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

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.

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.

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

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

[a] Includes *Streptococcus pneumoniae*, β-hemolytic streptococci and viridans streptococci.
[b] 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.

CLSI Disk Zone Interpretive Criteria

Organism	Disk inhibition zone diameter (mm)		
	Susceptible	Intermediate	Resistant
Haemophilus species	≥12	-	-

CLSI Disk Zone Interpretive Criteria

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

[a] 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)**
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 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**
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

[a] 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

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 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_{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 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 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.

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.

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 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.

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.

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 is a large amount of data from observational studies performed in several countries on exposure to azithromycin during pregnancy, compared to no antibiotic use or use of another antibiotic during the same period. 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.

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.

POSOLOGY 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.

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.

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 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

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.

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

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

PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

STORE IN TEMPERATURE BELOW 30°C FOR POWDER FOR ORAL SUSPENSION

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

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

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

-Brosur kemasan: Informasi bagi pengguna

ZITHROMAX 200 mg/5 mL Serbuk Suspensi Oral

Azitromisin

Bacalah brosur ini dengan teliti sebelum Anda meminum obat ini karena berisi informasi yang penting untuk Anda.

- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter, apoteker, atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, sekali pun gejala-gejala penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, berkonsultasilah dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala bentuk efek samping yang tidak tercantum di dalam brosur ini.

Isi brosur ini:

1. Nama Produk

Zithromax

2. Deskripsi Produk

Zithromax adalah antibiotik.

Serbuk Suspensi Oral: Serbuk Azitromisin untuk suspensi oral berwujud serbuk kering yang menghasilkan, setelah direkonstitusi dengan air, suspensi putih hingga putih pudar dengan kandungan setara azitromisin 200 mg per 5 ml.

3. Apa kandungan obat ini?

Serbuk Suspensi Oral – Serbuk untuk suspensi oral mengandung sukrosa 1,94 g per 100 mg dosis), natrium fosfat tribasa anhidrat, hidroksipropil selulosa, xanthan gum, perisa buatan ceri, krim vanila, dan pisang.

DISETUJUI OLEH BPOM: 22/04/2024 ID: EREG10024112300259

4. Kekuatan dosis obat

Serbuk Suspensi Oral: 200 mg/5 ml

5. Apa kegunaan obat ini?

Azitromisin diindikasikan untuk mengobati pasien dengan infeksi ringan hingga sedang (pneumonia: lihat bagian - **Apa saja yang perlu diperhatikan saat menggunakan obat ini?**) yang disebabkan oleh galur rentan dari mikroorganisme yang dimaksud dalam kondisi spesifik yang disebutkan di bawah ini:

Saluran Pernapasan Bawah
Eksaserbasi bakteri akut pada penyakit paru obstruktif kronis yang disebabkan oleh *Haemophilus influenzae, Moraxella catarrhalis,* atau *Streptococcus pneumoniae*.

Pneumonia yang didapat dari -masyarakat dengan tingkat keparahan ringan yang disebabkan oleh *Streptococcus pneumoniae* atau *Haemophilus influenzae* pada pasien yang memenuhi syarat untuk menjalani terapi oral rawat jalan.

Saluran Pernapasan Atas
Faringitis/tonsilitis streptokokus - Sebagai alternatif terapi lini pertama untuk faringitis/tonsilitis akut yang disebabkan oleh *Streptococcus pyogenes* yang dialami oleh individu yang tidak dapat menggunakan terapi lini pertama.

Kulit dan Struktur Kulit
Infeksi kulit dan struktur kulit tanpa komplikasi yang disebabkan oleh *Staphylococcus aureus, Streptococcus pyogenes*, atau *Streptococcus agalactiae*. Abses biasanya mengharuskan bedah drainase.

Penyakit Menular Seksual
Uretritis dan servisitis non-gonokokal yang disebabkan oleh *Chlamydia trachomatis.*

Azitromisin, pada dosis yang dianjurkan, tidak boleh diandalkan untuk mengobati gonore atau sifilis. Agen antimikroba yang digunakan dalam dosis tinggi untuk jangka waktu singkat guna mengobati uretritis non-gonokokal dapat menyamarkan atau menunda gejala inkubasi gonore atau sifilis. Semua pasien dengan uretritis atau servisitis yang ditularkan secara seksual harus menjalani tes serologis untuk sifilis dan tes kultur yang sesuai untuk gonore yang dilakukan pada saat diagnosis. Terapi antimikroba yang sesuai dan tes tindak lanjut untuk penyakit ini harus dimulai setelah diagnosis infeksi ditegakkan.

