

# AZEE Tablets/DT/Dry Syrup (Azithromycin)

## Composition

### **AZEE-250 Tablets**

Each film-coated tablet contains:

Azithromycin (anhydrous)..... 250 mg

(as Azithromycin Dihydrate, IP)

### **AZEE-500 Tablets**

Each film-coated tablet contains:

Azithromycin (anhydrous)..... 500 mg

(as Azithromycin Dihydrate, IP)

### **AZEE-1000 Tablets**

Each film-coated tablet contains:

Azithromycin (anhydrous)..... 1,000 mg

(as Azithromycin Dihydrate, IP)

### **AZEE-100 DT**

Each uncoated dispersible tablet contains:

Azithromycin (anhydrous).....100 mg

(as Azithromycin Dihydrate, IP)

### **AZEE-200 DT**

Each uncoated dispersible tablet contains:

Azithromycin (anhydrous).....200 mg

(as Azithromycin Dihydrate, IP)

### **AZEE-100 Dry Syrup**

Each 5 ml (after reconstitution) contains:

Azithromycin Dihydrate, IP, equivalent to  
Azithromycin (anhydrous) ..... 100 mg

**(Bottle of 15ml)**

### **AZEE-200 Dry Syrup**

Each 5 ml (after reconstitution) contains:

Azithromycin a Dihydrate, IP, equivalent to  
Azithromycin (anhydrous) ..... 200 mg

**(Bottle of 15 ml)**

### **AZEE-100 XL Dry Syrup**

Each 5 ml (after reconstitution) contains:

Azithromycin Dihydrate, IP, equivalent to  
Azithromycin (anhydrous) ..... 100 mg  
**(Bottle of 30 ml)**

### **AZEE-200 XL Dry Syrup**

Each 5 ml (after reconstitution) contains:  
Azithromycin a Dihydrate, IP, equivalent to  
Azithromycin (anhydrous) ..... 200 mg

**(Bottle of 30 ml)**

## **Dosage Forms**

Oral tablets, dispersible tablets and dry powder for oral suspension.

## **Pharmacology**

### **Pharmacodynamics**

Azithromycin is a macrolide antibiotic belonging to the azalide group. The mechanism of action of azithromycin is based on the suppression of bacterial protein synthesis, meaning it binds to the ribosomal 50s sub-unit and inhibits the translocation of peptides. Azithromycin acts as a bacteriostatic. Nucleic acid synthesis is not affected.

Azithromycin concentrates in phagocytes and fibroblasts as demonstrated by *in vitro* incubation techniques. Using such methodology, the ratio of intracellular to extracellular concentration was >30 after 1 hour of incubation. *In vivo* studies suggest that concentration in phagocytes may contribute to drug distribution to inflamed tissues.

Azithromycin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections:

#### ***Aerobic Gram-positive Bacteria***

*Methicillin-susceptible Staphylococcus aureus*

*Streptococcus agalactiae*

*Penicillin-susceptible Streptococcus pneumoniae*

*Streptococcus pyogenes (Group A)*

#### ***Aerobic Gram-negative Bacteria***

*Haemophilus influenzae*

*Moraxella catarrhalis*

*Neisseria gonorrhoeae*

*Haemophilus parainfluenzae*

*Pasteurella multocida*

### **Other Bacteria**

*Chlamydophila pneumoniae*

*Chlamydia trachomatis*

*Mycoplasma pneumoniae*

*Legionella pneumophila*

*Mycobacterium avium*

*Mycobacterium intracellulare*

The following *in vitro* data are available, **but their clinical significance is unknown.**

Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 4.0 mcg/ml or less against most ( $\geq 90\%$ ) isolates of the following bacteria; however, the safety and effectiveness of azithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

### **Aerobic Gram-positive Bacteria**

Beta-haemolytic streptococci (Groups C, F, G)

Viridans group streptococci

### **Aerobic Gram-negative Bacteria**

*Bordetella pertussis*

*Haemophilus ducreyi*

*Campylobacter jejuni*

### **Anaerobic Bacteria**

*Bacteroides bivius*

*Clostridium perfringens*

*Peptostreptococcus* spp.

*Prevotella bivia*

### **Other Bacteria**

*Ureaplasma urealyticum*

*Borrelia burgdorferi*

*Treponema pallidum*

### **Species for Which Acquired Resistance May Be a Problem**

Aerobic Gram-positive microorganisms

*Streptococcus pneumoniae*

Penicillin-intermediate

Penicillin-resistant

### ***Inherently Resistant Organisms***

Aerobic Gram-positive microorganisms

*Enterococcus faecalis*

Staphylococci MRSA, MRSE\*

Aerobic Gram-negative microorganisms

*Escherichia coli*

*Pseudomonas aeruginosa*

*Klebsiella* spp.

