**PT. PFIZER INDONESIA**
LOCAL PRODUCT DOCUMENT

Generic Name: Azithromycin
Trade Name: ZITHROMAX
CDS Effective Date: March 21, 2017
Supersedes: November 17, 2015

## FORM AND PRESENTATION

**Film-coated Tablets:** Azithromycin film-coated tablets are capsular shaped and contain azithromycin dihydrate equivalent to 500 mg, of azithromycin and engraved with "ZTM 500" and "Pfizer logo".

**Film-coated Captabs:** Azithromycin film-coated captabs are capsular shaped and contain azithromycin dihydrate equivalent to 250 mg, of azithromycin and engraved with "ZTM 250" and "Pfizer logo".

**Powder for Oral Suspension:** Azithromycin powder for oral suspension is presented as a dry powder which yields, on reconstitution with water, a white to off-white suspension containing the equivalent of 200 mg azithromycin per 5 mL.

**Powder for Intravenous (IV) Solution:** Azithromycin is supplied in lyophilized form under a vacuum in a 10 mL vial equivalent to 500 mg azithromycin for intravenous administration. Upon reconstitution, azithromycin powder yields a solution containing the equivalent of 100 mg azithromycin per 1 mL.

## DESCRIPTION

**Powder for Oral Suspension** – The powder for oral suspension contains sucrose (1.94 g per 100 mg dose), sodium phosphate tribasic anhydrous, hydroxypropyl cellulose, xanthan gum, artificial cherry, crème de vanilla and banana flavors.

**Film-coated Tablets** – The tablets contain pregelatinized starch, calcium phosphate dibasic anhydrous, croscarmellose sodium, magnesium stearate and sodium lauryl sulfate. The film coating contains hydroxypropyl methylcellulose, triacetin and titanium dioxide (E171).

**Film-coated Captabs** – The tablets contain pregelatinized starch, calcium phosphate dibasic anhydrous, croscarmellose sodium, magnesium stearate and sodium lauryl sulfate, and film coating solution.

**Powder for Intravenous (IV) Solution** – The IV formulation contains citric acid (anhydrous) 384.6 mg, and sodium hydroxide 198.3 mg.

## PHARMACOLOGICAL PROPERTIES

### *Pharmacodynamic Properties*

Pharmacotherapeutic group: Macrolides, ATC code J01FA.

**Mode of action**

Azithromycin is the first of a subclass of macrolide antibiotics, known as azalides, and is chemically different from erythromycin. Chemically it is derived by insertion of a nitrogen atom into 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.

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

Azithromycin demonstrates activity *in-vitro* against a wide range of bacteria including:

**Gram-positive Aerobic Bacteria**: *Staphylococcus aureus, Streptococcus pyogenes* (group A beta-haemolytic streptococci), *Streptococcus pneumoniae*, alpha-haemolytic streptococci (viridans group) and other streptococci, and *Corynebacterium diphtheriae*. Azithromycin demonstrates cross resistance with erythromycin resistant gram-positive strains, including *Streptococcus faecalis* (enterococcus) and most strains of methicillin-resistant Staphylococci.

**Gram-negative Aerobic Bacteria**: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Acinetobacter* species, *Yersinia* species, *Legionella pneumophila, Bordetella pertussis, Bordetella parapertussis, Shigella* species, *Pasteurella* species, *Vibrio cholera* and *parahaemolyticus, Plesiomonas shigelloides*. Activities against *Escherichia coli, Salmonella enteritidis, Salmonella typhi, Enterobacter* species, *Aeromonas hydrophila* and *Klebsiella* species are variable and susceptibility tests should be performed. *Proteus* species, *Serratia* species, *Morganella* species, and *Pseudomonas aeruginosa* are usually resistant.

**Anaerobic Bacteria**: *Bacteroides fragilis* and *Bacteroides* species, *Clostridium perfringens, Pepto-coccus* species and *Peptostreptococcus* species, *Fusobacterium necrophorum* and *Propionibacterium acnes.*

**Organism of Sexually Transmitted Diseases**: Azithromycin is active against *Chlamydia trachomatis* and also shows good activity against *Treponema pallidum, Neisseria gonorrhoeae* and *Haemophilus ducreyi.*

**Other Organisms**: *Borrelia burgdorferi* (Lyme disease agent), *Chlamydia pneumoniae, Mycoplasma pneumoniae, Mycoplasma hominis, Ureaplasma urealyticum, Campylobacter* species and *Listeria monocytogenes*.