Tes kerentanan dan kultur yang sesuai harus dilakukan sebelum pengobatan untuk menentukan organisme penyebab beserta kerentanannya terhadap azitromisin. Terapi dengan azitromisin dapat dimulai sebelum hasil tes ini diketahui; setelah hasil tes tersedia, terapi antimikroba dapat disesuaikan sebagaimana mestinya.

6. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini?

Azitromisin harus diberikan sebagai dosis harian tunggal. Periode pemberian dosis sehubungan dengan infeksi diberikan di bawah ini.

Tablet, kaplet, dan serbuk suspensi oral azitromisin dapat diminum sebelum atau sesudah makan.

Pada orang dewasa
Untuk mengobati penyakit menular seksual yang disebabkan oleh *Chlamydia trachomatis* dan *Haemophilus ducreyi*, atau *Neisseria gonorrhoeae* rentan, dosisnya adalah 1000 mg sebagai dosis oral tunggal.

Untuk semua indikasi lainnya yang mengharuskan pemberian formulasi oral, maka dosis total 1500 mg harus diberikan sebesar 500 mg setiap hari selama 3 hari. Sebagai alternatif, dosis total yang sama dapat diberikan dalam waktu 5 hari dengan dosis 500 mg diberikan pada Hari ke-1, kemudian 250 mg setiap hari pada hari ke-2 hingga ke-5.

Pada anak-anak
Tidak ada informasi mengenai anak-anak yang berusia di bawah enam bulan.

Dosis total 30 mg/kg harus diberikan sebagai dosis harian tunggal 10 mg/kg, atau sebagai alternatif, diberikan dalam jangka waktu 5 hari dengan dosis harian tunggal 10 mg/kg pada Hari ke-1, kemudian 5 mg/kg pada Hari ke-2 hingga ke-5.

Suspensi azitromisin harus diberikan sesuai dengan panduan di bawah ini:

Suspensi Azitromisin 30 mg/kg Dosis Total Pengobatan			
Berat (kg)	**Regimen Pengobatan 3 Hari**	**Regimen Pengobatan 5 Hari**	**Ukuran Botol (mg)**
15–25	200 mg (5 ml) satu kali setiap hari pada Hari ke-1 hingga ke-3	200 mg (5 ml) pada Hari ke-1, kemudian 100 mg (2,5 ml) satu kali setiap hari pada Hari ke-2 hingga ke-5	600
26-35	300 mg (7,5 ml) satu kali setiap hari pada Hari ke-1 hingga ke-3	300 mg (7,5 ml) pada Hari ke-1, kemudian 150 mg (3,75 ml) satu kali setiap hari pada Hari ke-2 hingga ke-5	900
36-45	400 mg (10 ml) satu kali setiap hari pada Hari ke-1 hingga ke-3	400 mg (10 ml) pada Hari ke-1, kemudian 200 mg (5 ml) satu kali setiap hari pada Hari ke-2 hingga ke-5	1200
>45	Dosis untuk orang dewasa.	Dosis untuk orang dewasa	1500

Populasi khusus

Pada Orang Lanjut Usia
Dosis yang sama seperti pada pasien dewasa juga digunakan pada pasien lanjut usia. Pasien lanjut usia mungkin lebih rentan untuk mengalami aritmia torsades de pointes dibandingkan pasien yang lebih muda (lihat **bagian - Apa saja yang perlu diperhatikan saat menggunakan obat ini?).**

Pada Pasien dengan Gangguan Ginjal
Penyesuaian dosis tidak diperlukan pada pasien dengan GFR 10-80 ml/menit. Diperlukan kehati-hatian jika memberikan azitromisin pada pasien dengan GFR < 10 ml/menit (lihat **bagian - Apa saja yang perlu diperhatikan saat menggunakan obat ini?**).

Pada Pasien dengan Gangguan Hati
Dosis yang sama seperti pada pasien dengan fungsi hati normal dapat digunakan pada pasien dengan gangguan hati ringan hingga sedang (lihat **bagian - Apa saja yang perlu diperhatikan saat menggunakan obat ini?)**.

Untuk pengobatan pasien dewasa dengan CAP yang disebabkan oleh organisme yang diindikasikan, dosis azitromisin IV yang dianjurkan adalah 500 mg sebagai dosis harian tunggal melalui rute IV selama setidaknya 2 hari. Terapi IV harus diikuti dengan azitromisin oral dengan dosis harian tunggal 500 mg untuk melengkapi rangkaian terapi 7 hingga 10 hari. Penentuan waktu konversi ke terapi oral harus dilakukan atas pertimbangan dokter dan sesuai dengan respons klinis.

