithromycin and ergotamine must not be co-administered.

As with all other antibiotic preparations, it is recommended to carefully monitor for any development of super infections with resistant micro-organisms including fungi.

Diarrhoea associated with *Clostridium difficile*
As with almost all antibiotics, including azithromycin, there have been reports of diarrhoea associated with *Clostridium difficile* (CDAD), the severity of which can vary from mild diarrhoea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon and results in excessive growth of *C. difficile.*

*C. difficile* produces toxins A and B, which contribute to the development of diarrhoea. The strains of *C. difficile* that produce excess toxins cause an increase in morbidity and mortality rates as these infections are usually refractory to antibacterial therapy and often require a colectomy. The possibility of diarrhoea associated with *C. difficile* must be considered in all patients who develop diarrhoea after a treatment with antibiotics. A detailed

patient history is also necessary because cases of diarrhoea associated with *C. difficile* have been reported over two months after the administration of antibiotics.

In patients with seriously compromised renal function (GFR < 10 mL/min) a 33% increase in systemic exposure to azithromycin was observed (see Section 5.2).

Prolonged QT interval
In treatment with macrolides, including azithromycin, a prolonged cardiac repolarisation and QT interval were found using ECG, with the risk of developing cardiac arrhythmia and torsade de pointes (see Section 4.8). Therefore, given that the following situations can cause an increase in the risk of ventricular arrhythmias (including torsade de pointes) that can lead to cardiac arrest, azithromycin should be administered with caution in patients who have concomitant proarrhythmic conditions (especially women and elderly patients).
Prescribers must take into account the risk of the prolongation of the QT interval, which can be fatal, in assessing the risks and benefits of azithromycin in groups of patients at risk, such as:

- Patients with congenital or documented prolonged QT interval.
- Patients under treatment with other active ingredients that prolong the QT interval such as class IA (quinidine and procainamide) and class III anti-arrhythmics (dofetilide, amiodarone and sotalol), cisapride and terfenadine, antipsychotic drugs such as pimozide, antidepressants such as citalopram, fluoroquinolones such as moxifloxacin, levofloxacin and chloroquine.
- Patients with electrolyte changes, especially in cases of hypopotassaemia and hypomagnesaemia.
- Patients with clinically significant bradycardia, cardiac arrhythmia or severe heart failure.
- Women and elderly patients who may demonstrate greater sensitivity to the (drug-related) effects of alteration of the QT interval.

In patients being treated with azithromycin, there have been reports of exacerbation in symptoms of myasthenia gravis and initial development of myasthenic syndrome (see paragraph 4.8).

This drug contains **lactose**. Patients affected by rare hereditary problems of galactose intolerance, total lactase deficiency, or malabsorption of glucose-galactose should not take this medicine.

## 4.5 Interactions with other medicinal products and other forms of interaction

Antacids
In a pharmacokinetic study on the effects caused by co-administration of antacids and azithromycin, no effect was detected on the bioavailability of azithromycin, even though a decrease of approximately 25% was observed in maximum serum concentrations. As such, patients being treated with azithromycin and antacids must not take the two drugs simultaneously.

Cetirizine
In healthy volunteers, the co-administration of a 5-day regimen of azithromycin and 20 mg of steady state cetirizine did not show any pharmacokinetic interactions or significant alterations in the QT interval.

Didanosine
It was observed that co-administration of daily doses of azithromycin 1,200 mg/day and didanosine 400 mg/day in six HIV-positive patients did not have any effect on the steady state pharmacokinetics of didanosine compared to placebo.

Digoxin and colchicine (P-glycoprotein substrates)
There have been reports that the administration of macrolide antibiotics, including azithromycin with P-glycoprotein substrates such as digoxin, has caused an increase in the blood serum levels of P-glycoprotein substrates. Therefore, the possibility of an increase in digoxin blood serum levels must be carefully considered when co-administering azithromycin and P-glycoprotein substrates, such as digoxin. Clinical monitoring is required both during and after interruption of azithromycin treatment, as well as monitoring for possible increases in digoxin levels.

Zidovudine

The administration of individual 1,000 mg doses and multiple 1,200 mg or 600 mg doses of azithromycin did not substantially modify the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, the administration of azithromycin resulted in increased concentrations of phosphorylated zidovudine, its clinically active metabolite, in the peripheral blood mononuclear cells. The clinical importance of this data is not clear, but it may still render benefits to the patient.