Anaerobic microorganisms

*Bacteroides fragilis* group

\*Methicillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

Based on animal models of infection, the antibacterial activity of azithromycin appears to correlate with the ratio of area under the concentration-time curve to minimum inhibitory concentration (AUC/MIC) for certain pathogens (*S. pneumoniae* and *S. aureus*). The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with azithromycin.

### ***Mechanism of Resistance***

Resistance to azithromycin may be natural or acquired. There are three main mechanisms of resistance affecting azithromycin:

- Efflux: resistance may be due to an increase in the number of efflux pumps on the cell membrane. In particular, 14- and 15-link macrolides are affected (M-phenotype).
- Alterations of the cell structure: methylation of the 23s rRNS may reduce the affinity of the ribosomal binding sites, which can result in microbial resistance to macrolides, lincosamides and group B streptogramins (S<sub>B</sub>) (MLS<sub>B</sub>-phenotype).
- Enzymatic deactivation of macrolides is only of limited clinical significance.

Azithromycin demonstrates cross resistance with erythromycin-resistant Gram-positive isolates. In the presence of the M-phenotype, complete cross-resistance exists between azithromycin and clarithromycin, erythromycin and roxithromycin. With the MLS<sub>B</sub>-phenotype, additional cross-resistance exists with clindamycin and streptogramin B. A partial cross-resistance exists with spiramycin.

## Cardiac Electrophysiology

QTc interval prolongation was studied in a randomized, placebo-controlled, parallel trial in 116 healthy subjects who received either chloroquine (1,000 mg) alone or in combination with azithromycin (500 mg, 1,000 mg and 1,500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison with 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, 1,000 mg and 1,500 mg azithromycin, respectively.

## Pharmacokinetics

Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were  $AUC_{0-72} = 4.3$  (1.2)  $\mu\text{g}\cdot\text{h}/\text{mL}$ ;  $C_{\text{max}} = 0.5$  (0.2)  $\mu\text{g}/\text{mL}$ ;  $T_{\text{max}} = 2.2$  (0.9) hours. Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.

In a two-way crossover study, 12 adult healthy volunteers (6 males, 6 females) received 1,500 mg of azithromycin administered in single daily doses over either 5 days (two 250 mg tablets on day 1, followed by one 250 mg tablet on days 2-5) or 3 days (500 mg per day for days 1-3). Due to limited serum samples on day 2 (3-day regimen) and days 2-4 (5-day regimen), the serum concentration-time profile of each subject was fit to a 3-compartment model and the  $AUC_{(0-\text{infinity})}$  for the fitted concentration profile was comparable between the 5-day and 3-day regimens.

Pharmacokinetic Parameter [mean (SD)]	3-Day Regimen		5-Day Regimen	
	Day 1	Day 3	Day 1	Day 5
$C_{\text{max}}$ (serum, $\mu\text{g}/\text{mL}$ )	0.44 (0.22)	0.54 (0.25)	0.43 (0.20)	0.24 (0.06)
Serum $AUC_{(0-\text{infinity})}$ ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	17.4 (6.2)*		14.9 (3.1)*	
Serum $T_{1/2}$	71.8 hours		68.9 hours	

\*Total AUC for the entire 3-day and 5-day regimens

## Absorption

Bioavailability after oral administration is approximately 37%. Peak concentrations in the plasma are attained 2-3 hours after taking the medicinal product.

In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of azithromycin (two 250 mg tablets) with or without a high-fat meal, food was shown to increase the  $C_{\text{max}}$  by 23% but had no effect on the AUC.

When azithromycin suspension was administered with food to 28 adult healthy male subjects, the  $C_{\text{max}}$  increased by 56% and the AUC was unchanged.

## Distribution

Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the

agent strongly binds to tissues. The antibacterial activity of azithromycin is pH related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VV<sub>ss</sub>) has been calculated to be 31.1 l/kg.

Azithromycin has been shown to penetrate into human tissues, including skin, lung, tonsil, and cervix. Extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of azithromycin treatment of infections in these additional body sites, the clinical significance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, very low concentrations were noted in cerebrospinal fluid (less than 0.01 µg/mL) in the presence of non-inflamed meninges.

Concentrations in the infected tissues such as lungs, tonsil and prostate are higher than the MIC<sub>90</sub> of the most frequently occurring pathogens after a single dose of 500 mg.

In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis, higher concentrations of azithromycin are released than are released from inactive phagocytes. In animal models the azithromycin concentrations measured in inflammation foci were high.

The antimicrobial activity of azithromycin is pH-related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

### **Metabolism**

*In vitro* and *in vivo* studies to assess the metabolism of azithromycin have not been performed.