**Opportunistic Pathogens Associated with HIV Infections:** *Mycobacterium avium-intracellulare complex, Pneumocystis carinii* and *Toxoplasma gondii.*

**Cardiac electrophysiology**

QTc interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were

5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

**Mechanism of resistance**

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

The two most important ribosomal modification that determines reduced binding of macrolides is post transcriptional (N6) dimethylation of adenine at nucleotide A2058 (*Escherichia coli* numbering system) of the 23S rRNA by methylases encoded by *erm* (erythromycin ribosome methylase) genes. Ribosomal modifications often determine cross resistance (MLSB phenotype) to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (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 minimal inhibitory concentrations [MICs]) and staphylococci. In streptococci and enterococci, an efflux pump that recognizes 14- and 15-membered macrolides (which include, respectively, erythromycin and azithromycin) is encoded by mef (A) genes.

**Methodology for determining the *in vitro* susceptibility of bacteria to azithromycin**

Susceptibility testing should be conducted using standardized 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 CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretive 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 $CO_2$ tensions, as often used for streptococci and anaerobes, and occasionally for other species, result 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.

The CLSI susceptibility breakpoints, based on broth microdilution or agar dilution testing, with incubation in ambient air, are given in the table below:

**CLSI Dilution Susceptibility Interpretive Criteria**

| | **Broth microdilution MIC (mg/L)** | | |
|---|---|---|---|
| | | | **Resistant** |
| *Haemophilus* species | ≤4 | - | -[b] |
| *Moraxella catarrhalis* | ≤0.25 | - | - |
| *Neisseria meningitidis* | ≤2 | - | -[b] |

**CLSI Dilution Susceptibility Interpretive Criteria**

| | Broth microdilution MIC (mg/L) | | |
|---|---|---|---|
| *Staphylococcus aureus* | ≤2 | 4 | ≥8 |
| Streptococci[a] | ≤0.5 | 1 | ≥2 |

[a] Includes *Streptococcuspneumoniae*,β-hemolytic streptococciandviridansstreptococci.
[b] The current absence of data on resistant strains precludes definingany category otherthan susceptible. If strains yield MIC results other than susceptible, they should be submitted to a referencelaboratory for further testing.
Incubation in a mbient air.
CLSI = Clinica l a nd Laboratory Standards Institute;
MIC = Minimalinhibitory concentration.
Source: CLSI, 2012 CLSI, 2010.

Susceptibility can also be determined by the disk diffusion method, measuring inhibition zone diameters after incubation in ambient air. Susceptibility disks contain 15 μg of azithromycin. Interpretive criteria for inhibition zones, established by the CLSI on the basis of their correlation with MIC susceptibility categories, are listed in the table below.

**CLSI Disk Zone Interpretive Criteria**

| Organism | Disk inhibition zone diameter (mm) | | |
|---|---|---|---|
| | **Susceptible** | **Intermediate** | **Resistant** |
| *Haemophilus* species | ≥12 | - | - |
| *Moraxella catarrhalis* | ≥26 | - | - |
| *Neisseria meningitidis* | ≥20 | - | - |
| *Staphylococcus aureus* | ≥18 | 14-17 | ≤13 |
| Streptococci[a] | ≥18 | 14-17 | ≤13 |

[a] Includes *Streptococcus pneumoniae*,β-hemolyticstreptococciand viridans streptococci.
Incubation in a mbient air.
CLSI = Clinicaland Laboratory Standards Institute; mm = Millimeters.
Source: CLSI, 2012 CLSI, 2010.

The validity of both the dilution and disk diffusion test methods should be verified using quality control (QC) strains, as indicated by the CLSI. Acceptable limits when testing azithromycin against these organisms are listed in the table below.

**Quality Control Ranges for Azithromycin Susceptibility Tests**

| Broth microdilution MIC | |
|---|---|
| **Organism** | **Quality control range (mg/L azithromycin)** |
| *Haemophilus influenzae* ATCC 49247 | 1-4 |
| *Staphylococcus aureus* ATCC 29213 | 0.5-2 |
| *Streptococcus pneumoniae* ATCC 49619 | 0.06-0.25 |

| Disk inhibition zone diameter (15 μg disk) | |
|---|---|
| **Organism** | **Quality control range (mm)** |
| *Haemophilus influenzae* ATCC 49247 | 13-21 |
| *Staphylococcus aureus* ATCC 25923 | 21-26 |
| *Streptococcus pneumoniae* ATCC 49619 | 19-25 |

