Azitma®
(Azithromycin) Tablets / Suspension

DESCRIPTION:
Azitma® (Azithromycin) is a macrolide or azalide antibacterial drug for oral administration

COMPOSITION:

Azitma® 250mg Tablets
Each film coated tablet contains:
Azithromycin Dihydrate USP
equivalent to Azithromycin.....250mg

Azitma® 500mg Tablets
Each film coated tablet contains:
Azithromycin Dihydrate USP
equivalent to Azithromycin.....500mg

Azitma® 200mg/5ml Suspension
Each 5ml of reconstituted suspension contains:
Azithromycin Dihydrate USP
equivalent to Azithromycin..... 200mg

PHARMACOLOGY:
Mechanism of Action
Azithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible organisms and thus interfering with microbial protein synthesis and inhibition of peptide translocation. Nucleic acid synthesis is not affected

Pharmacokinetics:
Absorption
After oral administration, the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (Cmax after a single dose of 500mg orally was approximately 0.4mg/l)

Distribution
Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 500mg
In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05mg/l to 12% in 0.5mg/l

Metabolism and Excretion
Plasma terminal elimination half life closely reflects the tissue depletion half life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended

Microbiology:
Azithromycin is an azalide, derived from the macrolide class of antibiotics. Azithromycin demonstrates activity in vitro, against a wide range of gram-positive and gram-negative bacteria including Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes (Group A) and other Streptococcal species; Haemophilus influenzae and para- influenzae; Moraxella catarrhalis; anaerobes including Bacteroides fragilis; Escherichia coli; Bordetella pertussis; Bordetella parapertussis; Borrelia burgdorferi; Haemophilus ducreyi: Neisseria gonorrhoeae and Chlamydia trachomatis. Azithromycin also demonstrates in-vitro activity against Legionella pneumophila, Mycoplasma pneumoniae and hominis, Campylobacter Sp., Toxoplasma gondii and Treponema pallidum

INDICATIONS:
Azitma® (Azithromycin) is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated micro-organisms in the specific conditions listed below:
- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- Skin and soft tissue infections
- Uncomplicated Chlamydia trachomatis urethritis and cervicitis

DOSAGE AND ADMINISTRATION:
Adults
In uncomplicated Chlamydia trachomatis urethritis and cervicitis, the dosage is 1000mg in one single oral dose. For all other indications the dose is 1500mg, to be administered as 500mg per day for three consecutive days. As an alternative the same total dose (1500mg) can also be administered over a period of five days with 500mg on the first day and 250mg on the second to the fifth day

Infection	Recommended Dose / Duration of Therapy
Community-acquired pneumonia (mild severity) Pharyngitis/Tonsillitis (Second-line therapy) Skin/skin structure infections (uncomplicated)	500mg as a single dose on day 1, followed by 250mg once daily on day 2 through 5
Acute bacterial exacerbations of chronic bronchitis (mild to moderate)	500mg as a single dose on day 1, followed by 250mg once daily on day 2 through 5 or 500mg once daily for 3 days
Acute bacterial sinusitis	500mg once daily for 3 days
Genital ulcer disease (Chancroid) Non-gonococcal urethritis and cervicitis	One single 1g dose
Gonococcal urethritis and cervicitis	One single 2g dose

Children
The total dosage in children aged 1 year and older is 30mg/kg administered as 10mg/kg once daily for three days, or over a period of five days starting with a single dose of 10mg/kg on the first day, followed by doses of 5mg/kg per day for the following 4 days, according to the tables shown below. There are limited data on use in children younger than 1 year

Weight (kg)	3-day therapy	5-day therapy	
	Day 1-3 10mg/kg/day	Day 1 10mg/kg/day	Day 2-5 5mg/kg/day
10kg	2.5ml	2.5ml	1.25ml
12kg	3ml	3ml	1.5ml
14kg	3.5ml	3.5ml	1.75ml
16kg	4ml	4ml	2ml
17 - 25kg	5ml	5ml	2.5ml
26 - 35kg	7.5ml	7.5ml	3.75ml
36 - 45kg	10ml	10ml	5ml
> 45kg	12.5ml	12.5ml	6.25ml

Infection	Recommended Dose / Duration of Therapy
Acute otitis media	30mg/kg as a single dose or 10mg/kg once daily for 3 days or 10mg/kg as single dose on day 1 followed by 5mg/kg/day on day 2 through 5
Acute bacterial sinusitis	10mg/kg once daily for 3 days
Community-acquired pneumonia	10mg/kg as a single dose on day 1 followed by 5mg/kg once daily on day 2 through 5
Pharyngitis/tonsillitis	12mg/kg once daily for 5 days

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

Cardiovascular: Palpitations and chest pain
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena and cholestatic jaundice
Genitourinary: Monilia, vaginitis and nephritis
Nervous System: Dizziness, headache, vertigo and somnolence
General: Fatigue
Allergic: Rash, pruritus, photosensitivity and angioedema