Azithromycin does not significantly interact with the cytochrome P450 hepatic system. It is not deemed to be involved in pharmacokinetic interactions as found with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Ergotamine
Due to the potential onset of convulsive ergotism, concomitant use of azithromycin and ergotamine derivatives is not recommended (see Section 4.4).

Pharmacokinetic studies have been conducted between azithromycin and the following drugs, for which significant metabolic activity was noted and mediated by cytochrome P450.

HMG-CoA Reductase Inhibitors (Statins)
The concomitant administration of atorvastatin (10 mg/day) and azithromycin (500 mg/day) did not alter the plasma concentrations of atorvastatin (based on an HMG-CoA reductase inhibition assay) and thus did not cause alterations of HMG-CoA reductase activity. However, post-marketing cases of rhabdomyolysis have been reported in patients treated with azithromycin and statins.

Carbamazepine
During an interaction study conducted in healthy volunteers, no significant effects were observed on plasma levels of carbamazepine or its active metabolite in patients who were taking azithromycin concomitantly.

Cimetidine
During a pharmacokinetic study conducted to assess the effects of a single dose of cimetidine administered 2 hours after azithromycin, no alterations were noted in azithromycin pharmacokinetics.

Cyclosporine
In a pharmacokinetic study conducted in healthy volunteers administered an oral dose of 500 mg/day of azithromycin for 3 days and then a single oral dose of 10 mg/kg of cyclosporine, significant increases in the $C_{max}$ and $AUC_{0-5}$ values for cyclosporine were observed. Therefore, any co-administration of these two drugs requires caution. If co-administration of these two drugs is absolutely necessary, cyclosporine levels must be closely monitored and the dose of cyclosporine must be adjusted as needed.

Efavirenz
Co-administration of a single daily dose of azithromycin (600 mg) and efavirenz (400 mg) for 7 days did not cause any clinically significant pharmacokinetic interactions.

Fluconazole
Co-administration of a single dose of azithromycin (1,200 mg) did not alter the pharmacokinetics of a single dose of fluconazole (800 mg). The total exposure time and half-life of azithromycin were not influenced by co-administration of fluconazole, although there was a clinically insignificant decrease in $C_{max}$ (18%).

Indinavir
Concomitant administration of a single dose of azithromycin (1,200 mg) did not show a statistically significant effect on the pharmacokinetics of indinavir administered three times a day for 5 days at doses of 800 mg.

Methylprednisolone
A pharmacokinetic study conducted on healthy volunteers showed that azithromycin does not significantly influence methylprednisolone pharmacokinetics.

Midazolam
Co-administration in healthy volunteers of 500 mg/day of azithromycin for 3 days did not lead to clinically significant changes of the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Nelfinavir
Co-administration of azithromycin (1,200 mg) and steady state nelfinavir (750 mg three times per day) caused an increase in the concentrations of azithromycin. No clinically significant adverse reactions were observed and no dose adjustment was necessary.

Rifabutin
Concomitant administration of azithromycin and rifabutin does not change the serum concentrations of the two drugs.
Cases of neutropenia have been observed in some patients taking the two drugs concomitantly; although it is known that rifabutin can cause neutropenia, it is not possible to verify a causal relation between the aforementioned episodes of neutropenia and the association of rifabutin and azithromycin (see Section 4.8).

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

Theophylline
Co-administration of azithromycin and theophylline to healthy volunteers did not show any clinically significant interaction between the two drugs.

Terfenadine
Pharmacokinetic studies did not show any interactions between azithromycin and terfenadine. Some rare cases were reported in which the possibility of this interaction could not be completely ruled out; however, there is no scientific evidence that the interaction occurred.

Triazolam
In 14 healthy volunteers, co-administration of 500 mg of azithromycin on Day 1 and 250 mg on Day 2 and 0.125 mg of triazolam on Day 2 did not have significant effects on the pharmacokinetic variables of triazolam compared to triazolam and placebo.

Trimethoprim/Sulfamethoxazole
After concomitant administration of trimetoprim/sulfamethoxazole (160 mg/800 mg) and azithromycin (1,200 mg) for 7 days, no significant effect was found on peak concentrations, exposure time, or urinary excretion of both trimethoprim and sulfamethoxazole on Day 7. Azithromycin serum concentrations were similar to those found in other studies.

Coumarin-type Oral Anticoagulants
In a pharmacokinetic study conducted on healthy volunteers, it was observed that azithromycin did not modify the anticoagulant effect of a single 15 mg dose of warfarin.
During the post-marketing phase, cases of increased anticoagulant action were reported following co-administration of azithromycin and coumarin-type oral anticoagulants. Even though a causal relationship has not been established, it is recommended to re-evaluate the frequency of monitoring prothrombin time when administering azithromycin to patients receiving coumarin-type anticoagulants.