Incubation in ambient air.
CLSI = Clinical and Laboratory Standards Institute;
MIC = Minimal inhibitory concentration; mm = Millimeters
Source: CLSI, 2012

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

**EUCAST Susceptibility Breakpoints for Azithromycin**

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

**EUCAST Susceptibility Breakpoints for Azithromycin**

| | MIC (mg/L) | |
|---|---|---|
| | **Susceptible** | **Resistant** |

[a] Includes Groups A, B, C, G.
EUCAST = Europea n Committee on AntimicrobialSusceptibility Testing; MIC = Minimal inhibitory concentra tion.
Source: EUCAST Web site.
**EUCAST Clinical Breakpoint Table v. 2.0, valid from 2012-01-01**
**www.eucast.org/.../EUCAST.../Breakpoint_table_v_2.0_120221.pdf**

## Antibacterial spectrum

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.

Azithromycin demonstrates cross resistance with erythromycin-resistant gram-positive isolates. As discussed above, some ribosomal modifications determine cross-resistance with other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). A decrease in macrolide susceptibility over time has been noted in particular in *Streptococcus pneumoniae* and *Staphylococcus aureus*, and has also been observed in viridans streptococci and *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 β-hemolytic streptococci (Groups C, F, G), and viridans streptococci. Macrolide-resistant isolates are encountered 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 most *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 eukaryotic microorganisms *Pneumocystis jirovecii* and *Toxoplasma gondii*.
∗The efficacy of azithromycin againstthe indicated species has been demonstrated in clinicaltrials.

***Pharmacokinetic Properties***

**Absorption**

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37%.The time taken to peak plasma levels is 2 to 3 hours. Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. In elderly volunteers (>65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (<40 years), but these are not considered clinically significant, and hence no dose adjustment is recommended.

**Distribution**

In animal studies, high azithromycin concentrations have been observed in phagocytes. In experimental models, higher concentrations of azithromycin are released during active phagocytosis than from non-stimulated phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

Pharmacokinetic studies in humans have shown markedly higher azithromycin levels in tissues than in plasma (up to 50 times the maximum observed concentration in plasma), indicating that the drug is heavily tissue bound. Concentrations in target tissues, such as lung, tonsil and prostate, exceed the $MIC_{90}$ for likely pathogens after a single dose of 500 mg.

**Elimination**

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. Approximately 12% of an intravenously administered dose is excreted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug following oral administration. Very high concentrations of unchanged drug have been found in human bile, together with 10 metabolites, formed by N- and O-demethylation, hydroxylation of the desosamine and aglycone rings, and cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues suggests that metabolites play no part in the microbiological activity of azithromycin.

***Pharmacokinetics in special patient groups***

**Elderly**

In elderly volunteers (>65 years), slightly higher AUC values were seen after a 5-day regimen than in young volunteers (<40 years), but these are not considered clinically significant, and hence no dose adjustment is recommended.

**Renal Impairment**

The pharmacokinetics of azithromycin in subjects with mild to moderate renal impairment (GFR 10-80 mL/min) were not affected following a single 1 gram dose of immediate release azithromycin. Statistically significant differences in $AUC_{0-120}$ (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) were observed

between the group with severe renal impairment (GFR <10 mL/min) and the group with normal renal function.

**Hepatic Impairment**

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients, urinary clearance of azithromycin appears to increase, perhaps to compensate for reduced hepatic clearance.

***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.

## THERAPEUTIC INDICATIONS

***Azithromycin oral:***

Azithromycin is indicated for the treatment of patient with mild to moderate infections (pneumonia: see **Special Warnings and Precautions for Use**) caused by susceptible strains of the designated microorganisms in the specific conditions listed below:

**Lower Respiratory Tract**
Acute bacterial exacerbations of chronic obstructive pulmonary disease due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae*.

Community-acquired pneumonia of mild severity due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients appropriate for outpatient oral therapy.

**Upper Respiratory Tract**
Streptococcal pharyngitis/tonsillitis - As an alternative to first line therapy of acute pharyngitis/tonsillitis due to *Streptococcus pyogenes*occurring in individuals who cannot use first line therapy.

**Skin and Skin Structure**
Uncomplicated skin and skin structure infections due to *Staphylococcus aureus, Streptococcus pyogenes*, or *Streptococcus agalactiae*. Abscesses usually require surgical drainage.

