AZEE I.V. Injection (Azithromycin)

Composition

AZEE I.V.

Each vial contains:

Azithromycin (anhydrous) ..... 500 mg (as Azithromycin Dihydrate, IP)

As a sterile freeze-dried powder for reconstitution with Sterile Water for Injection, IP

Each mL of reconstituted injection contains

Azithromycin (anhydrous)..... 100 mg (as Azithromycin Dihydrate, IP)

Dosage Form

Powder for I.V. infusion only

Pharmacology

Pharmacodynamics

Mechanism of Action

Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and, thus, interfering with microbial protein synthesis. Nucleic acid synthesis is not affected.

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

Gram-positive Bacteria
Staphylococcus aureus
Streptococcus pneumoniae

Streptococcus pyogenes (Group A)

Gram-negative Bacteria
Haemophilus influenzae

Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

Pasteurella multocida

Other Microorganisms

Chlamydia pneumoniae
Chlamydia trachomatis

Chlamydia psittaci
Legionella pneumophila
Mycoplasma hominis
Mycoplasma pneumoniae

Note

Azithromycin demonstrates cross-resistance with erythromycin-resistant Gram-positive isolates.

The following in vitro data are available, but their clinical significance is unknown. Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2.0 mcg/mL or less against most (≥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
Streptococci (Groups C, F, G)
Viridans group streptococci

Aerobic Gram-negative Bacteria
Bordetella pertussis

Anaerobic Bacteria
Peptostreptococcus species
Prevotella bivia

Other Bacteria
Ureaplasma urealyticum

Mechanism of Resistance

There are two dominant genes that determine the resistance of isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes*: mef and erm. The mef gene encodes a flow pump that mediates resistance to macrolides 14- and 15- only. The mef gene has also been described in a variety of other species. The erm gene codes for a 23S-rRNA methyltransferase that adds methyl groups to adenine 2058 of 23S rRNA (numbering system of *E. coli* rRNA).

The methylated nucleotide is located in a domain V and is thought to interact with the lincosamides and streptogramin B, in addition to macrolides, resulting in a phenotype known as MLSB resistance. Genes erm (B) and erm (A) are clinical isolates of *Streptococcus pneumoniae* and *Streptococcus pyogenes*.

The pump AcrAB-TolC of *Haemophilus influenzae* is responsible for the innate MIC values higher for macrolides.

In clinical isolates, mutations in 23S rRNA, specifically in nucleotides 2057–2059 or 2611 in domain V, or mutations in ribosomal protein L4 or L22, are rare.

A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for *Streptococcus pneumoniae*, beta-haemolytic streptococci of group A, Enterococcus

spp. and *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA). Penicillin-susceptible *Streptococcus pneumoniae* are more likely to be susceptible to azithromycin than are penicillin-resistant strains of *Streptococcus pneumoniae*. MRSA is less likely to be susceptible to azithromcyin than methicillin-susceptible *Staphylococcus aureus* (MSSA).

Note:

Breakpoints

The EUCAST susceptibility breakpoints for typical bacterial pathogens are as follows:

- *Staphylococcus* spp. ; susceptible ≤1 mg/l; resistant >2 mg/l
- *Haemophilus* spp.: susceptible ≤0,12 mg/l; resistant >4 mg/l
- *Streptococcus pneumoniae* and *Streptococcus A, B, C, G*: susceptible ≤0.25 mg/l; resistant >0.5 mg/l
- *Moraxella catarrhalis:* ≤0.5 mg/l; resistant >0.5 mg/l
- *Neisseria gonorrhoeae:* ≤0.25 mg/l; resistant >0.5 mg/l

General Pharmacodynamics

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 (*Streptococcus pneumoniae and Staphylococcus aureus*). The principal pharmacokinetic/pharmacodynamic parameter best associated with clinical and microbiological cure has not been elucidated in clinical trials with azithromycin.

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 oral 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 to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1,000 mg and 1,500 mg azithromycin, respectively.