Ten metabolites were also detected, which were formed through N- and O-demethylation, hydroxylation of desosamine- and aglycone rings and degradation of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

### **Elimination**

Plasma concentrations of azithromycin following single 500 mg oral and intravenous doses declined in a polyphasic pattern, with a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues.

Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

## **Specific Populations**

### **Renal Impairment**

Azithromycin pharmacokinetics was investigated in 42 adults (21-85 years of age) with varying

degrees of renal impairment. Following the oral administration of a single 1,000 mg dose of azithromycin, mean  $C_{\max}$  and  $AUC_{0-120}$  increased by 5.1% and 4.2%, respectively in subjects with mild-to-moderate renal impairment (GFR: 10 to 80 mL/min) compared with subjects with normal renal function (GFR >80 mL/min). The mean  $C_{\max}$  and  $AUC_{0-120}$  increased 61% and 35%, respectively, in subjects with severe renal impairment (GFR <10 mL/min) compared with subjects with normal renal function (GFR >80 mL/min).

### ***Hepatic Impairment***

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

### ***Gender***

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended based on gender.

### ***Geriatric Patients***

When studied in healthy elderly subjects aged 65–85 years, the pharmacokinetic parameters of azithromycin in elderly men were similar to those in young adults (18–40 years old); however, in elderly women, although higher peak concentrations (increased by 30–50%) were observed, no significant accumulation occurred. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen.

### ***Paediatric Patients***

In two clinical studies, azithromycin for oral suspension was dosed at 10 mg/kg on day 1, followed by 5 mg/kg on days 2 through 5 to two groups of paediatric patients (aged 1–5 years and 5–15 years, respectively). The mean pharmacokinetic parameters on day 5 were  $C_{\max}=0.216$  µg/mL,  $T_{\max}=1.9$  hours, and  $AUC_{0-24}=1.822$  µg•hr/mL for the 1- to 5-year-old group and were  $C_{\max}=0.383$  µg/mL,  $T_{\max}=2.4$  hours, and  $AUC_{0-24}=3.109$  µg•hr/mL for the 5- to 15-year-old group.

Two clinical studies were conducted in 68 paediatric patients aged 3–16 years to determine the pharmacokinetics and safety of azithromycin for oral suspension. Azithromycin was administered following a low-fat breakfast.

The first study consisted of 35 paediatric patients treated with 20 mg/kg/day (maximum daily dose 500 mg) for 3 days, of whom 34 patients were evaluated for pharmacokinetics. In the second study, 33 paediatric patients received doses of 12 mg/kg/day (maximum daily dose 500 mg) for 5 days, of whom 31 patients were evaluated for pharmacokinetics.

In both studies, azithromycin concentrations were determined over a 24-hour period following the last daily dose. Patients weighing above 25.0 kg in the 3-day study or 41.7 kg in the 5-day study received the maximum adult daily dose of 500 mg. Accordingly, 11 patients (weighing 25.0 kg or less) in the first study and 17 patients (weighing 41.7 kg or less) in the second study received a total dose of 60 mg/kg. The following table shows pharmacokinetic data in the subset of paediatric patients who received a total dose of 60 mg/kg.

Pharmacokinetic Parameter [mean (SD)]	3-Day Regimen (20 mg/kg × 3 days)	5-Day Regimen (12 mg/kg × 5 days)
N	11	17
C <sub>max</sub> (µg/mL)	1.1 (0.4)	0.5 (0.4)
T <sub>max</sub> (hr)	2.7 (1.9)	2.2 (0.8)
AUC <sub>0-24</sub> (µg•hr/mL)	7.9 (2.9)	3.9 (1.9)

The similarity of the overall exposure (AUC<sub>0-infinity</sub>) between the 3-day and 5-day regimens in paediatric patients is unknown.

Single-dose pharmacokinetics in paediatric patients given doses of 30 mg/kg has not been studied.

### Drug-Drug Interactions

Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. The effects of co-administration of azithromycin on the pharmacokinetics of other drugs are shown in Table 1 and the effects of other drugs on the pharmacokinetics of azithromycin are shown in Table 2.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 1. No dosage adjustment of drugs listed in Table 1 is recommended when co-administered with azithromycin.

Co-administration of azithromycin with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. Nelfinavir significantly increased the C<sub>max</sub> and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 2.