## 4.6 Fertility, pregnancy and lactation

There are insufficient data for the use of azithromycin in pregnant women. The safety of azithromycin during pregnancy has not been verified. Therefore, azithromycin must only be used during pregnancy if the benefits outweigh the risks.

Pregnancy

Animal reproduction studies have been conducted using scaled doses to reach moderately toxic maternal concentrations. No evidence of foetal risk due to azithromycin has emerged from these studies. In animal reproductive toxicology studies, there is evidence that azithromycin crosses the placenta, but no teratogenic effects have been observed. There are no adequate and well-controlled studies available in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin must only be used during pregnancy if absolutely necessary.

Breastfeeding
The limited information available from the published literature, indicates that azithromycin is present in human milk in a highest median daily dose estimated to be between 0.1 and 0.7 mg/kg/day. No side effects have been observed in breast-fed infants.
It must be decided whether to discontinue breastfeeding or discontinue/refrain from therapy with azithromycin taking into consideration the benefits of breastfeeding for the child and that of therapy for the woman.

Fertility
In fertility studies conducted in rats, a reduction in the fertility rate following administration of azithromycin was observed. The significance of these results in humans is unknown.

## 4.7 Effects on ability to drive and use machines

There is no evidence that azithromycin affects the ability of patients to drive vehicles or use machines.

## 4.8 Undesirable effects

The table below lists the side effects identified during clinical studies and during post-marketing surveillance, divided on the basis of systemic-organic classification and frequency. The possible adverse reactions identified during post-marketing surveillance are shown in italics. Frequency is defined using the following parameters: Very common (≥ 1/10); Common (≥ 1/100, < 1/10); Uncommon (≥ 1/1,000, < 1/100); Rare (≥ 1/10,000, < 1/1,000); Very Rare (< 1/10,000); Not known (frequency cannot be defined based on available data). Possible side effects are listed in order of decreasing severity within each frequency classification.

**Adverse reactions with possible or probable correlation to azithromycin based on the results of clinical studies and post-marketing surveillance.**

| System organ class | Adverse reaction | Frequency |
|---|---|---|
| **Infections and infestations** | Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis, respiratory disorders, rhinitis, oral candidiasis | Uncommon |
| | *Pseudomembranous colitis* (see par. 4.4) | Not known |
| **Blood and lymphatic system disorders** | Leukopaenia, neutropaenia, eosinophilia | Uncommon |
| | *Thrombocytopaenia, haemolytic anaemia* | Not known |
| ***Immune system disorders*** | *Angiooedema, hypersensitivity* | Uncommon |
| | *Anaphylactic reaction* (see Sec. 4.4) | Not known |
| **Metabolism and nutrition disorders** | Anorexia | Uncommon |
| **Psychiatric Disorders** | Nervousness, insomnia | Uncommon |
| | Agitation | Rare |
| | *Aggression, anxiety,* delirium, hallucinations | Not known |
| **Nervous System Disorders** | Headache | Common |
| | Dizziness, somnolence, dysgeusia, paraesthesia | Uncommon |
| | *Syncope, convulsions, hypoaesthesia, psychomotor hyperactivity, anosmia, ageusia, parosmia,*<br>*Myasthenia gravis* (see Sec. 4.4) | Not known |
| **Eye Disorders** | Vision impairment | Uncommon |