Since the mean C_{max} of azithromycin following a 500 mg I.V. dose given over 1 hour is higher than the mean C_{max} of azithromycin following the administration of a 1,500 mg oral dose, it is possible that QTc may be prolonged to a greater extent with I.V. azithromycin at close proximity to a 1-hour infusion of 500 mg.

Pharmacokinetics

In patients hospitalized with community-acquired pneumonia and receiving single, daily 1-hour I.V. infusions for 2–5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean C_{max} ± S.D. achieved was 3.63 ± 1.60 µg/mL, while the 24-hour trough level was 0.20 ± 0.15 µg/mL, and the AUC_{24} was 9.60 ± 4.80 µg•h/mL.

The mean C_{max}, 24-hour trough and AUC_{24} values were 1.14 ± 0.14 µg/mL, 0.18 ± 0.02 µg/mL, and 8.03 ±0.86 µg• h/mL, respectively, in normal volunteers receiving a 3-hour I.V. infusion of 500 mg azithromycin at a concentration of 1 mg/mL. Similar pharmacokinetic values were obtained in patients hospitalized with community-acquired pneumonia who received the same 3-hour dosage regimen for 2–5 days.

Infusion Concentration, Duration	**Time after starting the infusion (hour)**								
	0.5	1	2	3	4	6	8	12	24
2 mg/mL, 1 hour*	2.98	3.63	0.60	0.40	0.33	0.26	0.27	0.20	0.20
	±1.12	±1.73	±0.31	±0.23	±0.16	±0.14	±0.15	±0.12	±0.15
1 mg/mL, 3 hours†	0.91	1.02	1.14	1.13	0.32	0.28	0.27	0.22	0.18
	±0.13	±0.11	±0.13	±0.16	±0.05	±0.04	±0.03	±0.02	±0.02

* = 500 mg (2 mg/mL) for 2–5 days in community-acquired pneumonia patients.

† = 500 mg (1 mg/mL) for 5 days in healthy subjects.

Comparison of the plasma pharmacokinetic parameters following the first and fifth daily doses of 500 mg I.V. azithromycin showed only an 8% increase in the C_{max} but a 61% increase in the AUC_{24}, reflecting a threefold rise in C_{24} trough levels.

Following single oral doses of 500 mg azithromycin (two 250 mg capsules) to 12 healthy volunteers, C_{max}, trough level, and AUC_{24} were reported to be 0.41 µg/mL, 0.05 µg/mL, and 2.6 µg•h/mL, respectively. These oral values are approximately 38%, 83%, and 52% of the values observed following a single 500 mg, I.V., 3-hour infusion (C_{max}: 1.08 µg/mL, trough: 0.06 µg/mL, and AUC_{24}: 5.0 µg•h/mL). Thus, plasma concentrations are higher following the I.V. regimen throughout the 24-hour interval.

Distribution

The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 2 µg/mL.

Tissue concentrations have not been obtained following I.V. infusions of azithromycin, but following oral administration in humans azithromycin has been shown to penetrate into tissues, including skin, lungs, tonsils, and cervix.

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios following oral administration of azithromycin are shown in the following table

Table 1: Azithromycin concentrations following a 500 mg dose (two 250 mg capsules) in adults

Tissue Or Fluid	Time After Dose (H)	Tissue Or Fluid Concentration (Mcg/G Or Mcg/Ml)	Corresponding Plasma Or Serum Level (Mcg/Ml)	Tissue (Fluid) Plasma (Serum) Ratio[1]
Skin	72-96	0.4	0.012	35
Lung	72-96	4	0.012	>100
Sputum *	2-4	1	0.64	2
Sputum **	10-12	2.9	0.1	30
Tonsil ***	9-18	4.5	0.03	>100
Tonsil ***	180	0.9	0.006	>100
Cervix ****	19	2.8	0.04	70

[1] High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. 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.

* Sample was obtained 2 to 4 hours after the first dose.