<b>Table 1: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin</b>					
Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	n	Ratio (With/Without Azithromycin) of Co-administered Drug Pharmacokinetic Parameters (90% CI); No Effect = 1.00	
				Mean C <sub>max</sub>	Mean AUC
Atorvastatin	10 mg/day × 8 days	500 mg/day PO on days 6-8	12	0.83 (0.63 to 1.08)	1.01 (0.81 to 1.25)
Carbamazepine	200 mg/day × 2 days, then 200 mg b.i.d. × 18 days	500 mg/day PO for days 16-18	7	0.97 (0.88 to 1.06)	0.96 (0.88 to 1.06)

Cetirizine	20 mg/day × 11 days	500 mg PO on day 7, then 250 mg/day on days 8-11	14	1.03 (0.93 to 1.14)	1.02 (0.92 to 1.13)
Didanosine	200 mg PO b.i.d. × 21 days	1,200 mg/day PO on days 8-21	6	1.44 (0.85 to 2.43)	1.14 (0.83 to 1.57)
Efavirenz	400 mg/day × 7 days	600 mg PO on day 7	14	1.04*	0.95*
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	1.04 (0.98 to 1.11)	1.01 (0.97 to 1.05)
Indinavir	800 mg t.i.d. × 5 days	1,200 mg PO on day 5	18	0.96 (0.86 to 1.08)	0.90 (0.81 to 1.00)
Midazolam	15 mg PO on day 3	500 mg/day PO × 3 days	12	1.27 (0.89 to 1.81)	1.26 (1.01 to 1.56)
Nelfinavir	750 mg t.i.d. × 11 days	1,200 mg PO on day 9	14	0.90 (0.81 to 1.01)	0.85 (0.78 to 0.93)
Rifabutin	300 mg/day × 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	See footnote below	NA
Sildenafil	100 mg on days 1 and 4	500 mg/day PO × 3 days	12	1.16 (0.86 to 1.57)	0.92 (0.75 to 1.12)
Theophylline	4 mg/kg intravenous on days 1, 11, and 25	500 mg PO on day 7, 250 mg/day on days 8-11	10	1.19 (1.02 to 1.40)	1.02 (0.86 to 1.22)
Theophylline	300 mg PO b.i.d. × 15 days	500 mg PO on day 6, then 250 mg/day on days 7-10	8	1.09 (0.92 to 1.29)	1.08 (0.89 to 1.31)
Triazolam	0.125 mg on day 2	500 mg PO on day 1, then 250 mg/day on day 2	12	1.06*	1.02*
Trimethoprim/Sulphamethoxazole	160 mg/800 mg/day PO × 7 days	1,200 mg PO on day 7	12	0.85 (0.75 to 0.97)/ 0.90 (0.78 to 1.03)	0.87 (0.80 to 0.95)/ 0.96 (0.88 to 1.03)
Zidovudine	500 mg/day PO × 21 days	600 mg/day PO × 14 days	5	1.12 (0.42 to 3.02)	0.94 (0.52 to 1.70)
Zidovudine	500 mg/day PO × 21 days	1,200 mg/day PO × 14 days	4	1.31 (0.43 to 3.97)	1.30 (0.69 to 2.43)

NA - Not Available

Mean rifabutin concentrations, half a day after the last dose of rifabutin, were 60 ng/mL when co-administered with azithromycin and 71 ng/mL when co-administered with placebo.

\* 90% CI (confidence interval) not reported.

<b>Table 2: Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs</b>					
Co-administered Drug	Dose of Co-administered Drug	Dose of Azithromycin	N	Ratio (With/Without Co-Administered Drug) of Azithromycin Pharmacokinetic Parameters (90% CI); No Effect = 1.00	
				Mean C <sub>max</sub>	Mean AUC
Efavirenz	400 mg/day × 7 days	600 mg PO on day 7	14	1.22 (1.04 to 1.42)	0.92*
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	0.82 (0.66 to 1.02)	1.07 (0.94 to 1.22)
Nelfinavir	750 mg t.i.d. × 11 days	1,200 mg PO on day 9	14	2.36 (1.77 to 3.15)	2.12 (1.80 to 2.50)
Rifabutin	300 mg/day × 10 days	500 mg PO on day 1, then 250 mg/day on days 2-10	6	See footnote below	NA

NA - Not available

Mean azithromycin concentrations one day after the last dose were 53 ng/mL when co-administered with 300 mg daily rifabutin and 49 ng/mL when co-administered with placebo.

\* 90% CI not reported

## Indications

Azithromycin is a macrolide antibacterial drug indicated for the treatment of patients with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. Recommended dosages and durations of therapy in adult and paediatric patient populations vary in these indications.

### Adults

**Acute bacterial exacerbations of chronic bronchitis** due to *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Streptococcus pneumoniae*.

**Acute bacterial sinusitis** due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

**Community-acquired pneumonia** due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

**Pharyngitis/tonsillitis** caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

**Uncomplicated skin and skin structure infections** due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

**Urethritis and cervicitis** due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

**Genital ulcer disease** in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established.

## Paediatric Patients

**Acute otitis media** caused by *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

**Pharyngitis/tonsillitis** caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.

**Sinusitis** caused by *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae*.

**Acute bronchitis** caused by *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*.

**Community-acquired pneumonia** due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.

**Uncomplicated skin and soft tissues infections** like furunculosis, pyoderma and impetigo due to *Staphylococcus aureus*, *Streptococcus pyogenes* and *Streptococcus agalactiae*.