| | | |
|---|---|---|
| **Ear and Labyrinth Disorders** | Ear disorders, vertigo | Uncommon |
| | Hearing impairment including deafness and/or tinnitus | Not known |
| **Cardiac disorders** | Palpitations | Uncommon |
| | *Torsade de pointes (see Sec. 4.4), arrhythmia (see par. 4.4) including ventricular tachycardia, prolonged QT interval on the electrocardiogram (see Sec. 4.4)* | Not known |
| **Vascular disorders** | Hot flashes | Uncommon |
| | *Hypotension* | Not known |
| **Respiratory, Thoracic and Mediastinal Disorders** | Dyspnoea, epistaxis | Uncommon |
| **Gastrointestinal disorders** | Diarrhoea | Very common |
| | Vomiting, abdominal pain, nausea | Common |
| | Constipation, flatulence, dyspepsia, gastritis, dysphagia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion | Uncommon |
| | *Pancreatitis, tongue discolouration* | Not known |
| **Hepatobiliary disorders** | Impaired hepatic function, *cholestatic jaundice* | Rare |
| | *Hepatic failure (rarely fatal) (see Sec. 4.4), fulminant hepatitis, hepatic necrosis* | Not known |
| **Skin and subcutaneous tissue disorders** | Rash, pruritus, urticaria, dermatitis, dry skin, hyperhidrosis | Uncommon |
| | Photosensitivity reaction, *acute generalised exanthematous pustulosis (AGEP)§, Drug rash with eosinophilia and systemic symptoms (DRESS)§* | Rare |
| | Stevens-Johnson syndrome, *toxic epidermal necrolysis, erythema multiforme* | Not known |
| **Musculoskeletal and connective tissue disorders** | Osteoarthritis, myalgia, back pain, neck pain | Uncommon |
| | Arthralgia | Not known |
| **Renal and urinary disorders** | *Dysuria, renal pain* | Uncommon |
| | *Acute renal insufficiency, interstitial nephritis* | Not known |
| **Reproductive System and Breast Disorders** | Metrorrhagia, testicular disorders | Uncommon |
| **General disorders and administration site conditions** | Oedema, asthaenia, malaise, fatigue, facial oedema, chest pain, pyrexia, pain, peripheral oedema | Uncommon |
| **Diagnostic tests** | Decrease in lymphocyte count, increase in eosinophil count, decrease in blood bicarbonate, increase in basophils, increase in monocytes, increase in neutrophils | Common |
| | Increase in aspartate aminotransferase (AST), increase in alanine aminotransferase (ALT), increase in blood bilirubin, increase in blood urea, increase in blood creatinine, abnormal blood potassium, increase in blood alkaline phosphatase, increase in chloride levels, increase in glucose, increase in platelets, decrease in haematocrit, increase in blood bicarbonate, abnormal sodium levels | Uncommon |
| **Injury and Poisoning** | Post-procedural complications | Uncommon |

§ Frequency ADR represented by the estimated upper limit of the 95% confidence interval calculated using the "Rule of 3"

* only for the powder for solution for infusion

**Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or prolonged release formulations, in kind or in**

**frequency:**

| | **Very common (≥ 1/10)** | **Common (≥ 1/100, < 1/10)** | **Uncommon (≥ 1/1,000, < 1/100)** |
|---|---|---|---|
| **Metabolism and nutrition disorders** | | Anorexia | |
| **Nervous system disorders** | | Dizziness<br>Headache<br>Paraesthesia<br>Dysgeusia | Hypoesthesia |
| **Eye Disorders** | | Vision impairment | |
| **Ear and Labyrinth Disorders** | | Deafness | Impaired hearing<br>Tinnitus |
| **Cardiac disorders** | | | Palpitations |
| **Gastrointestinal disorders** | Diarrhoea<br>Abdominal pain<br>Nausea<br>Flatulence<br>Abdominal discomfort<br>Loose stools | | |
| **Hepatobiliary disorders** | | | Hepatitis |
| **Skin and subcutaneous tissue disorders** | | Rash<br>Pruritus | Stevens-Johnson syndrome<br>Photosensitivity reaction |
| **Musculoskeletal and connective tissue disorders** | | Arthralgia | |
| **General disorders and administration site conditions** | | Fatigue | Asthaenia<br>Malaise |

Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important. It allows constant monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

**Reporting side effects:**

Egypt:

Pharmacovigilance center, Pfizer Pharmaceutical Company: EGY.AEReporting@pfizer.com

Egyptian Pharmacovigilance center (EPVC), EDA: pv.report@edaegypt.gov.eg

### 4.9 Overdose

Side effects reported with doses greater than those recommended were similar to those reported with normal doses. In case of overdose, the appropriate general symptomatic and support measures are indicated.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use - Macrolides, ATC code: J01FA10.

Azithromycin is first in a sub-class of macrolide antibiotics called azalides, and is chemically different from erythromycin. It is chemically derived from the insertion of a nitrogen atom into the lactone ring of the erythromycin A.
Its chemical name is: 9-deoxy-9a-aza-9a-methyl-9a-homoerithromycin A. The molecular weight is 749.0.

Mechanism of action
Azithromycin binds to the 23S rRNA of 50S ribosomal subunit. Azithromycin blocks protein synthesis by inhibiting the transpeptidation/translocation step of protein synthesis and by inhibiting the assembly of the 50S ribosomal subunit.

Cardiac electrophysiology
The prolongation of the QT interval was studied in a randomized, placebo-controlled study in parallel groups on 116 healthy subjects who either took chloroquine (1,000 mg) alone or in combination with azithromycin (500 mg, 1,000 mg, 1,500 mg once a day). The coadministration with azithromycin resulted in an increase in QTc interval in a dose- and concentration-dependent way. Maximum increases in the QTcF compared with chloroquine monotherapy (whose differences observed with respect to the placebo vary in the range of between 18.4 and 35 ms) were on average (upper limit of the 95% confidence interval) 5 (10 ms), 7 (12 ms) and 9 (14) ms following the concomitant administration of 500 mg, 1,000 mg, 1,500 mg of azithromycin respectively.

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

The most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N)- 6 demethylation of adenine at nucleotide A2058 (*E.coli* numbering system) of the 23S rRNA by the methylases codified by *erm* (erythromycin ribosomal methylase) genes.
Ribosomal modifications often determine cross resistance ($MLS_B$ phenotype) to other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the Type B streptogramins (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different *erm* genes are present in different bacterial species, in particular streptococci and staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA or in the large subunit ribosomal proteins L4 and L22.

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

**Method for Determining In Vitro Susceptibility of Bacteria to Azithromycin**

Susceptibility testing should be conducted using standardised laboratory methods such as those described by the *Clinical and Laboratory Standards Institute* (CLSI). These include dilution methods (MIC determination) and disk susceptibility methods.
Both the CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretative criteria for these methods.
Based on a number of studies, it is recommended that the *in vitro* activity of azithromycin be tested in ambient air to ensure physiological pH of the growth medium. Elevated $CO_2$ pressures, such as those used for streptococci and anaerobic bacteria, and occasionally for other species, results in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides.

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

*Susceptibility breakpoints for azithromycin*

| | MIC (mg/L) | |
|---|---|---|
| | **Susceptible** | **Resistant** |
| *Staphylococcus* spp. | ≤ 1 | > 2 |
| *Streptococcus pneumoniae* | ≤ 0.25 | > 0.5 |
| Haemolytic β streptococcus [a] | ≤ 0.25 | > 0.5 |
| *Haemophilus influenzae* | ≤ 0.12 | > 4 |
| *Moraxella catarrhalis* | ≤ 0.25 | > 0.5 |
| *Neisseria gonorrhoeae* | ≤ 0.25 | > 0.5 |

[a] includes groups A, B, C, G.
EUCAST = *European Committee on Antimicrobial Susceptibility Testing*; MIC = Minimum inhibitory concentration.

Antibacterial spectrum

The prevalence of acquired resistance may vary geographically and over time for selected species, and it is helpful to have local information on resistances, in particular when treating serious infections. If necessary, expert advice should be requested if the local prevalence of resistant strains is such that the usefulness of agents, at least in certain types of infections, is disputable.

Azithromycin shows cross resistance with erythromycin resistant gram-positive germs. As described above, some ribosomal modifications determine cross resistance with other classes of antibiotics whose ribosomal binding sites overlap that of the macrolides: the lincosamides (including clindamycin), and the Type B streptogramins (which include, for example, the quinupristin component of quinupristin/dalfopristin). Over the course of time, a decrease has been noted in macrolide susceptibility, in particular in *Streptococcus pneumoniae and in Staphylococcus aureus,* and has also been observed in *viridans* group streptococci and in *Streptococcus agalactiae.*

Organisms that are commonly susceptible to azithromycin include:

Aerobic and facultative gram-positive bacteria (erythromycin-susceptible isolates): *S. aureus*, *Streptococcus agalactiae**, *S. pneumoniae**, *Streptococcus pyogenes**, other haemolytic β streptococci (groups C, F, G), *viridans* group streptococci. Macrolide-resistant germs are found relatively frequently among aerobic and facultative gram-positive bacteria, in particular among methicillin-resistant *S. aureus* (MRSA) and penicillin-resistant *S. pneumoniae* (PRSP).

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

Anaerobes: *Clostridium perfringens, Peptostreptococcus spp*. and *Prevotella bivia*.

Other bacterial species: *Borrelia burgdorferi*, *Chlamydia trachomatis*, *Chlamydophila pneumoniae**, *Mycoplasma pneumoniae**, *Treponema pallidum*, and *Ureaplasma urealyticum*.

Opportunistic pathogens associated with HIV infection. MAC*, and the eukaryote micro-organisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.

*The efficacy of azithromycin against the described species has been demonstrated in clinical studies

Paediatric population

Following the assessment of studies conducted on children, because non-inferiority has not been established with respect to the antimalarial drugs recommended in the treatment of uncomplicated malaria, the use of azithromycin is not recommended for the treatment of malaria, either as monotherapy or in combination with chloroquine or artemisinin-based drugs.

## 5.2 Pharmacokinetic properties

Absorption
Azithromycin is more stable at gastric pH compared to erythromycin.
In humans, following oral administration, azithromycin spreads quickly and fully to the entire body; the time required to achieve peak plasma levels is 2-3 hours.

Distribution
In animal studies, high concentrations of azithromycin were observed inside phagocyte cells. In experimental models, higher concentrations of azithromycin were released by activated phagocytes than by non-activated phagocytes. In the animal model, this phenomena causes high concentrations of azithromycin at the infection site. Pharmacokinetic studies in humans have shown higher azithromycin tissue levels compared to plasma levels (up to 50 times the maximum concentrations observed in plasma) indicating, therefore, that the drug is highly bound to tissues. Concentrations in tissues such as lung, tonsil, and prostate, exceed MIC90 values for the most common pathogens after a single oral administration of 500 mg.

Elimination
The terminal plasma half-life time closely reflects the tissue depletion half-life time (from 2 to 4 days). Approximately 12% of an IV dose is eliminated in urine as an unchanged drug after 3 days, the majority during the first 24 hours. Biliary elimination is the primary route of unchanged drug elimination after oral administration. Very elevated concentrations of unchanged drug were found in human bile along with 10 metabolites formed by the N- and O-demethylation processes, by hydroxylation of the desosamine and the glyconic ring and by cleavage of the cladinosium-conjugates. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

Pharmacokinetics in Special Patient Populations

Elderly
A study conducted in healthy volunteers highlighted that after a treatment period of 5 days, AUC values were slightly higher in elderly patients (> 65 years) compared to younger patients (< 40 years); however, because this data is not clinically significant, no dose adjustment is required.

Renal Impairment
Following a single oral administration of 1 gram of azithromycin, no pharmacokinetic effects were found in patients with slight to moderate renal impairment (GFR 10 - 80 mL/min). However, statistically significant differences were found in AUC values$_{0\text{-}120}$ (8.8 μg-h/mL vs. 11.7 μg-h/mL), $C_{max}$ (1.0 μg/mL vs. 1.6 μg/mL) and CLr (2.3 mL/min/kg vs. 0.2 mL/min/kg) among those with severe renal impairment (GFR < 10 mL/min) and those with normal renal function.

Hepatic Impairment
In patients with mild (Class A) and moderate (Class B) hepatic impairment, there was no evidence of significant changes in the blood pharmacokinetics of the azithromycin compared to patients with normal hepatic function. In these patients, elimination of azithromycin through urine seemed to increase, probably as compensation for reduced hepatic clearance.

## 5.3 Preclinical safety data

In animal studies conducted with elevated doses that exceeded 40 times the maximum dose used in clinical practice, it was found that azithromycin caused reversible phospholipidosis, generally without true toxicological consequences. The effect proved to be reversible with discontinuation of the azithromycin treatment. The significance of these results for animals as well as for humans is unknown.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**Zithromax 250 mg Capsule:**
Lactose anhydrous, Maize Starch, magnesium stearate, sodium lauryl sulphate.
*The capsule shells contain*: gelatin, titanium dioxide.

### 6.2 Incompatibility

Not relevant.

### 6.3 Shelf life

Do not use Zithromax after the expiry date which is stated on the carton / blister label after EXP: The expiry date refers to the last day of that month.

### 6.4 Special Precautions for Storage

Zithromax 250 mg Capsule: Store at a temperature not exceeding 30°C

### 6.5 Nature and Content of the Container

Zithromax 250 mg Capsule:
Carton box containing one (Aluminium/PVC) blister of 6 capsules and inner leaflet.

### 6.6 Special precautions for disposal and other handling

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Keep out of the sight and reach of children.

## 7. FURTHER INFORMATION

**MARKETING AUTHORISATION HOLDER**

Pfizer INC., USA

**MANUFACTURED, PACKED AND RELEASED BY**

Pfizer Egypt

## 8. DATE OF REVISION OF THE TEXT

June 2020

**THIS IS A MEDICAMENT**

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

**Keep all medicaments out of reach and sight of children**

**Council of Arab Health Ministers**
**Union of Arabic Pharmacists**