** Sample was obtained 10 to 12 hours after the first dose.

*** Dosing regimen of 2 doses of 250 mg each, separated by 12 hours.

**** Sample was obtained 19 hours after single 500 mg dose.

Tissue levels were determined following a single oral dose of 500 mg azithromycin in 7 gynaecological patients. Approximately 17 hours after dosing, azithromycin concentrations were 2.7 µg/g in ovarian tissue, 3.5 µg/g in uterine tissue, and 3.3 µg/g in the salpinx. Following a regimen of 500 mg on the first day followed by 250 mg daily for 4 days, concentrations in the cerebrospinal fluid were less than 0.01 µg/mL in the presence of non-inflamed meninges.

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 from inactive phagocytes. In animal models, this results in high concentrations of azithromycin being delivered to the site of infection.

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. Concentrations in target tissues such as lungs, tonsils and prostate exceed the MIC90 for likely pathogen agents after a single dose of 500 mg. High azithromycin concentrations were detected in gynaecological tissue 96 hours after a single dose of 500 mg azithromycin.

Metabolism

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

Elimination

Plasma concentrations of azithromycin following single 500 mg oral and I.V. 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.

In a multiple-dose study in 12 normal volunteers utilizing a 500 mg (1 mg/mL), 1-hour I.V. dosage regimen for 5 days, the amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the first dose and 14% after the fifth dose. These values are greater than the reported 6% excreted unchanged in urine after oral administration of azithromycin. Biliary excretion is a major route of elimination for unchanged drug, following oral administration.

Special 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

The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

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

Pharmacokinetic studies with I.V. azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65–85 years old) was similar to those in younger volunteers (18–40 years old) for the 5-day therapeutic regimen.

Paediatric Patients

Pharmacokinetic studies with I.V. azithromycin have not been performed in children.

Drug–Drug Interactions

Drug interaction studies were performed with oral 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 2** and the effects of other drugs on the pharmacokinetics of azithromycin are shown in **Table 3**.

Co-administration of azithromycin at therapeutic doses had a modest effect on the pharmacokinetics of the drugs listed in Table 2. No dosage adjustment of drugs listed in **Table 2** 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_{max} and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in **Table 3**.

Table 2: Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin

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_{max}	**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 (0.81–1.25)
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 (0.88–1.06)	0.96 (0.88–1.06)

Cetirizine	20 mg/day × 11 days	500 mg PO on day 7, then 250 mg/day on days 8–11	14	1.03 (0.93–1.14)	1.02 (0.92–1.13)
Didanosine	200 mg PO b.i.d. × 21 days	1,200 mg/day PO on days 8–21	6	1.44 (0.85–2.43)	1.14 (0.83–1.57)
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 (0.98–1.11)	1.01 (0.97–1.05)
Indinavir	800 mg t.i.d. × 5 days	1,200 mg PO on day 5	18	0.96 (0.86–1.08)	0.90 (0.81–1.00)
Midazolam	15 mg PO on day 3	500 mg/day PO × 3 days	12	1.27 (0.89–1.81)	1.26 (1.01–1.56)
Nelfinavir	750 mg t.i.d. × 11 days	1,200 mg PO on day 9	14	0.90 (0.81–1.01)	0.85 (0.78–0.93)
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 (0.86–1.57)	0.92 (0.75–1.12)
Theophylline	4 mg/kg I.V. on days 1, 11, 25	500 mg PO on day 7, 250 mg/day on days 8–11	10	1.19 (1.02–1.40)	1.02 (0.86–1.22)
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 (0.92–1.29)	1.08 (0.89–1.31)
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/ Sulfamethoxazole	160 mg/800 mg/day PO × 7 days	1,200 mg PO on day 7	12	0.85 (0.75–0.97)/ 0.90 (0.78–1.03)	0.87 (0.80–0.95/ 0.96 (0.88–1.03)
Zidovudine	500 mg/day PO × 21 days	600 mg/day PO × 14 days	5	1.12 (0.42–3.02)	0.94 (0.52–1.70)
Zidovudine	500 mg/day PO × 21 days	1,200 mg/day PO × 14 days	4	1.31 (0.43–3.97)	1.30 (0.69–2.43)

Table 3: Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Co-administered Drugs

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_{max}	**Mean AUC**

Efavirenz	400 mg/day × 7 days	600 mg PO on day 7	14	1.22 (1.04–1.42)	0.92*
Fluconazole	200 mg PO single dose	1,200 mg PO single dose	18	0.82 (0.66–1.02)	1.07 (0.94–1.22)
Nelfinavir	750 mg t.i.d. × 11 days	1,200 mg PO on day 9	14	2.36 (1.77–3.15)	2.12 (1.80–2.50)
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

* 90% confidence interval not reported
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.