**Uncomplicated genital infections** (in adolescents and older children) like urethritis and cervicitis due to *Chlamydia trachomatis*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin and other antibacterial drugs, azithromycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

## Limitations of Use

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

- Patients with cystic fibrosis;

- Patients with nosocomial 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).

## Dosage and Administration

### Dosage

#### Adults

<b>Infection*</b>	<b>Recommended Dose/Duration of Therapy</b>
Community-acquired pneumonia (mild severity) Pharyngitis/tonsillitis (second-line therapy) Skin/skin structure (uncomplicated)	500 mg as a single dose on day 1, followed by 250 mg once daily on days 2 through 5.
Acute bacterial exacerbations of chronic obstructive pulmonary disease (mild to moderate)	500 mg q.d. × 3 days OR 500 mg as a single dose on day 1, followed by 250 mg once daily on days 2 through 5.
Acute bacterial sinusitis	500 mg q.d. × 3 days
Genital ulcer disease (chancroid)	One single 1 gm dose
Non-gonococcal urethritis and cervicitis	One single 1 gm dose
Gonococcal urethritis and cervicitis	One single 2 gm dose

\*Due to the indicated organisms.

#### Paediatric Patients

<b>Age</b>	<b>Indications</b>	<b>1-Day Regimen</b>	<b>3-Day Regimen</b>	<b>5-Day Regimen</b>
------------	--------------------	----------------------	----------------------	----------------------

From 6 months and above	Acute otitis media	30 mg/kg single dose	10 mg/kg once daily	<b>Day 1:</b> 10 mg/kg single dose <b>Days 2-5:</b> 5 mg/kg/day
	Acute bacterial sinusitis		10 mg/kg once daily	<b>Day 1:</b> 10 mg/kg single dose <b>Days 2-5:</b> 5 mg/kg/day
	Community-acquired pneumonia/ Acute bronchitis		10 mg/kg once daily	<b>Day 1:</b> 10 mg/kg single dose <b>Days 2-5:</b> 5 mg/kg/day
	Uncomplicated Skin and soft tissue infections		10 mg/kg once daily	<b>Day 1:</b> 10 mg/kg single dose <b>Days 2-5:</b> 5 mg/kg/day
From 1 year - 2 years		--	10 or 20 mg/kg with max. daily dose of 500 mg	
From 2 years and above	Pharyngitis/ Tonsillitis	--	10 or 20 mg/kg with max. daily dose of 500 mg	12 mg/kg once daily
Adolescents and older children (weighing above 45 kg)	Uncomplicated genital infections	A single 1 gm dose		
Children above 45 kg weight	All above given indications	As per adult dosage		

Effectiveness of the 1-day regimen in paediatric patients with community-acquired pneumonia and acute bacterial sinusitis has not been established. The safety of re-dosing azithromycin in paediatric patients who vomit after receiving 30 mg/kg as a single dose has not been established.

### **Renal Impairment**

No dosage adjustment is recommended for subjects with mild-to-moderate renal impairment (GFR 10-80 ml/min). Caution should be exercised when azithromycin is administered to subjects with severe renal impairment (GFR <10 ml/min). In patients with severe renal impairment (GFR <10 ml/min), a 33% increase in systemic exposure to azithromycin was observed.

### **Hepatic Impairment**

A dose adjustment is not necessary for patients with mild-to-moderately impaired liver function. Since azithromycin is metabolized in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease.

### **Elderly Patients**

The same dosage as in adult patients is used in the elderly. Since elderly patients can be patients with ongoing pro-arrhythmic conditions, a particular caution is recommended due to the risk of developing cardiac arrhythmia and *torsades de pointes*.

### **Gender**

No dosage adjustment is recommended based on gender.

### **Administration**

**AZEE Tablets, Dry Syrup** and **DT** can be taken with or without food.

#### **AZEE DT**

Disperse the tablet in a teaspoonful (5 ml) of boiled and cooled water before administration.

#### **AZEE Dry Syrup**

#### ***Direction for Preparing the Suspension***

At the time of dispensing, the dry powder should be reconstituted to form an oral suspension. First, shake the bottle to loosen the powder. Pour boiled and cooled water into the bottle. Recap the bottle, and shake it vigorously. Adjust the suspension volume up to the arrow mark by adding more water, if necessary, and shake again. Store the reconstituted suspension in a cool place.

After reconstitution, the contents should be consumed within 5 days. Keep tightly closed. Shake well before each use. Discard the unused portion after 5 days.

### **Contraindications**

Azithromycin is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic or any of its excipients.