CONTRAINDICATIONS:
Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin or any macrolide antibiotics

PRECAUTIONS:
As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment
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. 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

Special Populations:
Pregnancy
There are no adequate and well-controlled studies in pregnant women. Azithromycin should not be used during pregnancy unless the benefits outweigh the potential risks

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

Renal Insufficiency
Following a single oral dose of azithromycin 1g, mean Cmax and AUC(0-120) increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80ml/min) compared with normal renal function (GFR > 80ml/min). In subjects with severe renal impairment, the mean Cmax and AUC (0-120) increased 61% and 33% respectively compared to normal

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

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

Geriatric Use
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 greater sensitivity of some older individuals cannot be ruled out

DRUG INTERACTIONS:
Antacids: In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid
Cyclosporine: Caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporine levels should be monitored and the dose should be adjusted accordingly
Theophylline: Theophylline levels may be increased in patients taking azithromycin
Coumarin-type oral anticoagulants: Consideration should be given to the frequency of monitoring prothrombin time, when azithromycin is used in patients receiving coumarin-type oral anti-coagulants
Digoxin: In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin, the possibility of raised digoxin levels should be borne in mind

OVERDOSE:
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 severe nausea, vomiting and diarrhea. In the event of overdosage, general symptomatic and supportive measures are indicated as required

DIRECTION FOR RECONSTITUTION:
Azitma® 200mg/5ml suspension (15ml)
Shake bottle to loosen the mass. Add one time completely filled provided measuring spoon (8ml) with freshly boiled cool water into bottle. Shake well to form uniform suspension
Azitma® 200mg/5ml suspension (30ml)
Shake bottle to loosen the mass. Add two times completely filled provided measuring spoon (8ml) with freshly boiled cool water into bottle. Shake well to form uniform suspension

STABILITY:
See expiry on the pack

PRESENTATION:
Azitma® 250mg tablets in a pack of 6`s
Azitma® 500mg tablets in a pack of 6`s
Azitma® 200mg/5ml suspension in a pack of 15ml
Azitma® 200mg/5ml suspension in a pack of 30ml

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine

The reconstituted suspension should be used within 5 days

ایزِٹما® ٹیبلٹ/سسپینشن

(ایزی تھرومائی سن)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی
تیار شدہ سسپینشن کو ۵ یوم کے اندر استعمال کر لیں

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

R.N-05/HA/12/18

Azitma® (Azithromycin) 500mg Injection

DESCRIPTION:
Azitma® contains the active ingredient azithromycin, an azalide, a subclass of macrolide antibiotics, for intravenous injection

COMPOSITION:
Azitma® 500mg Injection
Each vial contains:
Sterile Powder of Azithromycin Dihydrate USP
equivalent to Azithromycin …….....500mg

PHARMACOLOGY:
Mechanism of action
Azithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible organisms and thus interfering with microbial protein synthesis and inhibition of peptide translocation. Nucleic acid synthesis is not affected

Pharmacokinetics
In patients hospitalized with community acquired pneumonia receiving single daily one hour intravenous infusions for 2 to 5 days of 500mg azithromycin at a concentration of 2mg/mL, the mean Cmax± S.D. achieved was 3.63 ± 1.60µg/mL, while the 24 hours trough level was 0.20 ± 0.15µg/mL, and the AUC24 was 9.60 ± 4.80µg•h/mL

The mean Cmax, 24 hours trough and AUC24 values were 1.14 ± 0.14µg/mL, 0.18 ± 0.02µg/mL, and 8.03 ± 0.86 µg•h/mL, respectively, in normal volunteers receiving a 3 hours intravenous infusion of 500mg azithromycin at a concentration of 1mg/mL. Similar pharmacokinetic values were obtained in patients hospitalized with community acquired pneumonia that received the same 3hour dosage regimen for 2–5 days

Comparison of the plasma pharmacokinetic parameters following the 1st and 5th daily doses of 500mg intravenous azithromycin showed only an 8% increase in Cmax but a 61% increase in AUC24 reflecting a threefold rise in C24 trough levels

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

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

Elimination
Plasma concentrations of azithromycin following single 500mg oral and I.V. doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630mL/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

MICROBIOLOGY:
Azithromycin is an azalide, derived from the macrolide class of antibiotics. Azithromycin demonstrates activity in vitro, against a wide range of gram-positive and gram-negative bacteria including Staphylococcus aureus, Streptococcus pneumoniae, Streptococcus pyogenes (group A) and other Streptococcal species; Haemophilus influenzae and para- influenzae; Moraxella catarrhalis; anaerobes including Bacteroides fragilis; Escherichia coli; Bordetella pertussis; Bordetella parapertussis; Borrelia burgdorferi; Haemophilus ducreyi: Neisseria gonorrhoeae and Chlamydia trachomatis. Azithromycin also demonstrates in-vitro activity against Legionella pneumophila, Mycoplasma pneumoniae and hominis, Campylobacter spp. Toxoplasma gondii and Treponema pallidum

INDICATIONS:
Azithromycin for injection is 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 intravenous 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:
The recommended dose of azithromycin for injection for the treatment of adult patients with community acquired pneumonia due to the indicated organisms is: 500mg 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 500mg, administered as two 250mg 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

The recommended dose of azithromycin for the treatment of adult patients with pelvic inflammatory disease due to the indicated organisms is: 500mg 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 250mg to complete a 7day 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. If anaerobic microorganisms are suspected of contributing to the infection, an antimicrobial agent with anaerobic activity should be administered in combination with azithromycin

OR
As directed by the physician

ADVERSE REACTIONS:
Intravenous azithromycin for community acquired pneumonia, in which 2–5 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 had one or more comorbid diseases and were receiving concomitant medications. Approximately 1.2% of the patients discontinued intravenous azithromycin 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 patients with pelvic inflammatory disease, in which 1–2 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 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

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

PRECAUTIONS:
General
Because azithromycin is principally eliminated via the liver, caution should be exercised when azithromycin is administered to patients with impaired hepatic function

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

Local I.V. site reactions have been reported with the intravenous administration of azithromycin. The incidence and severity of these reactions were the same when 500mg azithromycin were given over 1 hour (2mg/mL as 250ml infusion) or over 3 hours (1mg/mL as 500ml infusion). Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes,have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization

Special Populations:
Pregnancy
Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Azithromycin should not be used during pregnancy unless the benefits outweigh the potential risks

Nursing Mothers
It is not known whether azithromycin is excreted in human milk. Because many drugs are excreted in human milk, 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 less than 16 years have not been established

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

Renal Insufficiency
No dosage adjustment is recommended for subjects with renal impairment (GFR -80mL/min). The mean AUC(0–120) was similar in subjects with GFR 10–80mL/min compared to subjects with normal renal function, whereas it increased 35% in subjects with GFR <10mL/min compared to subjects with normal renal function. Caution should be exercised when azithromycin is administered to subjects with severe renal impairment

Hepatic Insufficiency
The pharmacokinetics of azithromycin in subjects with hepatic impairment have not been established. No dose adjustment recommendations can be made in patients with impaired hepatic function

No dosage adjustment is recommended based on age or gender

The infusate concentration and rate of infusion for azithromycin for injection should be either 1mg/mL over 3 hours or 2mg/mL over 1 hour. Azithromycin for injection should not be given as a bolus or as an intramuscular injection

DRUG INTERACTIONS:
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 side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted

Azithromycin given by the oral route did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects

When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is co-administered with any of these agents

Interactions with the drugs listed below have not been reported with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful monitoring of patients is advised:

Digoxin - elevated digoxin concentrations

Ergotamine or dihydroergotamine - acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia

Terfenadine, cyclosporine, hexobarbital and phenytoin - elevated concentrations

METHOD OF RECONSTITUTION:
Prepare the initial solution of azithromycin for injection by adding 4.8ml of Sterile Water for Injection to the 500mg vial and shaking the vial until all of the drug is dissolved. It is recommended that a standard 5ml syringe be used to ensure that the exact amount of 4.8ml of Sterile Water is dispensed. Each ml of reconstituted solution contains 100mg azithromycin. Reconstituted solution is stable for 24 hours when stored at room temperature below (30°C or 86°F) or for 7 days in refrigerator

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

Dilute this solution further prior to administration as instructed below:

Dilution:
To provide azithromycin over a concentration range of 1.0–2.0mg/mL, transfer 5mL of the 100mg/mL azithromycin solution into the appropriate amount (500ml or 250ml) of any of the diluents listed below:

- Normal saline (0.9% sodium chloride)
- 1/2 Normal saline (0.45% sodium chloride)
- 5% Dextrose in water
- Lactated Ringer's solution
- 5% Dextrose in 1/2 normal saline (0.45% sodium chloride) with 20mEq KCl
- 5% Dextrose in Lactated Ringer's solution
- 5% Dextrose in 1/3 normal saline (0.3% sodium chloride)
- 5% Dextrose in 1/2 normal saline (0.45% sodium chloride)

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

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

STABILITY:
See expiry on the pack

AVAILABILITY:
Azitma® 500mg injection is available in a pack of 1 x 500mg (Lyophilized powder) vial + 5ml sterile water for injection

INSTRUCTIONS:
Keep out of reach of children
Avoid exposure to heat, light and humidity
Store between 15 to 30°C
Improper storage may deteriorate the medicine

ایزیٹما® ۵۰۰ ملی گرام انجکشن
(ایزی تھرومائی سن)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں
ہدایات: بچوں کی پہنچ سے دور رکھیں
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com

R.N-02/HA/01/18

220 mm

71 mm