Indications

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

Azithromycin for injection is a macrolide antibacterial drug indicated for the treatment of patients with infections caused by susceptible strains of the designated microorganisms in the conditions listed below.

Community-acquired pneumonia due to Chlamydia pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus, or Streptococcus pneumoniae in patients who require initial I.V. therapy.

Pelvic inflammatory disease due to Chlamydia trachomatis, Neisseria gonorrhoeae, or Mycoplasma hominis in patients who require initial intravenous therapy. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with azithromycin.

Azithromycin for injection should be followed by azithromycin by the oral route as required.

Dosage and Administration

Community-Acquired Pneumonia

The recommended dose of azithromycin for injection for the treatment of adult patients with community-acquired pneumonia due to the indicated organisms is 500 mg as a single daily dose by the I.V. route for at least 2 days. I.V. therapy should be followed by azithromycin by the oral route at a single, daily dose of 500 mg, administered as two 250 mg tablets to complete a 7- to 10-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

Pelvic Inflammatory Disease

The recommended dose of azithromycin for injection for the treatment of adult patients with pelvic inflammatory disease due to the indicated organisms is 500 mg as a single daily dose by the I.V. route for 1 or 2 days. I.V. therapy should be followed by azithromycin by the oral route at a single, daily dose of 250 mg to complete a 7-day course of therapy. The timing of the switch to oral therapy should be done at the discretion of the physician and in accordance with clinical response.

Use in the Elderly

No dose adjustment is required in elderly patients that require therapy with azithromycin.

Use in Patients with Renal Impairment

No dose adjustment is recommended in patients with mild-to-moderate renal impairment (GFR 10–80 ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR <10 ml/min)

Use in Patients with Hepatic Impairment

Dose adjustment is not required for patients with mild-to-moderate hepatic dysfunction but the medicinal product should be used with caution in patients with significant hepatic diseases.

Use in Children

The efficacy and safety of azithromycin as powder for solution for infusion for the treatment of infections in children and adolescents has not been established.

Reconstitution

- Prepare the initial solution of azithromycin Injection by adding 5 mL of Sterile Water for Injection to the 500 mg vial.
- Shake the vial until the entire drug is dissolved.
- Transfer the entire 5 mL of the above into either 500 ml/250 ml of the diluents (listed in the pack insert)
- For concentration of 1mg/ml, add 500 ml of the diluent to 5 ml of azithromycin solution.
- For concentration of 2 mg/ml, add 250 ml of the diluent to 5 ml of the azithromycin solution.

	Azithromycin solution	**Amount of diluent**	**Infusion period**
1 mg/ ml	5 ml	500 ml	Over 3 hours
2 mg/ ml	5 ml	250 ml	Over 1 hour

The infusate concentration and rate of infusion for azithromycin for injection should be either 1 mg/mL over 3 hours or 2 mg/mL over 1 hour.

Note:

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

Diluents that can be used are listed below:

- Normal saline (0.9% Sodium Chloride)
- Half of normal saline (0.45% Sodium Chloride)
- 5% Dextrose in water
- Lactated Ringer's solution
- 5% Dextrose in half of normal saline (0.45% Sodium Chloride) with 20 mEq KCl
- 5% Dextrose in Lactated Ringer's solution
- 5% Dextrose in one-third of normal saline (0.3% Sodium Chloride)
- 5% Dextrose in half of normal saline (0.45% Sodium Chloride)

It is recommended that a 500 mg dose of azithromycin for injection, diluted as above, be infused over a period of not less than 60 minutes.