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

### **Warnings and Precautions**

#### **General**

##### ***Hypersensitivity***

Serious allergic reactions, including angioneurotic oedema, anaphylaxis and dermatologic reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis), have been reported rarely in patients on azithromycin therapy.

Fatalities have been reported. Cases of drug reaction with eosinophilia and systemic symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure**. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is unknown at

present.

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.

Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

### ***Interaction with Ergot Derivative***

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.

### ***Clostridium difficile-associated Diarrhoea***

*Clostridium difficile*-associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *Clostridium difficile*.

*Clostridium difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of *Clostridium 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 diarrhoea 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 *Clostridium difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated.

### ***QT Prolongation***

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.

Cases of *torsades de pointes* have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers 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 known prolongation of the QT interval, a history of *torsades de pointes*, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure;
- patients on drugs known to prolong the QT interval; and,
- patients with ongoing pro-arrhythmic conditions such as uncorrected hypokalaemia or hypomagnesaemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) anti-arrhythmic agents, cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin.

Elderly patients may be more susceptible to drug-associated effects on the QT interval.

### ***Exacerbation of Myasthenia Gravis***

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.

### ***Use in Sexually Transmitted Infections***

Azithromycin at the recommended dose should not be relied upon to treat syphilis. Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhoea performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

### ***Development of Drug-resistant Bacteria***

Prescribing azithromycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

### ***Superinfection***

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

### ***Streptococcal Infections***

**Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of azithromycin in preventing acute rheumatic fever.**

### ***Effects on the 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.

## **Information for Patients**

Azithromycin tablets and oral suspension can be taken with or without food.

Patients should also be cautioned not to take aluminium- and magnesium-containing antacids and azithromycin simultaneously.

The patient should be directed to discontinue azithromycin immediately and contact a physician if any signs of an allergic reaction occur.

Patients should be counselled that antibacterial drugs, including azithromycin, should only be used to treat bacterial infections. They do not treat viral infections (e.g. the common cold). When azithromycin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of the therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment, and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by azithromycin or other antibacterial drugs in the future.

Diarrhoea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

## **Drug Interactions**

### ***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 cetirizine 20 mg 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 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

### ***Digoxin***

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered. Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. In patients receiving concomitant azithromycin, a

related azalide antibiotic, and digoxin, the possibility of raised digoxin levels should be borne in mind.

### ***Zidovudine***

Single 1,000 mg doses and multiple 1,200 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 (CY) P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic CYP450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

### ***Ergot Derivatives***

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

### ***Effects of Other Medicinal Products on Azithromycin***

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant CYP450-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, postmarketing 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.

#### *Cisapride*

Cisapride is metabolized in the liver by the enzyme CYP3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and *torsades de pointes*.

#### *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 15 mg dose of 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.

### Ciclosporin

In a pharmacokinetic study with healthy volunteers that 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 ciclosporin, the resulting ciclosporin  $C_{max}$  and  $AUC_{0-5}$  were found to be significantly elevated (by 24% and 21%, respectively); however, no significant changes were seen in  $AUC_{0-infinity}$ . Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

### Efavirenz

Co-administration of a 600 mg single dose of 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 1,200 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 azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

### Nelfinavir

Co-administration of azithromycin (1,200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

### 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.

### 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 azithromycin 500 mg 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 azithromycin 1,200 mg 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.

## **Renal Impairment**

No dosage adjustment is recommended for subjects with mild-to-moderate renal impairment (GFR 10–80 ml/min). Caution should be exercised when azithromycin is administered to subjects with severe renal impairment (GFR <10 ml/min). In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

## **Hepatic Impairment**

A dose adjustment is not necessary for patients with mild-to-moderately impaired liver function.

## **Pregnancy**

### ***Pregnancy Category B***

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

## Lactation

Azithromycin has been reported to be excreted in human breast milk in small amounts. Caution should be exercised when azithromycin is administered to a nursing mother.

## Paediatric Use

Safety and effectiveness in the treatment of paediatric patients with acute otitis media, acute bacterial sinusitis and community-acquired pneumonia under 6 months of age have not been established. Use of azithromycin for the treatment of acute bacterial sinusitis and community-acquired pneumonia in paediatric patients (6 months of age or greater) is supported by adequate and well controlled trials in adults. Safety and effectiveness in the treatment of paediatric patients with pharyngitis/tonsillitis under 1 year of age have not been established.

Safety and efficacy for prevention or treatment of *M. avium* complex in children have not been established.

## Geriatric Use

In multiple-dose clinical trials of oral azithromycin, 9% of patients were at least 65 years of age (458/4,949) and 3% of patients (144/4,949) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but the greater sensitivity of some older individuals cannot be ruled out.