Untuk pengobatan pasien dewasa dengan PID yang disebabkan oleh organisme yang diindikasikan, dosis azitromisin IV yang dianjurkan adalah 500 mg sebagai dosis tunggal melalui rute IV selama 1 atau 2 hari. Terapi IV harus diikuti dengan azitromisin oral dengan dosis harian tunggal 250 mg untuk melengkapi rangkaian terapi 7 hari. Penentuan waktu konversi ke terapi oral harus dilakukan atas pertimbangan dokter dan sesuai dengan respons klinis. Jika mikroorganisme anaerob diduga turut menyebabkan infeksi, maka agen antimikroba anaerob dapat diberikan dalam kombinasi dengan azitromisin.

Petunjuk Penggunaan, Penanganan, dan Pembuangan

Serbuk Suspensi Oral: Ketuk-ketuk botol agar serbuk terurai. Tambahkan 9 ml air ke dalam botol 600 mg. Kocok sempurna. Kocok segera sebelum digunakan.

Untuk anak-anak dengan berat badan kurang dari 15 kg, maka suspensi harus diukur seakurat mungkin. Untuk anak-anak dengan berat badan 15 kg atau lebih, maka suspensi harus diberikan dengan menggunakan alat pengukur yang tepat.

7. Kapan seharusnya Anda tidak menggunakan obat ini?

Penggunaan produk ini tidak dianjurkan untuk pasien yang memiliki reaksi hipersensitivitas terhadap azitromisin, eritromisin, setiap antibiotik makrolida atau ketolida, atau terhadap eksipiennya.

8. Efek yang tidak diinginkan

Azitromisin dapat ditoleransi dengan baik dengan kejadian efek samping yang rendah

Dalam uji klinis, telah dilaporkan adanya efek tidak diinginkan berikut ini:

Gangguan Darah dan Sistem Limfatik: Kejadian neutropenia ringan yang bersifat sementara kadang-kadang teramati dalam uji klinis.

Gangguan Telinga dan Labirin: Gangguan pendengaran (termasuk hilangnya pendengaran, ketulian, dan/atau telinga berdenging) telah dilaporkan dialami beberapa pasien yang menerima azitromisin. Banyak dari kejadian ini dikaitkan dengan penggunaan dosis tinggi yang berkepanjangan dalam penelitian investigasi. Dalam kasus-kasus yang didukung oleh informasi tindak lanjut, maka sebagian besar dari kejadian ini dapat dipulihkan.

Gangguan Gastrointestinal: Mual, muntah, diare, BAB lembek, perut tidak nyaman (nyeri/kram), dan kembung.

Gangguan Hepatobilier: Fungsi hati abnormal.

Gangguan Kulit dan Jaringan Subkutan: Reaksi alergi termasuk ruam dan angioedema.

Gangguan Umum: Nyeri lokal.

Pada pengalaman pasca pemasaran, dilaporkan adanya tambahan efek yang tidak diinginkan berikut:

Infeksi dan Infestasi: Moniliasis, dan vaginitis.

Gangguan Darah dan Sistem Limfatik: Trombositopenia.

Gangguan Sistem Imun: Anafilaksis (jarang bersifat fatal) (lihat bagian - **Apa saja yang perlu diperhatikan saat menggunakan obat ini?**).

Gangguan Metabolisme dan Nutrisi: Anoreksia.

Gangguan Psikiatrik: Reaksi agresif, ketegangan, agitasi, dan kecemasan.

Gangguan Sistem Saraf: Pening, kejang, sakit kepala, hiperaktivitas, hipoestesia, parestesia, penurunan kesadaran, dan pingsan.

Terdapat laporan yang jarang terkait ketidakwajaran dan/atau hilangnya indra perasa/penciuman.

Gangguan Telinga dan Labirin: Ketulian, telinga berdenging, gangguan pendengaran, dan vertigo.

Gangguan Jantung: Palpitasi dan aritmia termasuk takikardia ventrikular telah dilaporkan. Terdapat laporan yang jarang terkait memanjangnya QT dan torsades de pointes (lihat Bagian - **Apa saja yang perlu diperhatikan saat menggunakan obat ini?**).

Gangguan Vaskular: Hipotensi.

Gangguan Gastrointestinal: Muntah/diare (jarang mengakibatkan dehidrasi), dispepsia, sembelit, kolitis pseudomembranosa, pankreatitis, dan laporan yang jarang untuk perubahan warna lidah.