Azithromycin for injection should not be given as a bolus or as an intramuscular injection.

Other I.V. substances, additives, or medications should not be added to azithromycin for injection, or infused simultaneously through the same I.V. line.

Contraindications

Hypersensitivity

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

Hepatic Dysfunction

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

Interaction with Ergot Derivatives

Azithromycin should not be co-administered with ergot derivatives because of the theoretical possibility of ergotism.

Warnings and Precautions

Hypersensitivity

Serious allergic reactions, including angio-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. 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

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.

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, brady arrhythmias 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, aminodarone, sotalol) anti-arrhythmic agents.

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

Clostridium difficile-associated Diarrhoea

Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin for injection, 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 a 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.

Exacerbation of Myasthenia Gravis

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

General

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

In patients treated with ergotamine derivatives, ergotism has been precipitated by co-administration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administrated.

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

Safety and efficacy for prevention or treatment of MAC in children have not been established.

Safety and efficacy of azithromycin I.V. infusion for treatment of infections in children have not been established.

Infusion Site Reactions

Azithromycin for injection should be reconstituted and diluted as directed and administered as an I.V. infusion over not less than 60 minutes.

Local I.V. site reactions have been reported with the I.V. administration of azithromycin. The incidence and severity of these reactions were the same when 500 mg azithromycin was given over 1 hour (2 mg/mL as 250 mL infusion) or over 3 hours (1 mg/mL as 500 mL infusion). All volunteers who received infusate concentrations above 2.0 mg/mL experienced local I.V. site reactions and, therefore, higher concentrations should be avoided.

Development of Drug-Resistant Bacteria

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

Drug Interactions

Nelfinavir

Co-administration of nelfinavir at steady state with a single oral dose of azithromycin resulted in increased azithromycin serum 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.

Warfarin

Spontaneous postmarketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral

anticoagulants concomitantly.

Potential Drug–Drug Interaction with Macrolides

Interactions with the following drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug–drug interaction. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin or phenytoin is used with azithromycin, careful monitoring of patients is advised.

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with oral azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 25%. In patients taking azithromycin by oral administration, azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

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 1,200 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

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 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.

Ergot Derivatives (Ergotamine)

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

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450-mediated metabolism:

Atorvastatin

Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay).

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 15 mg dose of warfarin administered to healthy volunteers. There have been reports received in the postmarketing 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 were found to be significantly elevated (by 24% and 21%, respectively); however, no significant changes were seen in AUC_{0-5}. 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 1,200 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. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin

Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

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

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 1200 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

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproductive and development studies have not been conducted using I.V. administration of azithromycin to animals. Reproduction studies have been performed in rats and mice using oral administration at doses up to moderately maternally toxic dose concentrations (i.e. 200 mg/kg/day). These daily doses in rats and mice based on body surface area, are estimated to be 4 and 2 times, respectively, an adult daily dose of 500 mg. In the animal studies, no evidence of harm to the foetus due to azithromycin was found. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.

Lactation

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

Paediatric Use

Safety and effectiveness of azithromycin for injection in children or adolescents aged under 16 years have not been established.

Geriatric Use

Pharmacokinetic studies with I.V. azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65–85 years old) was similar to those in younger volunteers (18–40 years old) for the 5-day therapeutic regimen.

In multiple-dose clinical trials of I.V. azithromycin in the treatment of community-acquired pneumonia, 45% of patients (188/414) were at least 65 years of age and 22% of patients (91/414) were at least 75 years of age. No overall differences in safety were observed between these subjects and younger subjects in terms of adverse reactions, laboratory abnormalities, and discontinuations. Similar decreases in clinical response were noted in azithromycin-and comparator-treated patients with increasing age.

Azithromycin for injection contains 114 mg (4.96 mEq) of sodium per vial. At the usual recommended doses, patients would receive 114 mg (4.96 mEq) of sodium.

The geriatric population may respond with a blunted natriuresis to salt loading. The total sodium content from dietary and non-dietary sources may be clinically important with regard to such diseases as congestive heart failure.