Elderly patients may be more susceptible to development of *torsades de pointes* arrhythmia than younger patients

## Undesirable Effects

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious side effects of angio-oedema and cholestatic jaundice were reported rarely. Approximately 0.7% of the patients (adults and paediatric patients) from the 5-day multiple-dose clinical trials discontinued azithromycin therapy because of treatment-related side effects. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related side effects was 0.6%. In clinical trials in paediatric patients given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related side effects was approximately 1%. Most of the side effects leading to discontinuation were related to the gastrointestinal tract, e.g. nausea, vomiting, diarrhoea or abdominal pain.

## Clinical

### Adults

#### Multiple-Dose Regimens

Overall, the most common treatment-related side effects in adult patients receiving multiple-dose regimens of azithromycin were related to the gastrointestinal system, with diarrhoea/loose stools

(4-5%), nausea (3%), and abdominal pain (2-3%) being the most frequently reported.

No other treatment-related side effects occurred in patients on the multiple-dose regimens of azithromycin with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

*Cardiovascular:* Palpitations, chest pain.

*Gastrointestinal:* Dyspepsia, flatulence, vomiting, melaena and cholestatic jaundice.

*Genitourinary:* Monilia, vaginitis and nephritis.

*Nervous System:* Dizziness, headache, vertigo and somnolence.

*General:* Fatigue.

*Allergic:* Rash, pruritus, photosensitivity and angio-oedema.

### Single 1 gm Dose Regimen

Overall, the most common side effects in patients receiving a single-dose regimen of 1 gm of azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.

Side effects that occurred in patients on the single 1 gm dosing regimen of azithromycin with a frequency of 1% or greater included diarrhoea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

### Single 2 gm Dose Regimen

Overall, the most common side effects in patients receiving a single 2 gm dose of azithromycin were related to the gastrointestinal system. Side effects that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhoea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%) and dizziness (1%). The majority of these complaints were mild in nature.

## **Paediatric Patients**

### Single- and Multiple-Dose Regimens

The types of side effects in paediatric patients were comparable with those seen in adults, with different incidence rates for the dosage regimens recommended in paediatric patients.

#### *Acute Otitis Media*

For the recommended total dosage regimen of 30 mg/kg, the most frequent side effects ( $\geq 1\%$ ) attributed to treatment were diarrhoea, abdominal pain, vomiting, nausea and rash.

The incidence, based on dosing regimen, is described in the table below:

<b>Dosage Regimen</b>	<b>Diarrhoea, %</b>	<b>Abdominal Pain, %</b>	<b>Vomiting, %</b>	<b>Nausea, %</b>	<b>Rash, %</b>
1-day	4.3%	1.4%	4.9%	1.0%	1.0%

3-day	2.6%	1.7%	2.3%	0.4%	0.6%
5-day	1.8%	1.2%	1.1%	0.5%	0.4%

### **Community-acquired Pneumonia**

For the recommended dosage regimen of 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the most frequent side effects attributed to treatment were diarrhoea/loose stools, abdominal pain, vomiting, nausea and rash.

The incidence is described in the table below:

<b>Dosage Regimen</b>	<b>Diarrhoea/Loose stools, %</b>	<b>Abdominal Pain, %</b>	<b>Vomiting, %</b>	<b>Nausea, %</b>	<b>Rash, %</b>
5-day	5.8%	1.9%	1.1.9%	1.9%	1.6%

### **Pharyngitis/Tonsillitis**

For the recommended dosage regimen of 12 mg/kg on days 1-5, the most frequent side effects attributed to treatment were diarrhoea, vomiting, abdominal pain, nausea and headache.

The incidence is described in the table below:

<b>Dosage Regimen</b>	<b>Diarrhoea, %</b>	<b>Abdominal Pain, %</b>	<b>Vomiting, %</b>	<b>Nausea, %</b>	<b>Rash, %</b>	<b>Headache, %</b>
5-day	5.4%	3.4%	5.6%	1.8%	0.7%	1.1%

With any of the treatment regimens, no other treatment-related side effects occurred in paediatric patients treated with azithromycin with a frequency greater than 1%. Side effects that occurred with a frequency of 1% or less included the following:

*Cardiovascular:* Chest pain.

*Gastrointestinal:* Dyspepsia, constipation, anorexia, enteritis, flatulence, gastritis, jaundice, loose stools and oral moniliasis.

*Haematologic and Lymphatic:* Anaemia and leucopenia.

*Nervous System:* Headache (otitis media dosage), hyperkinesia, dizziness, agitation, nervousness and insomnia.

*General:* Fever, face oedema, fatigue, fungal infection, malaise and pain.

*Allergic:* Rash and allergic reaction.

*Respiratory:* Cough increased, pharyngitis, pleural effusion and rhinitis.

