Xithrone Vial

Azithromycin 500 mg
Lyophilized powder for solution for IV infusion

1. Indications and usage
Xithrone® (Azithromycin) for injection is a macrolide antibacterial drug indicated for the treatment of patients with infectious caused by susceptible strains of the designated microorganisms in the condition listed below
1.1 Community-Acquired Pneumonia due to Chlamydophila pneumoniae, Haemophilus influenzae, Legionella pneumophila, Moraxella catarrhalis, Mycoplasma pneumoniae, Staphylococcus aureus, or Streptococcus pneumoniae in patients who require initial intravenous therapy.
1.2 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 **Xithrone®** (azithromycin).
NOTE: For injection should be followed by **Xithrone®** by the oral route as required.
1.3 Usage
To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Xithrone®** (azithromycin) and other antibacterial drugs, **Xithrone®** (azithromycin) should be used only to treat 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.
2. DOSAGE AND ADMINISTRATION
2.1 **Community-Acquired Pneumonia**
The recommended dose of **Xithrone®** 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 intravenous route for at least two days. Intravenous 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.
2.2 **Pelvic Inflammatory Disease**
The recommended dose of **Xithrone®** 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 intravenous route for one or two days. Intravenous 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.
2.3 **Preparation of the Solution for Intravenous Administration**
The infusable concentration and rate of infusion for **Xithrone®** for injection should be either 1 mg/mL over 3 hr or 2 mg/mL over 1 hr **Xithrone®** for injection should not be given as a bolus or as an intramuscular injection.
Reconstitution
Prepare the initial solution of **Xithrone®** for injection by adding 4.8 mL of Sterile Water for Injection to the 500 mg vial, and shaking the vial until all of the drug is dissolved. Since **Xithrone®** for injection is supplied under vacuum, it is recommended that a standard 5 mL (non-automated) syringe be used to ensure that the proper amount of 4.8 mL of Sterile Water is dispensed. Each mL of reconstituted solution contains 100 mg azithromycin. Reconstituted with 4.8 mL 0.9% Sterile Water at a temperature not exceeding 2-8 °C, the resultant 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. Dilute this solution further prior to administration as instructed below.
Dilution
To provide azithromycin over a concentration range of 1.0-2.0 mg/mL, transfer 5 mL of the 100 mg/mL azithromycin solution into the appropriate amount of any of the diluents listed below:
- Normosol-M in 5 % Dextrose
- 5% Dextrose
- 5% Dextrose in 0.45% NaCl
- 5% Dextrose in 0.45% NaCl + 20 meq KCl/L
- Normosol-R in 5% Dextrose
- 5% Dextrose in Lactated Ringer's Solution
- Lactated Ringer's Solution
- 0.9% NaCl IVS Solution

Final Infusion Solution Concentration (mg/mL)	Amount of Diluent (mL)
10 mg/mL	500 mL
2.0 mg/mL	250 mL

Other intravenous substances, additives, or medications should not be added to **Xithrone®** for injection, or infused simultaneously through the same intravenous line.
Stability
When diluted according to the instructions (1.0 mg/mL to 2.0 mg/mL) by Normosol M in 5% Dextrose, 5% Dextrose, 5% Dextrose in 0.45% NaCl, 5% Dextrose in 0.45% NaCl + 20meq KCl, Normosol R in 5% Dextrose, 5% Dextrose in Lactated Ringer's Solution, Lactated Ringer's Solution, 0.9 % NaCl IVS Solution Store at temperature not exceeding 2-8° C and use for 7 days
3. DOSAGE FORMS AND STRENGTHS
Xithrone® 500mg lyophilized powder for solution for IV infusion.
Physical characters:
Before reconstitution: white to off-white colorless lyophilized spongy mass
After reconstitution with water for injection clear colorless solution
4. CONTRAINDICATIONS
4.1 **Hypersensitivity**
Xithrone® is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drugs.
4.2 **Hepatic Dysfunction**
Xithrone® is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of **Xithrone®**.
5. WARNINGS AND PRECAUTIONS
5.1 **Hypersensitivity**
Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome, and toxic epidermal necrolysis have been reported 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 even in the absence of continued exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long (mean half-life of azithromycin and subsequent prolonged) exposure to antigens 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 the allergic symptoms may reappear after symptomatic therapy has been discontinued.
5.2 **Hepatotoxicity**
Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue **Xithrone®** immediately if signs and symptoms of hepatitis occur.
5.3 **Infantile Hypertrophic Pyloric Stenosis (IHPS)**
Following the use of azithromycin in neonates (treatment up to 42 days of life), IHPS has been reported. Direct parents and caregivers to contact their physician if vomiting or irritability with feeding occurs.
5.4 **QT Prolongation**
Azithromycin have been associated with cardiovascular effects; specifically Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with 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, bradyarrhythmia or uncompensated heart failure.
- patients on drugs known to prolong the QT interval.
- patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.

Elderly patients may be more susceptible to drugs associated effects on the QT interval.
5.5 **Cardiovascular Death**
Some observational studies have shown an approximately two-fold increased short-term potential risk of acute cardiovascular death in adults exposed to azithromycin relative to other antibacterial drugs, including amoxicillin. The five-day cardiovascular mortality observed in these studies ranged from 20 to 400 per million azithromycin treatment courses. This potential risk was noted to be greater during the first five days of azithromycin use and does not appear to be limited to those patients with preexisting cardiovascular diseases. The data in these observational studies are insufficient to establish or exclude a causal relationship between azithromycin and cardiovascular death. Consider balancing this potential risk with treatment benefits when prescribing **Xithrone®**.
5.6 **Clostridioides difficile-Associated Diarrhea**
Clostridioides difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Xithrone (azithromycin for injection), and may range in severity from mild diarrhea to fatal colitis.
Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.
C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued.
Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
5.7 **Exacerbation of Myasthenia Gravis**
Exacerbations of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azithromycin therapy.
5.8 Infusion Site Reactions **Xithrone®** for injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes.
Local IV site reactions have been reported with the intravenous 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 hr (1 mg/mL as 500 mL infusion). All volunteers who received infusate concentrations above 2.0 mg/mL experienced local IV site reactions and, therefore, higher concentrations should be avoided.
5.9 **Development of Drug-Resistant Bacteria**
Prescribing **Xithrone®** 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.
6. ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in labeling:
- Hypersensitivity
- Hepatotoxicity
- Infantile Hypertrophic Pyloric Stenosis (IHPS)
- QT Prolongation
- Cardiovascular Death
- Clostridioides difficile-Associated Diarrhea (CDAD)
- Exacerbation of Myasthenia Gravis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: The Egyptian Pharmacovigilance Center (EPVC) Email: pv@pharmacy.eg.com
6.1 **Clinical Trials Experience**
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 of intravenous azithromycin for community-acquired pneumonia, in which 2 to 3.5 doses were given, the reported adverse reactions 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 co-morbid diseases and were receiving concomitant medications. Approximately 12% of the patients discontinued intravenous **Xithrone®** therapy, and a total of 2.4% discontinued azithromycin therapy by either the intravenous or oral route because of clinical or laboratory side effects.
In clinical trials conducted in patients with pelvic inflammatory disease, in which 1 to 2 IV 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 adverse reactions leading to discontinuations from these studies were gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), and rashes; laboratory side effects leading to discontinuation were increases in transaminase levels and/or alkaline phosphatase levels.
Overall, the most common adverse reactions associated with treatment in adult patients who received IV/Oral azithromycin in studies of community-acquired pneumonia were related to the gastrointestinal system with diarrhea/loose stools (13.5%), nausea (5.9%), abdominal pain (2.7%), and vomiting (1.4%) being the most frequently reported.
Approximately 32% of patients experienced a side effect related to the intravenous infusion; most common were pain at the injection site (6.3%) and local inflammation (5.1%).
The most common adverse reactions associated with treatment in adult women who received IV/Oral azithromycin in trials of pelvic inflammatory disease were related to the gastrointestinal system: Diarrhea (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 trials, a higher proportion of women experienced adverse reactions of nausea (10.3%), abdominal pain (3.2%), vomiting (2.8%), infusion site reaction, stomatitis, dizziness, or dyspnea (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
Genitourinary: Vaginal inflammation.
6.2 **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 reactions reported with azithromycin during the postmarketing period in adult and/or pediatric patients for which a causal relationship may not be established include:
Allergic: Arthralgia, edema, urticaria and angioedema.
Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension. There have been reports of QT prolongation, torsades de pointes, and cardiovascular death.
Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.
General: Asthenia, paresthesia, fatigue, malaise and anaphylaxis (including fatalities).
Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.
Hematopoietic: 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, serious skin reactions including, erythema multiforme, AGEP, 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.
6.3 **Laboratory Abnormalities**
Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:
- elevated (2% Creatinine >1 to >3 x)
- elevated (2% Bilirubin >1 to >3x)
- Leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase (less than 1%)

When follow-up was provided, changes in laboratory limits appeared to be reversible.
In multiple-dose clinical trials involving more than 750 patients treated with azithromycin IV/Oral, less than 2% of patients discontinued azithromycin therapy because of treatment-related liver enzyme abnormalities.
7. DRUG INTERACTIONS
7.1 **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.
7.2 **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.
7.3 **Potential Drug-Drug Interaction with Macrolides**
Interactions with digoxin, colchicine or phenytoin have not been reported in clinical trials with azithromycin. 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, colchicine or phenytoin are used with azithromycin, careful monitoring of patients is advised.
8. USE IN SPECIFIC POPULATIONS
8.1 **Pregnancy**
Risk Summary
Available data from published literature and postmarketing experience over several decades with azithromycin use in pregnant women have not identified any drug-associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes.
The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.
Data
Human Data
Available data from published observational studies, case series, and case reports over several decades do not suggest an increased risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes with azithromycin use in pregnant women. Limitations of these data include the lack of randomization and inability to control for confounders such as underlying maternal disease and maternal use of concomitant medications.
8.2 **Lactation**
Risk Summary
Azithromycin is present in human milk (see Data). Non-serious adverse reactions have been reported in breastfed infants after maternal administration of azithromycin (see Clinical Considerations). There are no available data on the effects of azithromycin on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Azithromycin and any potential adverse effects on the breastfed infant from Azithromycin or from the underlying maternal condition.
Clinical Considerations
Advise women to monitor the breastfed infant for diarrhea, vomiting, or rash.
Data
Azithromycin breastmilk concentrations were measured in 20 women after receiving a single 2 g oral dose of azithromycin during labor. Breastmilk samples collected on days 3 and 6 postpartum as well as 2 and 4 weeks postpartum revealed the presence of azithromycin in breastmilk up to 4 weeks after dosing. In another study, a single dose of azithromycin 500 mg was administered intravenously to 9 women prior to incision for cesarean section. Breastmilk (colostrum) samples obtained between 12 and 48 hours after dosing revealed that azithromycin is persisted in breastmilk up to 48 hours.
8.3 **Pediatric Use**
Safety and effectiveness of azithromycin for injection in children or adolescents under 16 years have not been established. In controlled clinical studies, azithromycin has been administered to pediatric patients (age 6 months to 16 years) by the oral route.
8.4 **Geriatric Use**
Pharmacokinetic studies with intravenous azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65-83 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen.
In multiple-dose clinical trials of intravenous azithromycin in the treatment of community-acquired pneumonia, 65% of patients (188/416) were at least 65 years of age and 22% of patients (91/416) 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.
Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients.
9. OVERDOSAGE
Adverse reactions experienced at higher than recommended doses were similar to those seen at normal doses particularly nausea, diarrhea, and vomiting. In the event of overdosage, general symptomatic and supportive measures are indicated as required.
10. Description

Each vial contains:
Active ingredient
Azithromycin dihydrate 524mg equivalent to azithromycin 500 mg.
Inactive ingredients
- citric acid Anhydrous
- sodium hydroxide (to adjust PH between 6.4-6.8)

Water for Injection (adjusted with 4.8 ml/vial)
11. CLINICAL PHARMACOLOGY
11.1 Mechanism of Action
Azithromycin is a macrolide antibacterial drug [see Microbiology (11.4)]
11.2 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 (S. pneumoniae and S. aureus). The principal pharmacokinetic/pharmacodynamic parameter host associated with clinical and microbiological cure has not been elucidated in clinical trials with azithromycin.
Cardiac Electrophysiology
QT c interval prolongation was studied in a randomized, placebo-controlled parallel trial in 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with oral azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration- dependent manner in comparison to chloroquine alone; the maximum mean (95% upper confidence bound) increases in QTc,b were 5 (90 ms, 7 (92 ms and 9 (94 ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.
Since the mean Cmax of azithromycin following a 500 mg IV dose given over 1 hr is higher than the mean Cmax of azithromycin following the administration of a 1500 mg oral dose, it is possible that QTc may be prolonged to a greater extent with IV azithromycin at dose proximity to a one hour infusion of 500 mg.
11.3 Pharmacokinetics
In patients hospitalized with community-acquired pneumonia receiving single daily one-hour intravenous infusions for 2 to 5 days of 500 mg azithromycin at a concentration of 2 mg/mL, the mean Cmax ± S.D. achieved was 3.63 ± 1.40 mcg/mL, while the 24-hour trough level was 0.20 ± 0.05 mcg/mL, and the AUC24 was 9.61 ± 4.80 mcg hr/mL.
The mean Cmax, 24-hour trough and AUC24 values were 1.94 ± 0.14 mcg/mL, 0.18 ± 0.02 mcg/mL, and 8.05 ±0.86 mcg hr/mL, respectively, in normal volunteers receiving a 3-hour intravenous 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.

Infusate Concentration,	Time after starting the infusion (hr)								
	0.5	1	2	3	4	6	8	12	24
2 mg/mL	2.58	3.63	0.60	0.40	0.33	0.26	0.22±0.05	0.20	0.20
1 Dr*	±1.12	±1.75	±0.31	±0.25	±0.16	±0.14		±0.02	±0.05
1 mg/mL	0.91	1.80	0.19	0.16	0.12	0.08	0.27±0.09	0.14	0.11
1 Dr*	±0.03	±0.11	±0.15	±0.16	±0.05	±0.04		±0.02	±0.02

* 500 mg (2 mg/mL) for 2-5 days in community-acquired pneumonia patients.
* 500 mg (1 mg/mL) for 3 days in healthy subjects.

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500 mg intravenous azithromycin showed only an 8% increase in Cmax but a 41% increase in AUC24 reflecting a threshold rise in C24 trough levels.
Following single-oral doses of 500 mg azithromycin (two 250 mg capsules) to 12 healthy volunteers, Cmax, trough level, and AUC24 were reported to be 0.41 mcg/mL, 0.05 mcg/mL, and 2.6 mcg hr/mL, respectively. These oral values are approximately 38%, 83%, and 32% of the values observed following a single 500-mg, 1- 3-hour infusion (Cmax: 1.08 mcg/mL, trough: 0.06 mcg/mL, and AUC24: 3.0 mcg hr/mL). Thus, plasma concentrations are higher following the intravenous 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 mcg/mL to 7% at 2 mcg/mL.
Tissue concentrations have not been obtained following intravenous infusions of azithromycin, but following oral administration in humans azithromycin has been shown to penetrate into tissues, including skin, lung, tonsil, and cervix.
Tissue levels were determined following a single oral dose of 500 mg azithromycin in 7 gynecological patients. Approximately 37 hr after dosing, azithromycin concentrations were 27 mcg/g in ovarian tissue, 53 mcg/g in uterine tissue, and 53 mcg/g in salpinx. Following a regimen of 500 mg on the first day followed by 250 mg daily for 4 days, concentrations in the cervix were higher than 0.00 mcg/mL in the presence of non-inflamed meningeal.
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 IV doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. 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) one-hour intravenous-dosage regimen for five days, the amount of administered azithromycin dose excreted in urine in 24 hr was about 11% after the 1st dose and 14% after the 5th 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.
Specific Populations
Patients with Renal Impairment
Azithromycin pharmacokinetics were investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment.Following the oral administration of a single 1000 mg dose of azithromycin, mean Cmax and AUC0-120 increased by 33% and 42%, respectively in subjects with mild to moderate renal impairment (GFR 10 to 80 mL/min) compared to subjects with normal renal function (GFR >80 mL/min). The mean Cmax and AUC0-120 increased 61% and 55%, respectively in subjects with severe renal impairment (GFR <10 mL/min) compared to subjects with normal renal function (GFR >80 mL/min).
Patients with Hepatic Impairment
The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.
Male and Female Patients
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 intravenous azithromycin have not been performed in older volunteers. Pharmacokinetics of azithromycin following oral administration in older volunteers (65-83 years old) were similar to those in younger volunteers (18-40 years old) for the 5-day therapeutic regimen.
Pediatric Patients
Pharmacokinetic studies with intravenous azithromycin have not been performed in children.
Drug Interaction Studies
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 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 Cmax and AUC of azithromycin. No dosage adjustment of azithromycin is recommended when administered with drugs listed in Table 2.

Table 1. Drug Interactions: Pharmacokinetic Parameters for Co-administered Drugs in the Presence of Azithromycin

Co-administered Drug	Dose of Coadministered Drug	Dose of Azithromycin	n	Ratio (with/without azithromycin) of Coadministered Drug Pharmacokinetic Parameters (90% CI; No Effect = 100)	
				Mean Cmax	Mean AUC
Atorvastatin	10 mg/day for 8 days	500 mg/day orally on days 6-8	12	0.63 (0.43 to 1.08)	1.18 (0.81 to 1.25)
Carbamazepine	200 mg/day for 2 days, then 200 mg twice a day for 18 days	500 mg/day orally for days 16-18	7	0.97 (0.88 to 1.08)	0.90 (0.80 to 1.01)
Cetirizine	20 mg/day for 11 days	500 mg orally on day 7, then 250 mg/day on days 8-11	14	1.03 (0.93 to 1.14)	1.02 (0.92 to 1.15)
Chloroquine	200 mg orally twice a day for 21 days	1200 mg/day orally on days 8-21	6	1.44 (0.85 to 2.43)	1.14 (0.83 to 1.32)
Cyclosporine	450 mg/day for 2 days	600 mg orally on day 2	14	1.24*	0.92*
Fluconazole	200 mg orally single dose	1200 mg orally single dose	18	1.04 (0.98 to 1.11)	1.18 (0.97 to 1.05)
Indinavir	800 mg three times a day for 5 days	1200 mg orally on day 5	18	0.96 (0.86 to 1.06)	0.90 (0.81 to 1.00)
Midazolam	15 mg orally on day 3	500 mg/day orally for 3 days	12	1.27 (0.89 to 1.81)	1.26 (0.93 to 1.71)
Nelfinavir	750 mg three times a day for 11 days	1200 mg orally on day 9	14	0.90 (0.81 to 1.00)	0.85 (0.78 to 0.93)
Sildenafil	100 mg on days 1 and 4	500 mg/day orally for 3 days	12	1.16 (0.84 to 1.52)	0.92 (0.75 to 0.92)
Theophylline	4 mg/kg IV on days 1, 11, 25	500 mg orally on day 7, 250 mg/day on days 8-11	10	1.19 (1.02 to 1.40)	1.02 (0.86 to 1.21)
Theophylline	300 mg orally BID 13 days	500 mg orally on day 6, then 250 mg/day on days 7-10	8	1.09 (0.92 to 1.36)	1.08 (0.89 to 1.31)
Trazolam	0.125 mg on day 2	500 mg orally on day 1, then 250 mg/day on day 2	12	0.94*	1.05*
Trimethoprim/Sulfamethoxazole	160 mg/800 mg/day orally for 7 days	1200 mg orally on day 7	12	0.85 (0.75 to 0.97)	0.87 (0.80 to 0.96)
				0.90 (0.78 to 1.05)	0.96 (0.88 to 1.05)
Zidovudine	500 mg/day orally for 21 days	600 mg/day orally for 14 days	5	1.12 (0.42 to 3.02)	0.94 (0.52 to 1.70)
Zidovudine	500 mg/day orally for 21 days	1200 mg/day orally for 14 days	4	1.31 (0.43 to 3.95)	1.50 (0.69 to 3.42)

* 90% confidence interval not reported

Table 2. Drug Interactions: Pharmacokinetic Parameters for Azithromycin in the Presence of Coadministered Drugs.

Co-administered Drug	Dose of Coadministered Drug	Dose of Azithromycin	n	Ratio (with/without co-administered drug) of Azithromycin Pharmacokinetic Parameters (90% CI; No Effect = 100)	
				Mean Cmax	Mean AUC
Efavirenz	400 mg/day for 7 days	600 mg orally on day 7	14	0.72 (0.55 to 1.62)	0.77 (0.64 to 1.22)
Fluconazole	200 mg orally single dose	1200 mg orally single dose	18	0.82 (0.44 to 1.02)	1.07 (0.84 to 1.22)
Nelfinavir	750 mg three times a day for 11 days	1200 mg orally on day 9	14	2.36 (1.77 to 3.15)	2.12 (1.80 to 2.50)

* 90% confidence interval not reported

11.4 Microbiology
Mechanism of Action
Azithromycin acts by binding to the 23S rRNA of the 50S ribosomal subunit of susceptible microorganisms inhibiting bacterial protein synthesis and impeding the assembly of the 50S ribosomal subunit.
Resistance
Azithromycin demonstrates cross-resistance with erythromycin. The most frequently encountered mechanism of resistance to azithromycin is modification of the 23S rRNA target, most often by methylation. Ribosomal modifications can determine cross resistance to other macrolides, lincosamides and streptogramin B (MLSB phenotype).
Antimicrobial Activity
Azithromycin has been shown to be active against the following microorganisms, both in vitro and in clinical infections.
Gram-positive Bacteria
Staphylococcus aureus
Streptococcus pneumoniae
Gram-negative Bacteria
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Legionella pneumophila
Other Bacteria
Chlamydophila pneumoniae
Chlamydia trachomatis
Mycoplasma hominis
Mycoplasma pneumoniae
The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for azithromycin against isolates of similar genus or organism group. However, the efficacy of azithromycin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.
Aerobic Gram-Positive Bacteria
Streptococci (Groups C, F, G) (Viridans group streptococci)
Gram-Negative Bacteria Bordetella pertussis
Anaerobic Bacteria
Peptostreptococcus species
Prevotella bivia
Other Bacteria
Ureaplasma urealyticum
Susceptibility Testing
12. HOW SUPPLIED/STORAGE AND HANDLING
Shelf life
2 years
SPECIAL PRECAUTIONS FOR STORAGE
Store at Temperature not exceeding 30° C.
After Reconstitution with 4.8 ml IVH Store at temperature not exceeding 2-8 ° C for 7 days
After Dilution by Normosol M in 5% Dextrose, 5% Dextrose, 5% Dextrose in 0.45% NaCl + 20meq KCl, Normosol R in 5% Dextrose, 5% Dextrose in Lactated Ringer's Solution, Lactated Ringer's Solution, 0.9 % NaCl IVS Solution : Store at temperature not exceeding 2-8 ° C and use for 7 days
Pack: Carton box containing: colorless transparent (Type I) glass vial contains 10.90 mg powder gives about 6 ml solution after reconstitution with gray rubber (Type I) with Al. flip off enclosed with insert leaflet.
License Holder: amount Pharmaceutical company
Manufacturer: Chemipharm Pharmaceutical industries
EDA revision date: November 2022

Keep all medicaments out of reach of children

AMOUN

V04-23/11/2022
P.150158.01
232

Manufactured By:
Chemipharm Pharmaceutical industries
for **AMOUN PHARMACEUTICAL CO.** S.A.E.
El-Obour City, Al Qalyubia, Egypt.