Gangguan Hepatobilier: Hepatitis dan penyakit kuning kolestasis telah dilaporkan, serta kasus yang jarang untuk nekrosis hati dan gagal hati, yang menyebabkan kematian (lihat Bagian - **Apa saja yang perlu diperhatikan saat menggunakan obat ini?**).

Gangguan Kulit dan Jaringan Subkutan: Reaksi alergi termasuk pruritus, ruam, fotosensitivitas, edema, urtikaria, dan angioedema. Gangguan yang dilaporkan jarang terjadi adalah reaksi merugikan pada kutan di antaranya eritema multiformis, AGEP, SJS, TEN, dan DRESS.

Gangguan Muskuloskeletal dan Jaringan Ikat: Artralgia.

Gangguan Ginjal dan Kemih: Nefritis interstisial dan gagal ginjal akut.

Gangguan Umum: Astenia, kelelahan, dan malaise.

9. Apa saja obat atau makanan lain yang harus dihindari selama menggunakan obat ini?

Sampaikan kepada dokter atau apoteker Anda jika Anda sedang, belum lama ini, atau akan menggunakan obat lain. Sebagian obat-obatan bisa memengaruhi cara kerja Zithromax atau Zithromax bisa memengaruhi cara kerja obat-obatan tersebut, jika diminum bersamaan.

Antasida
Dalam penelitian farmakokinetik yang menyelidiki efek dari pemberian antasida bersamaan dengan azitromisin, tidak teramati adanya efek terhadap ketersediaan hayati secara keseluruhan, meskipun konsentrasi serum puncak menurun sekitar 24%. Pada pasien yang menerima azitromisin dan antasida, maka kedua obat tidak boleh diminum secara bersamaan.

Cetirizine
Pada sukarelawan sehat, pemberian regimen pengobatan azitromisin selama 5 hari bersamaan dengan cetirizine 20 mg pada kondisi stabil tidak menghasilkan interaksi farmakokinetik dan tidak ada perubahan signifikan pada interval QT.

Didanosin (Dideoksiinosin)
Pemberian azitromisin 1200 mg/hari bersama dengan didanosin 400 mg/hari pada 6 subjek positif HIV tampaknya tidak memengaruhi kondisi farmakokinetik stabil dari didanosin jika dibandingkan dengan plasebo.

Digoksin dan kolkisin
Banyak pasien yang menerima azitromisin bersamaan dengan glikosida jantung, dan hal ini tidak menunjukkan adanya interaksi.

Pemberian antibiotik makrolida, termasuk azitromisin, bersama dengan substrat P-glikoprotein seperti digoksin dan kolkisin, telah dilaporkan mengakibatkan peningkatan kadar serum substrat P-glikoprotein. Karenanya, jika azitromisin dan substrat P-glikoprotein seperti digoksin diberikan secara bersamaan, maka kemungkinan adanya peningkatan konsentrasi digoksin dalam serum perlu dipertimbangkan. Perlu dilakukan pemantauan klinis, dan kemungkinan kadar digoksin dalam serum, selama pengobatan menggunakan azitromisin dan setelah dihentikan.

Ergot
Terdapat kemungkinan teoretis terkait interaksi antara azitromisin dan turunan ergot (lihat Bagian - **Apa saja yang perlu diperhatikan saat menggunakan obat ini?**).

Zidovudin
Azitromisin dalam dosis tunggal 1000 mg dan dosis ganda 1200 mg atau 600 mg memberikan efek kecil terhadap farmakokinetik plasma atau ekskresi urine dari zidovudin atau metabolit glukurodinnya. Namun demikian, pemberian azitromisin meningkatkan konsentrasi zidovudin terfosforilasi, metabolit yang aktif secara klinis, dalam sel mononuklear darah perifer. Signifikansi klinis dari temuan ini masih belum jelas, tetapi hal ini mungkin bermanfaat bagi pasien.

Azitromisin tidak berinteraksi secara signifikan dengan sistem P450 sitokrom hepatik. Tidak diyakini adanya interaksi obat farmakokinetik sebagaimana terlihat pada eritromisin dan makrolida lainnya. Induksi atau inaktivasi P450 sitokrom hepatik melalui kompleks sitokrom-metabolit tidak terjadi dengan pemberian azitromisin.

Penelitian farmakokinetik telah dilakukan antara azitromisin dan obat-obatan berikut yang diketahui mengalami metabolisme termediasi P450 sitokrom yang signifikan.