*Skin and appendages:* Eczema, fungal dermatitis, pruritus, sweating, urticaria and vesiculobullous rash.

*Special senses:* Conjunctivitis.

## **Postmarketing Experience**

**The following adverse reactions have been identified during post-approval use of azithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.**

Adverse events reported with azithromycin during the postmarketing period in adult and/or paediatric patients for which a causal relationship may not be established included the following:

**Allergic:** Arthralgia, oedema, urticaria and angio-oedema.

**Cardiovascular:** Arrhythmias, including ventricular tachycardia and hypotension. There have been rare reports of QT prolongation and *torsades de pointes*.

**Gastrointestinal:** Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhoea rarely resulting in dehydration, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and rare reports of tongue discolouration.

**General:** Asthenia, paraesthesia, fatigue, malaise and anaphylaxis (rarely fatal).

**Genitourinary:** Interstitial nephritis and acute renal failure and vaginitis.

**Haematopoietic:** Thrombocytopenia.

**Liver/Biliary:** Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure.

**Nervous System:** Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation and syncope.

**Psychiatric:** Aggressive reaction and anxiety.

**Skin/Appendages:** Pruritus; rarely, serious skin reactions, including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS

**Special Senses:** Hearing disturbances, including hearing loss, deafness and/or tinnitus, and reports of taste/smell perversion and/or loss.

## **Laboratory Abnormalities**

### **Adults**

Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:

#### *With an Incidence of Greater Than 1%*

Decreased haemoglobin, haematocrit, lymphocytes, neutrophils and blood glucose; elevated serum creatine phosphokinase, potassium, chloride, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils and eosinophils

### With an Incidence of Less Than 1%

Leucopaenia, neutropaenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline.

When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 5,000 patients, 4 patients discontinued therapy because of treatment-related liver enzyme abnormalities and 1 because of a renal function abnormality.

### **Paediatric Patients**

#### Regimens for 1, 3 and 5 Days

Laboratory data collected from comparative clinical trials employing two 3-day regimens (30 mg/kg or 60 mg/kg in divided doses over 3 days), or two 5-day regimens (30 mg/kg or 60 mg/kg in divided doses over 5 days) were similar for regimens of azithromycin and all comparators combined, with most clinically significant laboratory abnormalities occurring at incidences of 1-5%. Laboratory data for patients receiving 30 mg/kg as a single dose were collected in one single-centre trial. In that trial, an absolute neutrophil count between 500 and 1,500 cells/mm<sup>3</sup> was observed in 10/64 patients receiving 30 mg/kg as a single dose, 9/62 patients receiving 30 mg/kg given over 3 days, and 8/63 comparator patients. No patient had an absolute neutrophil count <500 cells/mm<sup>3</sup>.

In multiple-dose clinical trials involving approximately 4,700 paediatric patients, no patients discontinued therapy because of treatment-related laboratory abnormalities.

### **Other Adverse Reactions**

Other adverse reactions possibly or probably related to azithromycin based on clinical trial experience and postmarketing surveillance are as below:

Common (>1/100 <1/10): Dysgeusia, visual impairment, lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased

Uncommon ( $\geq 1/1,000$  to <1/100): Candidiasis, angio-oedema, hypersensitivity, hypoesthesia, photosensitivity reaction, dysphagia, dyspnoea, epistaxis, gastroenteritis, hot flush, vaginal infection, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion, hyperhidrosis, osteoarthritis, myalgia, back pain, neck pain, dysuria, renal pain, metrorrhagia, testicular disorder, pyrexia, peripheral oedema.

Not Known (Cannot Be Estimated from Available Data): Haemolytic anaemia, anaphylactic reaction, psychomotor hyperactivity, anosmia, ageusia, parosmia, renal failure acute, nephritis interstitial, myasthenia gravis, delirium, hallucination, psychomotor hyperactivity.

## **Overdosage**

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

## Incompatibility

None reported.

## Storage and Handling Instructions

### Before Opening

Store at room temperature. Protect from moisture.

### After Reconstitution

Store the reconstituted suspension in cool place. Contents need to be consumed within 5 days. Any extra portion left is to be thrown away.

## Packaging Information

**AZEE-250 Tablets:** Strip pack of six tablets

**AZEE-500 Tablets:** Strip pack of three tablets

**AZEE-1000 Tablets:** Strip pack of one tablet

**AZEE-100 DT:** Strip pack of six tablets

**AZEE-200 DT:** Strip pack of six tablets

**AZEE-100 Dry Syrup:** Bottle of 15 ml

**AZEE-200 Dry Syrup:** Bottle of 15 ml

**AZEE-100 XL Dry Syrup:** Bottle of 30 ml

**AZEE-200 XL Dry Syrup:** Bottle of 30 ml

**Last updated:** *June 2016*

**Last reviewed:** *June 2016*