Zithromax® 200 mg/5 ml POS

Zithromax 500 mg film-coated tablets

Zithromax 250 mg capsules hard

Azithromycin

CDS

AfME Markets using same as LPD: Ethiopia, Ghana, Kenya, Nigeria, Tanzania and Uganda

1. NAME OF THE MEDICINAL PRODUCT

ZITHROMAX

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Powder for Oral Suspension: Azithromycin dihydrate 209.64 mg/5 ml equivalent to 200 mg/5 ml of azithromycin base.

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

3. PHARMACEUTICAL FORM

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

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.

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

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in odontostomatological infections, in skin and soft tissue infections, in acute otitis media and in upper respiratory tract infections including acute otitis media, sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx; however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present.)

In sexually transmitted diseases in men and women, azithromycin is indicated for the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated for the treatment of chancroid due to *Haemophilus ducreyi* and uncomplicated genital infections due to non-multiresistant *Neisseria gonorrhoeae*; concurrent infection with *Treponema pallidum* should be excluded.

Azithromycin is indicated, either alone or in combination with rifabutin, for prophylaxis against *Mycobacterium avium*-intracellulare complex (MAC) infection, an opportunistic infection prevalent in patients with advanced human immunodeficiency virus (HIV).

Azithromycin is indicated in combination with ethambutol for the treatment of disseminated MAC (DMAC) infection in patients with advanced HIV infection.

4.2. Posology and method of administration

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

Administration of azithromycin capsules following a substantial meal reduces bioavailability by at least 50%. Therefore, in common with many other antibiotics, each dose of the capsules should be taken at least 1 hour before or 2 hours after food.

Azithromycin tablets, 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,* the dose is 1000 mg as a single oral dose. For susceptible *Neisseria gonorrhoeae,* the recommended dose is 1000 mg or 2000 mg of azithromycin in combination with 250 mg or 500 mg ceftriaxone according to local clinical treatment guidelines.

For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

For prophylaxis against MAC infections in patients infected with the HIV, the dose is 1200 mg once per week.

For the treatment of DMAC infections in patients with advanced HIV infection, the recommended dose is 600 mg once a day. Azithromycin should be administered in combination with other antimycobacterial agents that have shown *in vitro* activity against MAC, such as ethambutol, at the approved dose.

For the treatment of lower and upper respiratory tract infections, odontostomatological infections and in skin and soft tissue infections the total dosage of 1500 mg should be given as 500 mg daily for 3 days. As an alternative, the same total dose can be given over 5 days with 500 mg given on Day 1, then 250 mg daily on Days 2 to 5.

In children

The maximum recommended total dose for any treatment is 1500 mg for children.

In general, the total dose in children is 30 mg/kg. Treatment for pediatric streptococcal pharyngitis should be dosed at a different regimen (see below).

The total dose of 30 mg/kg should be given as a single daily dose of 10 mg/kg daily for 3 days, or given over 5 days with a single daily dose of 10 mg/kg on Day 1, then 5 mg/kg on Days 2-5.

As an alternative to the above dosing, treatment for children with acute otitis media can be given as a single dose of 30 mg/kg.

For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective; however, a daily dose of 500 mg must not be exceeded. In clinical trials comparing these two dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg/day dose. However, penicillin is the usual drug of choice for the treatment of *Streptococcus pyogenes* pharyngitis, including prophylaxis of rheumatic fever.

For children weighing less than 15 kg, azithromycin suspension should be measured as closely as possible. For children weighing 15 kg or more, 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	10 mg/kg once daily on Days 1-3	10 mg/kg on Day 1, then 5 mg/kg once daily on Days 2-5	600
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

Azithromycin capsules or tablets should only be administered to children weighing more than 45 kg.

Safety and efficacy for the prevention or treatment of MAC in children have not been established. Based on pediatric pharmacokinetic data, a dose of 20 mg/kg would be similar to the adult dose of 1200 mg but with a higher C_{max}.

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 4.4).**

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 4.4** and **section 5.2**).

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 4.4**).

4.3. 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 6.1**.

4.4. 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.

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

Ergot derivatives

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration 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 coadministered.

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.

Renal impairment

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

Diabetes

Azithromycin 40 mg/ml powder for oral suspension: 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.

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 4.8**). 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.

4.5. Interaction with other medicinal products and other forms of interaction

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

Cetirizine

In healthy volunteers, coadministration 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)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

Digoxin and colchicine

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with azithromycin and after its discontinuation are necessary.

Ergot

There is a theoretical possibility of interaction between azithromycin and ergot derivatives (see **section 4.4**).

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

Coadministration 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 coadministration 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 coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz

Coadministration 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

Coadministration 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 coadministration of fluconazole; however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Indinavir

Coadministration 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, coadministration 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

Coadministration 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

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see **section 4.8**).

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 coadministered to healthy volunteers.