**Sexually Transmitted Diseases**
Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis.*

Azithromycin, at the recommended dose, should not be relied upon to treat gonorrheae or syphilis. Antimicrobial agents used in high doses for short periods of time to treat non-gonococcal urethritis may mask or delay the symptoms of incubating gonorrheae or syphilis. All patients with

sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrheae performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

Appropriate culture and susceptibility tests should be performed before treatment to determine the causative organism and its susceptibility to azithromycin. Therapy with azithromycin may be initiated before results of these tests are known; once the results become available, antimicrobial therapy should be adjusted accordingly.

***Azithromycin IV:***

Azithromycin IV is indicated for the treatment of community acquired pneumonia (CAP) caused by susceptible organisms, including *Legionella pneumophila*, in patients who require initial IV therapy.

In combination with metronidazole, Azithromycin IV is indicated for the treatment of pelvic inflammatory diseases causedby susceptible organisms, in patients who require initial IV therapy.

## CONTRAINDICATIONS

The use of this product is contraindicated in patients with a hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any excipient listed in **section – Description.**

## SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**Hypersensitivity**
As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), Dermatologic reactions, including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) (rarely fatal), 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.

If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

**Hepatotoxicity**
Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease.

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function. In these patients urinary recovery of azithromycin appears to increase, perhaps

to compensate for reduced hepatic clearance. Hence no dose adjustment is recommended for patients with mild to moderate hepatic impairment.

**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-administered.

**Superinfection**
As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.

***Clostridium difficile*-associated diarrhea**
*Clostridium difficile*-associated diarrhea (CDAD) has been reported with the 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 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile,* and surgical evaluation should be instituted as clinically indicated.

Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* infections and the prophylaxis of rheumatic fever. Azithromycin is often effective in the eradication of susceptible strains of *Streptococcus pyogenes* from the nasopharynx. Because some strains are resistant to azithromycin, susceptibility test should be performed when patients are treated with azithromycin. Data establishing efficacy of azithromycin in subsequent prevention of rheumatic fever are not available. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physician should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for outpatient oral therapy because of moderate to severe illness or risk factors such as any of the following:

- patients with nosocomially acquired infections
- patients with known or suspected bacteremia
- patients requiring hospitalization
- elderly or debilitated patients, or
- patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

**Renal impairment**
In patients with severe renal impairment (GFR <10 mL/min) a 33% increase in systemic exposure to azithromycin was observed (see **section – Pharmacokinetic Properties**).

**Diabetes**
Caution in diabetic patients: 5 mL of reconstituted suspension contains 3.87 g of sucrose.

Due to the sucrose content (3.87 g/5 mL of reconstituted suspension), this medicinal product is not indicated for persons with fructose intolerance (hereditary fructose intolerance), glucose-galactose malabsorption or saccharase-isomaltase deficiency.

No dose adjustment is needed in patients with mild renal impairment (creatinine clearance >40 mg/min) but there are no data regarding azithromycin usage in patients with more severe renal impairment; thus, caution should be exercised before prescribing Zithromax in these patients.

**Prolongation of the QT interval**
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides, including azithromycin (see **section – Undesirable Effects**). Prescribers should consider the risk of QT prolongation, which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- Patients with congenital or documented QT prolongation
- Patients currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones
- Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval

**Myasthenia gravis**
Exacerbations of the symptoms of myasthenia gravis have been reported in patients receiving azithromycin therapy.

**Intravenous administration**
Azithromycin for injection should be reconstituted and diluted as directed and administered as an IV infusion over not less than 60 minutes. **Do not administer as an IV bolus or an intramuscular injection (see section – Posology and Method of Administration and section – Instruction for Use and Handling, and Disposal).**

## 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**
Many patients have received co-administration of azithromycin and cardiac glycosides, and no interactions have been reported.

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-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.

**Ergot**
There is a theoretical possibility of interaction between azithromycin and ergot derivatives (see **section – Special warnings and precautions for use**).

**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.

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).

However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

**Carbamazepine**
In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

**Cimetidine**
In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

**Coumarin-type oral anticoagulants**
In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 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.

**Cyclosporin**
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 cyclosporin, the resulting cyclosporin $C_{max}$ and $AUC_{0-5}$ were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin 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 – 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.

***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 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.

**Lactation**

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

**Fertility**

In fertility studies conducted in rats, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

***Effect on ability to drive and use machines***

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

## UNDESIRABLE EFFECTS

Azithromycin is well tolerated with a low incidence of side effects

**In clinical trials, the following undesirable effects have been reported:**

Blood and Lymphatic System Disorders: Transient episodes of mild neutropenia have occasionally been observed in clinical trials.

