

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

**PT. PFIZER INDONESIA**  
**LOCAL PRODUCT DOCUMENT**

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018

**FORM AND PRESENTATION**

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

**Film-coated Captabs:** Azithromycin film-coated captabs are capsular shaped and contain azithromycin dihydrate equivalent to 250 mg of azithromycin.

**DESCRIPTION**

**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.

**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*.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

**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

Generic Name: Azithromycin

Trade Name: ZITHROMAX

CDS Effective Date: August 10, 2022

Supersedes: May 2, 2018

Approved by BPOM: February 13, 2024

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<sub>2</sub> 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**

Organism	Broth microdilution MIC (mg/L)		
	Susceptible	Intermediate	Resistant
<i>Haemophilus</i> species	≤4	-	≥ <sup>b</sup>
<i>Moraxella catarrhalis</i>	≤0.25	-	-
<i>Neisseria meningitidis</i>	≤2	-	≥ <sup>b</sup>
<i>Staphylococcus aureus</i>	≤2	4	≥8
Streptococci <sup>a</sup>	≤0.5	1	≥2

<sup>a</sup> Includes *Streptococcus pneumoniae*, β-hemolytic streptococci and viridans streptococci.

<sup>b</sup> The current absence of data on resistant strains precludes defining any category other than susceptible. If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing. Incubation in ambient air.

CLSI = Clinical and Laboratory Standards Institute;

MIC = Minimal inhibitory concentration.

Source: CLSI M45, 2015 CLSI M100, 2018.

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.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

### CLSI Disk Zone Interpretive Criteria

Organism	Disk inhibition zone diameter (mm)		
	Susceptible	Intermediate	Resistant
<i>Haemophilus</i> species	≥12	-	-
<i>Moraxella catarrhalis</i>	≥26	-	-
<i>Neisseria meningitidis</i>	≥20	-	-
<i>Staphylococcus aureus</i>	≥18	14-17	≤13
Streptococci <sup>a</sup>	≥18	14-17	≤13

<sup>a</sup> Includes *Streptococcus pneumoniae*, β-hemolytic streptococci and viridans streptococci.

Incubation in ambient air.

CLSI = Clinical and Laboratory Standards Institute; mm = Millimeters.

Source: CLSI M45, 2015 CLSI M100, 2018.

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)
<i>Haemophilus influenzae</i> ATCC 49247	1-4
<i>Staphylococcus aureus</i> ATCC 29213	0.5-2
<i>Streptococcus pneumoniae</i> ATCC 49619	0.06-0.25
Disk inhibition zone diameter (15 µg disk)	
Organism	Quality control range (mm)
<i>Haemophilus influenzae</i> ATCC 49247	13-21
<i>Staphylococcus aureus</i> ATCC 25923	21-26
<i>Streptococcus pneumoniae</i> ATCC 49619	19-25

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

### Quality Control Ranges for Azithromycin Susceptibility Tests

Broth microdilution MIC	
Organism	Quality control range (mg/L azithromycin)
Incubation in ambient air. CLSI = Clinical and Laboratory Standards Institute; MIC = Minimal inhibitory concentration; mm = Millimeters Source: CLSI M100, 2018	

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
<i>Staphylococcus</i> species	≤1	>2
<i>Streptococcus pneumoniae</i>	≤0.25	>0.5
β-hemolytic streptococci <sup>a</sup>	≤0.25	>0.5
<i>Haemophilus influenzae</i>	≤0.12	>4
<i>Moraxella catarrhalis</i>	≤0.25	>0.5
<i>Neisseria gonorrhoeae</i>	≤0.25	>0.5

<sup>a</sup> Includes Groups A, B, C, G.

EUCAST = European Committee on Antimicrobial Susceptibility Testing; MIC = Minimal inhibitory concentration.

Source: EUCAST Web site.

**EUCAST Clinical Breakpoint Table v. 8.0, valid from 2018-01-01**

[www.eucast.org/.../EUCAST.../Breakpoint\\_tables/v\\_8.0\\_Breakpoint\\_Tables.pdf](http://www.eucast.org/.../EUCAST.../Breakpoint_tables/v_8.0_Breakpoint_Tables.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*.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

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  $\beta$ -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 against the indicated species has been demonstrated in clinical trials.

## ***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<sub>90</sub> 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

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

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 GFR 10-80 mL/min were not affected following a single 1 gram dose of immediate release azithromycin. Statistically significant differences in AUC<sub>0-120</sub> (8.8 µg·h/mL vs. 11.7 µg·h/mL), C<sub>max</sub> (1.0 µg/mL vs. 1.6 µg/mL) and CL<sub>r</sub> (2.3 mL/min/kg vs. 0.2 mL/min/kg) were observed between the group with GFR <10 mL/min and GFR >80 mL/min.

#### **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 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.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

### **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 gonorrhea 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 gonorrhea or syphilis. All patients with sexually-transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate cultures for gonorrhea 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.

## **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.



Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

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.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

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 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 mL/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.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

## **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**

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 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.

### **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.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

### **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.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

### **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 is a large amount of data from observational studies performed in several countries

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. While most studies do not suggest an association with adverse fetal 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.

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.

### **Lactation**

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.

### **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: Local pain.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

**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: Asthenia, fatigue, and malaise.

## **POSODOLOGY AND METHOD OF ADMINISTRATION**

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.

Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

### 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 2-5.

### 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.

### 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 GFR 10-80 mL/min. Caution should be exercised when azithromycin is administered to patients with 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.

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

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



Generic Name: Azithromycin  
Trade Name: ZITHROMAX  
CDS Effective Date: August 10, 2022  
Supersedes: May 2, 2018  
Approved by BPOM: February 13, 2024

## 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

PRESCRIPTION ONLY  
HARUS DENGAN RESEP DOKTER

STORE IN DRY PLACE BELOW 30°C FOR FILM-COATED TABLETS AND FILM-COATED CAPTABS

ZITHROMAX Tablet 250 mg & 500 mg

Manufactured by:  
PT. Pfizer Indonesia  
Jakarta, Indonesia