Triazolam

In 14 healthy volunteers, coadministration 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

Coadministration 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.

4.6. Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the 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.

4.7. Effects 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.

4.8. Undesirable effects

Azithromycin is well tolerated with a low incidence of side effects.

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

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

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

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

Hepatobiliary Disorders: Abnormal liver function.

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

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

The following undesirable effects have been reported in association with DMAC prophylaxis and treatment clinical trials:

The most frequent (>5% in any treatment group) adverse reactions in HIV-infected patients receiving azithromycin for prophylaxis for DMAC were diarrhea, abdominal pain, nausea, loose stools, flatulence, vomiting, dyspepsia, rash, pruritus, headache, and arthralgia.

When 600 mg azithromycin is given daily for the treatment of DMAC infection for prolonged periods, the most frequently reported treatment-related side effects are abdominal pain, nausea, vomiting, diarrhea, flatulence, headache, abnormal vision, and hearing impairment.

4.9. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1. 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.

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). Coadministration 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 coadministration 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 most important ribosomal modification that determines reduced binding of macrolides is post-transcriptional (N_6)-dimethylation of adenine at nucleotide A2058 (*Escherichia coli* numbering system) of the 23S rRNA by methylases encoded by *erm* (*e*rythromycin *r*ibosome *m*ethylase) genes. Ribosomal modifications often determine cross-resistance (MLS_B phenotype) to other classes of antibiotics whose ribosomal binding sites overlap those of the macrolides: the lincosamides (including clindamycin), and the streptogramin B (which include, for example, the quinupristin component of quinupristin/dalfopristin). Different *erm* genes are present in different bacterial species, in particular streptococci and staphylococci. Susceptibility to macrolides can also be affected by less frequently encountered mutational changes in nucleotides A2058 and A2059, and at some other positions of 23S rRNA, or in the large subunit ribosomal proteins L4 and L22.

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

Methodology for determining the in vitro susceptibility of bacteria to azithromycin

Susceptibility testing should be conducted using standardized laboratory methods, such as those described by the Clinical and Laboratory Standards Institute (CLSI). These include dilution methods (MIC determination) and disk susceptibility methods. Both CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) provide interpretive criteria for these methods.

Based on a number of studies, it is recommended that the in vitro activity of azithromycin be tested in ambient air to ensure physiological pH of the growth medium. Elevated CO_2 tensions, as often used for streptococci and anaerobes, and occasionally for other species, result in a reduction in the pH of the medium. This has a greater adverse effect on the apparent potency of azithromycin than on that of other macrolides.

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

CLSI Dilution Susceptibility Interpretive Criteria

	Broth microdilution MIC (mg/L)		
Organism	**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

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

[a] Includes *Streptococcus pneumoniae*, β-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.

5.2. Pharmacokinetic properties

Absorption

Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37%. Administration of azithromycin capsules following a substantial meal reduces bioavailability by at least 50%. The time taken to peak plasma levels is 2 to 3 hours.

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.

Following oral administration of daily doses of 600 mg azithromycin, C_{max} was 0.33 μg/ml and 0.55 μg/ml at Day 1 and Day 22, respectively. Mean peak concentrations observed in leukocytes, the major site of disseminated MAC infection, were 252 μg/ml (±49%) and remained above 146 μg/ml (±33%) for 24 hours at steady state.

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.

5.3. Preclinical safety data

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

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

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, creme de vanilla and banana flavors.

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

6.2. Incompatibilities

Not applicable

6.3. Shelf life

Keep out of the sight and reach of children.

Do not use ZITHROMAX after the expiry date which is stated on the Carton / Blister / Label after EXP:. The expiry date refers to the last day of that month. The reconstituted Powder for Oral Suspension should be used within 5 days.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

6.4. Special precautions for storage

Capsules: Store below 30 °C.

Powder for Oral Suspension: Store below 30 °C for the powder and the reconstituted suspension.

Film-coated Tablets: Store below 30 °C.

6.5. Nature and contents of container

Capsules: The capsules are packed in clear PVC blister packs.

Available pack sizes are 6 and 24
Not all pack sizes may be marketed

Powder for Oral Suspension: The powder for oral suspension is packed in high-density polyethylene bottles.

Available pack sizes are 15mls and 30mls
Not all pack sizes may be marketed

Film-coated Tablets: The tablets are packed in clear PVC blister packs.

Available pack size is 3

Not all presentations may be marketed

6.6. Special precautions for disposal and other handling

Capsules: The capsules should be swallowed whole.

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

Azithromycin capsules or tablets should only be administered to children weighing more than 45 kg.

Powder for Oral Suspension: Tap the bottle to loosen the powder. To the 600 mg bottle, add 9 ml of water and to the 1200 mg bottle add 15 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.

The reconstituted suspension must be administered using the measuring device included in the package.

MANUFACTURED BY

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PRESCRIPTION STATUS

Prescription only medicine

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