Ear and Labyrinth Disorders: Hearing impairment (including hearing loss, deafness and/or tinnitus) has been reported in some patients receiving azithromycin. Many of these have been associated with prolonged use of high doses in investigational studies. In those cases where follow-up information was available, the majority of these events were reversible.

Gastrointestinal Disorders: Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps) and flatulence.

Hepatobiliary Disorders: Abnormal liver function.

Skin and Subcutaneous Tissue Disorders: Allergic reactions including rash and angioedema.

General Disorders and Administration Site Conditions: Local pain and inflammation at the site of infusion.

**In post-marketing experience, the following additional undesirable effects have been reported:**

Infections and Infestations: Moniliasis, and vaginitis.

Blood and Lymphatic System Disorders: Thrombocytopenia.

Immune System Disorders: Anaphylaxis (rarely fatal) (see **section – Special Warnings and Precautions for Use**).

Metabolism and Nutrition Disorders: Anorexia.

Psychiatric Disorders: Aggressive reaction, nervousness, agitation, and anxiety.

Nervous System Disorders: Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paresthesia, somnolence, and syncope.

There have been rare reports of taste/smell perversion and/or loss.

Ear and Labyrinth Disorders: Deafness, tinnitus, hearing impaired and vertigo.

Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see **section – Special Warnings and Precautions for Use**).

Vascular Disorders: Hypotension.

Gastrointestinal Disorders: Vomiting/diarrhea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, and rare reports of tongue discoloration.

Hepatobiliary Disorders: Hepatitis and cholestatic jaundice have been reported, as well as rare cases of hepatic necrosis and hepatic failure, which have resulted in death (see **section – Special Warnings and Precautions for Use**).

Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, AGEP, SJS, TEN, and DRESS have been reported.

Musculoskeletal and Connective Tissue Disorders: Arthralgia.

Renal and Urinary Disorders: Interstitial nephritis and acute renal failure.

General Disorders and Administration Site Conditions: Asthenia, fatigue, and malaise.

## POSOLOGY AND METHOD OF ADMINISTRATION

***Azithromycin oral:***

Azithromycin should be administered as a single daily dose. The period of dosing with regard to infection is given below.

Azithromycin tablets, captabs and powder for oral suspension can be taken with or without food.

In adults

For the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis* and Haemophilus ducreyi, or susceptible *Neisseria gonorrhoeae* the dose is 1000 mg as a single oral dose.

For all other indications in which the oral formulation is administered, the total dosage of 1500 mg should be given as 500 mg daily for 3 days. As an alternative, the same total dose can be given over 5 days with 500 mg given on day 1, then 250 mg daily on days 2 to 5.

In children
There is no information on children under six months of age.

The total dose of 30 mg/kg should be given as a single daily dose of 10 mg/kg, or as an alternative, given over 5 days with single daily dose of 10 mg/kg dose on Day 1, then 5 mg/kg on Days 2-5.

Azithromycin suspension should be administered according to the guide provided below:

| **Azithromycin Suspension 30 mg/kg Total Treatment Dose** | | | |
|---|---|---|---|
| **Weight (kg)** | **3-Day Regimen** | **5-Day Regimen** | **Bottle Size (mg)** |
| 15-25 | 200 mg (5 mL) once daily on Days 1-3 | 200 mg (5 mL) on Day 1, then 100 mg (2.5 mL) once daily on Days 2-5 | 600 |
| 26-35 | 300 mg (7.5 mL) once daily on Days 1-3 | 300 mg (7.5 mL) on Day 1, then 150 mg (3.75 mL) once daily on Days 2-5 | 900 |
| 36-45 | 400 mg (10 mL) once daily on Days 1-3 | 400 mg (10 mL) on Day 1, then 200 mg (5 mL) once daily on Days 2-5 | 1200 |
| >45 | Dose as per adults. | Dose as per adults | 1500 |

**Special populations**

In the Elderly
The same dosage as in adult patients is used in the elderly. Elderly patients may be more susceptible to the development of torsades de pointes arrhythmia than younger patients (see **section – Special Warnings and Precautions for Use).**

In 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 – Special Warnings and Precautions for Use** and **section - Pharmacokinetic Properties**).

In Patients with Hepatic Impairment
The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment (see **section – Special Warnings and Precautions for Use**).