Atorvastatin
Pemberian atorvastatin (10 mg setiap hari) bersamaan dengan azitromisin (500 mg setiap hari) tidak mengubah konsentrasi plasma atorvastatin (berdasarkan pemeriksaan penghambatan HMG CoA-reduktase). Namun demikian, kasus rabdomiolisis pascapemasaran pada pasien yang menggunakan azitromisin bersamaan dengan statin telah dilaporkan.

Karbamazepin
Dalam penelitian interaksi farmakokinetik pada sukarelawan sehat, tidak ada efek signifikan yang teramati pada kadar plasma karbamazepin atau metabolit aktifnya pada pasien yang juga menerima azitromisin.

Simetidin
Pada penelitian farmakokinetik yang meneliti efek dosis tunggal simetidin, yang diberikan 2 jam sebelum pemberian azitromisin, terhadap farmakokinetik azitromisin, tidak ada perubahan farmakokinetik azitromisin yang teramati.

Antikoagulan oral tipe-kumarin
Dalam penelitian interaksi farmakokinetik, azitromisin tidak mengubah efek antikoagulan dari dosis tunggal warfarin 15 mg yang diberikan kepada sukarelawan sehat. Terdapat laporan yang diterima dalam periode pascapemasaran mengenai penguatan kinerja antikoagulasi setelah pemberian azitromisin bersama dengan antikoagulan oral tipe-kumarin. Meskipun hubungan sebab akibatnya belum ditetapkan, namun frekuensi pemantauan waktu protrombin perlu dipertimbangkan jika azitromisin diberikan pada pasien yang juga menggunakan antikoagulan oral tipe kumarin.

Siklosporin
Dalam penelitian farmakokinetik terhadap sukarelawan sehat yang diberi dosis oral azitromisin 500 mg/hari selama 3 hari dan kemudian menerima dosis tunggal siklosporin 10 mg/kg secara oral, maka C_{maks} dan AUC_{0-5} siklosporin yang dihasilkan menunjukkan kenaikan yang signifikan. Dengan demikian, diperlukan kehati-hatian sebelum memberikan obat-obatan ini secara bersamaan. Jika obat-obatan ini perlu diberikan secara bersamaan, maka diperlukan pemantauan kadar siklosporin serta penyesuaian dosis sebagaimana mestinya.

Efavirenz
Pemberian dosis tunggal azitromisin 600 mg bersamaan dengan efavirenz 400 mg setiap hari selama 7 hari tidak menunjukkan adanya interaksi farmakokinetik yang signifikan secara klinis.

Flukonazol
Pemberian secara bersamaan dosis tunggal azitromisin 1200 mg tidak mengubah farmakokinetik dosis tunggal flukonazol 800 mg. Paparan total dan waktu paruh azitromisin tidak berubah jika diberikan bersamaan dengan flukonazol; namun teramati adanya penurunan C_{maks} (18%) yang tidak signifikan secara klinis.

Indinavir
Pemberian secara bersamaan dosis tunggal azitromisin 1200 mg tidak memberikan efek yang signifikan secara statistik terhadap farmakokinetik indinavir yang diberikan dalam dosis 800 mg tiga kali setiap hari selama 5 hari.

Metilprednisolon
Dalam penelitian interaksi farmakokinetik terhadap sukarelawan sehat, azitromisin tidak memberikan efek yang signifikan terhadap farmakokinetik metilprednisolon.

Midazolam
Pada sukarelawan sehat, pemberian bersamaan azitromisin 500 mg/hari selama 3 hari tidak menyebabkan perubahan yang signifikan secara klinis terhadap farmakokinetik dan farmakodinamik dosis tunggal midazolam 15 mg.

Nelfinavir
Pemberian azitromisin (1200 mg) bersamaan dengan nelfinavir dalam kondisi stabil (750 mg tiga kali sehari) menghasilkan peningkatan konsentrasi azitromisin. Tidak teramati adanya efek merugikan yang signifikan secara klinis dan penyesuaian dosis tidak perlu dilakukan.

Rifabutin
Pemberian azitromisin bersamaan dengan rifabutin tidak berpengaruh terhadap konsentrasi serum kedua obat.

Neutropenia teramati pada subjek yang menerima pengobatan azitromisin bersama dengan rifabutin. Meskipun neutropenia telah dikaitkan dengan penggunaan rifabutin, namun hubungan sebab akibat antara kombinasi dengan azitromisin masih belum ditetapkan (lihat Bagian - **Efek yang tidak diinginkan**).

Sildenafil
Pada sukarelawan laki-laki yang normal dan sehat, tidak terdapat bukti efek azitromisin (500 mg setiap hari selama 3 hari) terhadap AUC dan C_{maks} dari sildenafil atau metabolit utamanya yang beredar.

Terfenadin
Penelitian farmakokinetik telah melaporkan tidak adanya bukti interaksi antara azitromisin dan terfenadin. Telah dilaporkan sejumlah kasus yang jarang terjadi di mana kemungkinan interaksi tersebut tidak dapat dikecualikan sepenuhnya; namun demikian, tidak ada bukti spesifik terjadinya interaksi tersebut.

Teofilin
Tidak ada bukti adanya interaksi farmakokinetik yang signifikan secara klinis ketika azitromisin dan teofilin diberikan secara bersamaan kepada sukarelawan yang sehat.

Triazolam
Pada 14 sukarelawan yang sehat, pemberian azitromisin 500 mg pada Hari ke-1 dan 250 mg pada Hari ke-2 bersama dengan triazolam 0,125 mg pada Hari ke-2 tidak memberikan efek yang signifikan terhadap variabel farmakokinetik untuk triazolam dibandingkan dengan triazolam dan plasebo.

Trimetoprim/sulfametoksazol
Pemberian trimetroprim/sulfametoksazol DS (160 mg/800 mg) selama 7 hari bersamaan dengan azitromisin 1200 mg pada Hari ke-7 tidak memberikan efek yang signifikan terhadap konsentrasi puncak, paparan total, atau ekskresi urine dari trimetoprim maupun sulfametoksazol. Konsentrasi serum azitromisin serupa dengan yang terlihat dalam penelitian lain.

10. Apa yang harus dilakukan jika ada dosis terlewat?
Beri tahu dokter atau perawat jika Anda merasa terlupa melewati satu dosis.

11. Bagaimana cara menyimpan obat ini?
Simpan pada suhu di bawah 30 °C untuk serbuk suspensi oral
Suspensi yang telah direkonstitusi harus disimpan di bawah suhu 30 °C dan harus digunakan dalam waktu 5 hari setelah direkonstitusi.

12. Tanda-tanda dan gejala overdosis
Kejadian merugikan yang dialami akibat dosis yang melebihi anjuran serupa dengan yang terlihat pada dosis normal. Jika terjadi overdosis, langkah-langkah penunjang dan simtomatik umum diindikasikan sesuai kebutuhan.

13. Apa yang harus dilakukan jika Anda menggunakan dosis melebihi anjuran?
Jika Anda merasa terlalu banyak meminum Zithromax, segera konsultasikan dengan dokter Anda.

14. Apa saja yang perlu diperhatikan saat menggunakan obat ini?

Hipersensitivitas
Seperti halnya eritromisin dan makrolida lainnya, reaksi alergi serius yang jarang terjadi, termasuk di antaranya angioedema dan anafilaksis (jarang berakibat fatal), reaksi Dermatologis, termasuk di antaranya Pustulosis Eksantema Generalisata Akut (AGEP), Sindrom Stevens-Johnson (SJS), Nekrolisis Epidermal Toksik (TEN) (jarang berakibat fatal), dan Reaksi Obat dengan Eosinofilia dan Gejala Sistemik (DRESS) telah dilaporkan. Sebagian dari reaksi dengan azitromisin ini telah menyebabkan gejala berulang dan memerlukan periode observasi dan pengobatan yang lebih lama.

Jika reaksi alergi terjadi, maka obat harus dihentikan dan terapi yang sesuai harus dimulai. Dokter harus mengetahui bahwa munculnya kembali reaksi alergi dapat terjadi jika terapi simtomatik dihentikan.

Hepatotoksisitas
Karena hati adalah rute utama untuk eliminasi azitromisin, penggunaan azitromisin harus dilakukan dengan hati-hati pada pasien dengan penyakit hati yang signifikan.

Fungsi hati abnormal, hepatitis, penyakit kuning kolestasis, nekrosis hati, dan gagal hati telah dilaporkan, sebagian di antaranya mengakibatkan kematian. Hentikan azitromisin segera jika terjadi tanda-tanda dan gejala adanya penyakit hepatitis.

Pada pasien dengan gangguan hati ringan (Kelas A) hingga sedang (Kelas B), tidak ada bukti perubahan yang jelas dalam farmakokinetik azitromisin dalam serum jika dibandingkan dengan pada fungsi hati normal. Pada pasien-pasien pemulihan masalah kandung kemih, azitromisin pada urine tampaknya meningkat, mungkin merupakan kompensasi bersihan hati yang menurun. Oleh karena itu penyesuaian dosis tidak dianjurkan bagi pasien yang menderita gangguan hati ringan hingga sedang.

Turunan ergot
Pada pasien yang menerima turunan ergot, ergotisme muncul jika diberikan bersamaan dengan sebagian antibiotik makrolida. Tidak terdapat data mengenai kemungkinan interaksi antara ergot dan azitromisin. Namun demikian, dikarenakan adanya teori kemungkinan terjadinya ergotisme, azitromisin dan turunan ergot tidak boleh diberikan secara bersamaan.

Superinfeksi
Seperti halnya sediaan antibiotik lainnya, dianjurkan untuk melakukan observasi terhadap tanda-tanda superinfeksi dengan organisme non-rentan, termasuk jamur.

Diare yang terkait dengan *Clostridium difficile*
Diare yang terkait dengan *Clostridium difficile* (CDAD) telah dilaporkan dengan penggunaan hampir semua agen antibakteri, termasuk azitromisin, dan dapat berkisar antara diare berat hingga ringan bahkan kolitis yang berakibat fatal. Pengobatan menggunakan agen antibakteri mengubah flora normal pada usus besar sehingga menyebabkan pertumbuhan berlebihan *C. difficile*.

C. difficile menghasilkan toksin A dan B, yang turut menyebabkan munculnya CDAD. Galur *C. difficile* yang menghasilkan hipertoksin menyebabkan peningkatan morbiditas dan mortalitas, karena infeksi ini dapat resistan terhadap terapi antimikroba dan mungkin mengharuskan prosedur kolektomi. CDAD harus dipertimbangkan pada semua pasien yang menunjukkan gejala diare setelah menggunakan antibiotik. Pengamatan riwayat medis diperlukan karena CDAD telah dilaporkan terjadi dalam waktu 2 bulan setelah pemberian agen antibakteri.

Jika diduga atau didiagnosis terjadi CDAD, penggunaan antibiotik berkelanjutan yang tidak ditujukan untuk mengatasi *C. difficile* mungkin perlu dihentikan. Penatalaksanaan cairan dan

elektrolit yang sesuai, suplementasi protein, pengobatan antibiotik untuk *C. difficile,* dan evaluasi pembedahan harus dilakukan sebagaimana diindikasikan secara klinis.

Penisilin adalah obat yang biasanya dipilih untuk mengobati infeksi *Streptococcus pyogenes* dan profilaksis untuk demam rematik. Azitromisin seringkali efektif dalam memberantas galur *Streptococcus pyogenes* yang rentan dari nasofaring. Karena sebagian galur resistan terhadap azitromisin, maka tes kerentanan harus dilakukan jika pasien diterapi dengan azitromisin. Data yang menetapkan efikasi azitromisin dalam pencegahan demam rematik berikutnya tidak tersedia. Jika reaksi alergi terjadi, maka obat harus dihentikan dan terapi yang sesuai harus dimulai. Dokter harus mengetahui bahwa munculnya kembali reaksi alergi dapat terjadi jika terapi simtomatik dihentikan.

Azitromisin tidak boleh digunakan pada pasien dengan pneumonia yang dinilai tidak layak untuk menjalani terapi oral rawat jalan dikarenakan penyakit yang bersifat sedang hingga berat atau faktor risiko sebagaimana yang berikut ini:

- Pasien dengan infeksi yang didapat dari nosokomial
- Pasien yang diketahui atau diduga menderita bakteremia
- Pasien yang memerlukan rawat inap
- Pasien lanjut usia atau yang sangat lemah, atau
- Pasien dengan masalah kesehatan yang signifikan yang dapat membahayakan kemampuan mereka untuk merespons penyakit mereka (termasuk imunodefisiensi atau asplenia fungsional).

Gangguan ginjal
Pada pasien dengan GFR < 10 ml/menit, teramati adanya peningkatan paparan sistemik terhadap azitromisin sebesar 33%.

Diabetes
Perhatian untuk pasien diabetes: 5 ml suspensi yang direkonstitusi mengandung 3,87 g sukrosa.

Dikarenakan kandungan sukrosa tersebut (3,87 g/5 ml suspensi yang direkonstitusi), produk obat ini tidak diindikasikan untuk orang yang memiliki intoleransi fruktosa (intoleransi fruktosa yang diturunkan), malabsorpsi glukosa-galaktosa, atau defisiensi sakarase-isomaltase.

Penyesuaian dosis tidak perlu dilakukan pada pasien dengan gangguan ginjal ringan (bersihan kreatinin > 40 mg/menit) tetapi tidak terdapat data mengenai penggunaan azitromisin pada pasien yang menderita gangguan ginjal lebih berat; sehingga kehati-hatian diperlukan sebelum meresepkan Zithromax pada pasien ini.

Memanjangnya interval QT
Memanjangnya repolarisasi jantung dan interval QT yang memicu risiko berkembangnya aritmia jantung dan torsades de pointes, telah teramati dalam pengobatan menggunakan makrolida, termasuk azitromisin (lihat bagian - **Efek yang Tidak Diinginkan**). Dokter yang meresepkan harus mempertimbangkan risiko memanjangnya QT, yang dapat berakibat fatal saat menimbang risiko dan manfaat azitromisin untuk kelompok yang berisiko di antaranya:

- Pasien yang mengalami perpanjangan QT bawaan atau yang didokumentasikan
- Pasien yang saat ini menerima pengobatan dengan zat aktif lain yang diketahui dapat memperpanjang interval QT seperti antiaritmik dari Golongan IA dan III, agen antipsikotik, antidepresan, dan fluorokuinolon
- Pasien yang menderita gangguan elektrolit, terutama dalam kasus hipokalemia dan hipomagnesemia
- Pasien dengan bradikardia, aritmia jantung, atau insufisiensi jantung yang relevan secara klinis
- Pasien lanjut usia: pasien lanjut usia mungkin lebih rentan terhadap efek obat terhadap interval QT

Myasthenia gravis
Memburuknya gejala myasthenia gravis telah dilaporkan dialami oleh pasien yang menerima terapi azitromisin.

Fertilitas, kehamilan, dan menyusui

Kehamilan
Penelitian terhadap reproduksi hewan telah dilakukan pada dosis hingga konsentrasi dosis yang memberikan toksisitas sedang bagi kehamilan. Dalam penelitian ini, tidak ada bukti adanya bahaya bagi janin dikarenakan pemberian azitromisin. Terdapat data dalam jumlah besar dari studi observasi yang dilakukan di beberapa negara mengenai paparan azitromisin selama kehamilan dibandingkan dengan tanpa penggunaan antibiotik atau penggunaan antibiotik lain dalam periode yang sama. Meskipun sebagian besar penelitian tidak menunjukkan adanya keterkaitan dengan efek merugikan terhadap janin seperti kelainan kongenital mayor atau kelainan kardiovaskular, terdapat bukti epidemiologis yang terbatas sehubungan dengan peningkatan risiko keguguran setelah paparan azitromisin pada awal masa kehamilan.

Azitromisin hanya boleh digunakan selama kehamilan jika dibutuhkan secara klinis dan manfaat pengobatannya diperkirakan melebihi setiap peningkatan risiko kecil yang mungkin ada.

Menyusui
Informasi terbatas yang tersedia dari literatur yang dipublikasikan menunjukkan bahwa azitromisin terkandung dalam ASI dengan estimasi median tertinggi dosis harian 0,1 hingga 0,7 mg/kg/hari. Tidak teramati adanya efek merugikan serius dari azitromisin terhadap bayi yang menyusui.

Keputusan harus diambil apakah harus menghentikan pemberian ASI atau menghentikan/tidak menggunakan terapi azitromisin dengan mempertimbangkan manfaat pemberian ASI bagi bayi dan manfaat terapi bagi pasien.

Kesuburan
Pada penelitian kesuburan yang dilakukan terhadap tikus, penurunan angka kehamilan teramati setelah pemberian azitromisin. Relevansi temuan ini terhadap manusia masih belum diketahui.

Efek terhadap kemampuan mengemudi dan mengoperasikan mesin
Tidak terdapat bukti yang menunjukkan bahwa azitromisin dapat memengaruhi kemampuan pasien untuk mengemudi atau mengoperasikan mesin.

15. Kapan sebaiknya Anda berkonsultasi dengan dokter?
Jika Anda memiliki pertanyaan lebih lanjut mengenai kegunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

16. Nama/logo produsen/importir/Pemegang Hak Pemasaran

ZITHROMAX Serbuk Suspensi Oral
Diproduksi oleh:
Haupt Pharma Latina S.r.l., Italia

Diimpor oleh:
PT. Pfizer Indonesia
Jakarta, Indonesia

HARUS DENGAN RESEP DOKTER

Serbuk Suspensi Oral 200 mg/5 ml:
Dus berisi 1 botol plastik yang berisi 600 mg serbuk (15 ml); No. Reg. DKI9684800538A1