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

Effects on Ability to Drive and Use Machines

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

Undesirable Effects

In clinical trials of I.V. azithromycin for community-acquired pneumonia, in which two to five I.V. doses were given, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. The majority of patients in these trials had one or more comorbid diseases and were receiving concomitant medications. Approximately 1.2% of the patients discontinued I.V. azithromycin therapy, and a total of 2.4% discontinued azithromycin therapy by either the I.V. or oral route because of clinical or laboratory side effects.

In clinical trials conducted in patients with pelvic inflammatory disease, in which one to two I.V. doses were given, 2% of women who received monotherapy with azithromycin and 4% who received azithromycin plus metronidazole discontinued therapy due to clinical side effects.

Clinical side effects leading to discontinuations from these studies were most commonly gastrointestinal (abdominal pain, nausea, vomiting, diarrhoea), and rashes; laboratory side effects leading to discontinuation were increases in transaminase levels and/or alkaline phosphatase levels.

Overall, the most common side effects associated with treatment in adult patients who received I.V./PO azithromycin. Azithromycin in studies of community-acquired pneumonia were related to the gastrointestinal system with diarrhoea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%) being the most frequently reported. Approximately 12% of patients experienced a side effect related to the I.V. infusion; most common were pain at the injection site (6.5%) and local inflammation (3.1%).

The most common side effects associated with treatment in adult women who received I.V./PO. Azithromycin in studies of pelvic inflammatory disease were related to the gastrointestinal system. Diarrhoea (8.5%) and nausea (6.6%) were most commonly reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was co-administered with metronidazole in these studies, a higher proportion of women experienced side effects of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), application site reaction, stomatitis, dizziness, or dyspnoea (all at 1.9%).

Adverse reactions that occurred with a frequency of 1% or less included the following:

Gastrointestinal: Dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis.
Nervous System: Headache, somnolence.
Allergic: Bronchospasm.
Special Senses: Taste perversion.

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: Palpitations, 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: Hepatitis, hepatic function abnormal, hepatic failure, hepatitis fulminant, hepatic necrosis, jaundice cholestatic
Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, hypoaesethesia ,agitation ,syncope, psychomotor anosmia, ageusia, parosmia, and myasthenia gravis.
Psychiatric: Aggressive reaction and anxiety.
Skin/Appendages: Pruritus; rarely, serious skin reactions, including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis.
Special Senses: Visual impairment, hearing disturbances, including hearing loss, deafness and/or tinnitus, and reports of taste/smell perversion and/or loss.

Musculoskeletal and Connective Tissue Disorders: Athralgia.

Infections and Infestations: Candidiasis, oral candidiasis, vaginal infection.

Blood and Lymphatic System Disorders: Leucopenia, neutropenia, thrombocytopenia, haemolytic anaemia.

Metabolism and Nutrition Disorders: Anorexia.

Renal and Urinary Disorders: Renal failure acute, nephritis interstitial.

General Disorders and Administration Site Conditions: Pain and inflammation on the local injection site, fatigue, chest pain, oedema, malaise, asthenia.

Investigations: Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal and Electrocardiogram QT prolonged.

Laboratory Abnormalities

Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:
Elevated ALT (SGPT), AST (SGOT), creatinine (4–6%)

Elevated LDH, bilirubin (1–3%)

Leucopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase (<1%)

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

In multiple-dose clinical trials involving more than 750 patients treated with azithromycin (I.V./PO), less than 2% of patients discontinued azithromycin therapy because of treatment-related liver enzyme abnormalities.

Overdosage

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

Incompatibility

In the case of injection, other intravenous substances, additives, or medications should not be added to AZEE 500 injection (azithromycin for injection), or infused simultaneously through the same intravenous line**.**

Storage and Handling Instructions

When diluted according to the instructions (1.0–2.0 mg/mL), Azithromycin for injection is stable for 24 hours at or below room temperature 30°C (86°F), or for 7 days if stored under refrigeration 5°C (41°F).

Packaging Information

AZEE I.V Injection ……. Available in a vial of 10 ml

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