For the treatment of adult patients with CAP due to the indicated organisms, the recommended dose of IV azithromycin is 500 mg as a single daily dose by the IV route for at least 2 days. IV therapy should be followed by oral azithromycin at a single daily dose of 500 mg to complete a 7- to 10-day course of therapy. The timing of the conversion to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

For the treatment of adult patients with PID due to the indicated organisms, the recommended dose of IV azithromycin is 500 mg as a single dose by the IV route for 1 or 2 days. IV therapy should be followed by oral azithromycin at a single daily dose of 250 mg to complete a 7-day course of therapy. The timing of the conversion to oral therapy should be done at the discretion of the physician and in accordance with clinical response. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial anaerobic agent may be administered in combination with azithromycin.

Intravenous Administration
After reconstitution and dilution, the recommended route of administration for IV azithromycin is by IV infusion only. **Do not administer as an IV bolus or an intramuscular injection** (see **section – Special Warnings and Precautions for Use** and **section – Instruction for Use and Handling, and Disposal).**

The infusate concentration and rate of infusion for azithromycin IV should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour. An IV dose of 500 mg azithromycin should be infused for a minimum duration of 1 hour.

The safety and efficacy of IV azithromycin for the treatment of infections in children have not been established.

**Instruction for Use and Handling, and Disposal**

**Powder for Oral Suspension:** Tap the bottle to loosen the powder. To the 600 mg bottle, add 9 mL of water. Shake well. Shake immediately prior to use.

For children weighing less than 15 kg, the suspension should be measured as closely as possible. For children weighing 15 kg or more, the suspension should be administered using an appropriate measuring device.

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

**Powder for Intravenous Solution**

Reconstitution:
Prepare the initial IV solution for infusion by adding 4.8 mL of sterilized Water for Injection to the 500 mg vial and shaking the vial until all of the drug is dissolved. Since azithromycin IV is supplied under vacuum, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the exact amount of 4.8 mL of sterilized Water for Injection is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 24 hours below 30°C. When diluted according to the instructions, the diluted solution is chemically and physically stable for 24 hours at or below 30°C or for 7 days if stored under refrigeration at 5°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours at 2°C to 8°C, unless reconstitution and dilution have taken place in controlled and validated aseptic conditions.

Dilute this solution further prior to administration as instructed below:

Dilution:
To provide azithromycin over a concentration range of 1.0 mg/mL to 2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:

| Final Infusion Solution Concentration (mg/mL) | Amount of Diluent (mL) |
|---|---|
| 1.0 | 500 |
| 2.0 | 250 |

The reconstituted solution can be diluted with:

Normal Saline (0.9% sodium chloride)
½ Normal Saline (0.45% sodium chloride)
5% Dextrose in Water
Lactated Ringer's Solution
5% Dextrose in ½ Normal Saline (0.45% sodium chloride) with 20 mEq KCl
5% Dextrose in Lactated Ringer's Solution
5% Dextrose in ⅓ Normal Saline (0.3% sodium chloride)
5% Dextrose in ½ Normal Saline (0.45% sodium chloride)
Normosol®-M in 5% Dextrose
Normosol®-R in 5% Dextrose

Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is evident in reconstituted fluids, the drug solution should be discarded.

## OVERDOSE

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

## SUPPLY

Captabs 250 mg: Box of 1 blister @ 6 film coated captabs Reg No. DKL9319803309A1
Tablets 500 mg: Box of 1 blister @ 3 film coated tablets Reg No. DKL9519804017A1

Powder for Oral Suspension 200 mg/5 mL: Box of 1 plastic bottle containing 600 mg powder (15 mL)Reg No. DKI9684800538A1

Zithromax IV 500 mg/vial: Box of 1 vial @ 500 mg Reg No. DKI0890400980A1

PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

STORE IN DRY PLACE BELOW 30°C FOR FILM-COATED TABLETS AND FILM-COATED CAPTABS
STORE IN TEMPERATURE BELOW 30°C FOR POWDER FOR ORAL SUSPENSION
STORE IN DRY PLACE BELOW 30°C FOR INTRAVENOUS INFUSION

Reconstituted suspension should be stored below 30°C and should be used within 5 days after reconstituted.

ZITHROMAX Tablet 250 mg & 500 mg
Manufactured by:
PT. Pfizer Indonesia
Jakarta, Indonesia

ZITHROMAX Powder for Oral Suspension
Manufactured by:
Haupt Pharma Latina S.r.l., Italy

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

ZITHROMAX Powder for Solution for Infusion
Manufactured by:
Pharmacia and Upjohn Company LLC,
Kalamazoo, Michigan,
USA.

Packed and released by:
Fareva Amboise,
Pocé-sur-cisse, France

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia