Summary of Product Characteristics

Azitma® Tablets

Azitma® Suspension

Azitma® Injection

Azitma®
(Azithromycin)

1. NAME OF THE PRODUCT
Azitma® (Azithromycin) 250mg Tablets
Azitma® (Azithromycin) 500mg Tablets

2. QUALITATIVE AND QUANTITATIVE 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

3. PHARMACEUTICAL FORM
Tablet

Appearance:
Azitma® 250mg Tablets: Pink, capsular tablet, engraved "**SAMI**" on one side and plain on other side.
Azitma® 500mg Tablets: Light yellow to yellow colored, film coated oblong shaped tablets, plain on both sides.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Treatment of the following bacterial infections induced by micro-organisms susceptible to azithromycin:

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Community acquired pneumonia
- Skin and soft tissue infections e.g. folliculitis, cellulitis, erysipelas.
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:

This medicine should be taken in a single daily dose. The tablets should be swallowed whole and may be taken with or without food. The length of treatment for various infectious diseases is set out below.

Children and adolescents with a body weight above 45kg, adults and the elderly: The total dosage of azithromycin is 1500mg, staggered over three days (500mg once daily). Alternatively, the dosage may be staggered over five days (500mg as a single dose on the first day, and then 250mg once daily). In the case of uncomplicated *Chlamydia trachomatis* urethritis and cervicitis, the dosage is 1000mg as a single oral dose.

Paediatric population: *Children and adolescents with a body weight below 45kg:* Azithromycin tablets are not suitable for these patients. Other dosage forms of azithromycin may be used, such as suspensions.

Elderly patients: For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

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

Patients with hepatic impairment: Since azithromycin is metabolized in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin.

Method of administration:

Azitma® is for oral use. The tablets can be taken with or without food.

4.3. CONTRAINDICATIONS:

Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients listed.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Hypersensitivity: As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatological reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

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

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

Prolongation of the QT interval: Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization; therefore, caution is required when treating patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia.
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

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

***Clostridium difficile* associated diarrhoea:** *Clostridium difficile* associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis.

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

Renal impairment: In patients with severe renal impairment (GFR <10ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Myasthenia gravis: Exacerbations of the symptoms of myasthenia and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Co-administration with hydroxychloroquine or chloroquine: Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality.

Excipients: ***Sodium:*** This medicine contains less than 1mmol sodium (23mg) per film-coated tablet, that is to say essentially 'sodium-free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

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

Cetirizine: In healthy volunteers, co-administration of a 5-day regimen of azithromycin with 20mg cetirizine at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine): Co-administration of 1200mg/day azithromycin with 400mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

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

Zidovudine: Single 1000mg doses and multiple 1200mg or 600mg 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: 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 (10mg daily) and azithromycin (500mg 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 15mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500mg/day oral dose of azithromycin for 3 days and were then administered a single 10mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in $AUC_{0-\infty}$. 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: Coadministration of a single dose of 600mg azithromycin and 400mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole: Co-administration of a single dose of 1200mg azithromycin did not alter the pharmacokinetics of a single dose of 800mg 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 1200mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800mg 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 500mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single dose of 15mg midazolam.

Nelfinavir: Co-administration of azithromycin (1200mg) and nelfinavir at steady state (750mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was 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 (500mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its major circulating metabolite.

Terfenadine: Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however, there was no specific evidence that such an interaction had occurred.

Theophylline: There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are coadministered to healthy volunteers.

Triazolam: In 14 healthy volunteers, co-administration of azithromycin 500mg on Day 1 and 250mg on Day 2 with 0.125mg 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 (160mg/800mg) for 7 days with azithromycin 1200mg 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.

Hydroxychloroquine and chloroquine: Azithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine. Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin.

4.6. FERTILITY, PREGNANCY AND LACTATION:

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

Breast-feeding: Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7mg/kg/day. As many drugs are excreted in human milk, azithromycin should not be used in the treatment of a lactating woman unless the physician feels that the potential benefits justify the potential risks to the infant.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

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

4.8. UNDESIRABLE EFFECTS:

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

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. The frequency grouping is defined using the following convention: Very common (>_1/10); Common (>_ 1/100 to <1/10); Uncommon (>_1/1,000 to <1/100); Rare (>_ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:

Infections and infestations: ***Uncommon:*** Candidiasis, oral candidiasis, vaginal infection. ***Not known:*** Pseudomembranous colitis.

Blood and lymphatic system disorders: ***Uncommon:*** Leukopenia, neutropenia. ***Not known:*** Thrombocytopenia, haemolytic anaemia.

Immune system disorders: ***Uncommon:*** Angioedema, hypersentivity. ***Not knwon:*** Anaphylactic reactions.

Metabolism and nutrition disorders: ***Common:*** Anorexia.

Psychiatric disorders: ***Uncommon:*** Nervousness. ***Rare:*** Agitation. ***Not known:*** Aggression, anxiety

Nervous system disorders: ***Common:*** Dizziness, headache, paraesthesia, dysgeusia. ***Uncommon:*** Hypoaesthesia, somnolence, insomnia. ***Not known:***

Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis.
Eye disorders: ***Common:*** Visual imapairment
Ear and labyrinth disorders: ***Common:*** Deafness. ***Uncommon:*** Hearing impaired, tinnitus. ***Rare:*** Vertigo.
Cardiac disorders: ***Uncommon:*** Palpitations. ***Not known:*** Torsades de pointes, arrhythmia including ventricular tachycardia.
Vascular disorders: ***Not known:*** Hypotension.
Gastrointestinal disorders: ***Very common:*** Diarrhoea, abdominal pain, nausea, flatulence. ***Common:*** Vomiting, dyspepsia. ***Uncommon:*** Gastritits, constipation. ***Not known:*** Pancreatitis, tongue discoloration.
Hepatobiliary disorders: ***Uncommon:*** Hepatitis. ***Rare:*** Hepatic function abnormal. ***Not known:*** Hepatic failure, which has rarely resulted in death, hepatitis fulminant, hepatic necrosis, jaundice cholestatic.
Skin and subcutaneous tissues disorders: ***Common:*** Pruritus and rash. ***Uncommon:*** Stevens-Johnson syndrome, photosensitivity reaction, urticaria. ***Rare:*** Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms. ***Not known:*** Toxic epidermal necrolysis, erythema multiforme.
Musculoskeletal and connective tissue disorders: ***Common:*** Arthralgia.
Renal and urinary disorders: ***Not known:*** Renal failure acute, nephritis interstitial.
General disorders and administration site conditions: ***Common:*** Fatigue. ***Uncommon:*** Chest pain, oedema, malaise asthenia.
Investigations: ***Common:*** Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased. ***Uncommon:*** Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal. ***Not known:*** Electrocardiogram QT prolonged.

4.9. 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 reversible loss of hearing, severe nausea, vomiting and diarrhoea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.
ATC code: J01FA10.

Mechanism of action: Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl9a-homoerythromycin A. The molecular weight is 749.0. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

5.2. PHARMACOKINETICS:

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

Distribution: Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues. Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5µg/ml up to 52% at 0.05µg azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg. 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.

Elimination: The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days. Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O- demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.

5.3. PRECLINICAL SAFETY DATA:

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

Mutagenic potential: There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

Carcinogenic potential: Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

Reproductive toxicity: In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50mg/kg/day azithromycin and above was observed.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Azitma® 250mg Tablets:

- Dicalcium phosphate
- Pregelatinized starch
- Crosscarmellose sodium
- Sodium lauryl sulphate
- Magnesium stearate
- Hydroxypropyl methyl cellulose
- Titanium dioxide
- Talcum powder
- Poly vinyl pyrrolidone
- Polyethylene glycol
- Simethicone
- Erythrosine lake color
- Purified water

Azitma® 500mg Tablets:

- Dicalcium phosphate
- Pregelatinized starch
- Crosscarmellose sodium
- Sodium lauryl sulphate
- Magnesium stearate
- Hydroxypropyl methyl cellulose
- Titanium dioxide
- Talcum powder
- Poly vinyl pyrrolidone
- Polyethylene glycol
- Simethicone
- Yellow iron oxide color
- Purified water

6.2. INCOMPATIBILITIES:
Not applicable.

6.3. SHELF LIFE:
See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:
Avoid exposure to heat, light and humidity. Store between 15 to 30°C.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:
Azitma® 250mg Tablets: Alu/Alu blister, pack size is 12's.
Azitma® 500mg Tablets: Alu/Alu blister, pack size is 6's.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:
Any unused medicinal product or waste material should be disposed in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:
Azitma® 50mg Tablets: USP Specs.
Azitma® 500mg Tablets: USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)
Azitma® 250mg Tablets: 074899
Azitma® 500mg Tablets: 074900

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
Azitma® 250mg Tablets: 7th August, 2015
Azitma® 500mg Tablets: 7th August, 2015

10. DATE OF REVISION OF THE TEXT

ایزِٹما® ٹیبلٹ

(ایزی تھرومائی سن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں

بچوں کی پہنچ سے دور رکھیں

دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

Azitma®
(Azithromycin)

1. NAME OF THE PRODUCT
Azitma® (Azithromycin) 200mg/5ml Suspension

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

3. PHARMACEUTICAL FORM
Powder for oral suspension

Appearance: Light green to green color granular powder for suspension having characteristic odor.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
Azitma® is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms:

- bronchitis
- community-acquired pneumonia
- sinusitis
- pharyngitis/tonsillitis
- otitis media
- skin and soft tissue infections
- uncomplicated genital infections due to *Chlamydia trachomatis* and *Neisseria gonorrhoeae.*

Considerations should be given to official guidance regarding the appropriate use of antibacterial agents.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
Children over 45kg body weight and adults, including elderly patients: The total dose of azithromycin is 1500mg which should be given over three days (500mg once daily). In uncomplicated genital infections due to *Chlamydia trachomatis,* the dose is 1000mg as a single oral dose. For susceptible *Neisseria gonorrhea* the recommended dose is 2000mg of azithromycin as a single dose together with 500mg of ceftriaxone intramuscularly as a single dose according to local clinical treatment guidelines. For patients who are allergic to

penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

Paediatric population:

Children and adolescents with a body weight below 45 kg: Azithromycin Suspension should be used for children under 45kg. There is no information on children less than 6 months of age. The dose in children is 10mg/kg as a single daily dose for 3 days:

Up to 15kg (less than 3 years): Measure the dose as closely as possible using the measuring dropper provided.

For children weighing more than 15kg: Azithromycin Suspension should be administered using teaspoon according to the following guidance:

- 15-25kg (3-7 years): 5ml (200mg) given as 1 x 5ml teaspoonful, once daily for 3 days.
- 26-35kg (8-11 years): 7.5ml (300mg) given as 1 x 7.5ml teaspoonful, once daily for 3 days.
- 36-45kg (12-14 years): 10ml (400mg) given as 1 x 10ml teaspoonful, once daily for 3 days.

Over 45kg: Dose as per adults: Appropriate pack size to use depending on age/body weight of child. The specially supplied measure should be used to administer azithromycin suspension to children.

Elderly patients: The same dosage as in adult patients is used in the elderly. However, since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

Renal impairment: No dose adjustment is necessary in patients with GFR 10-80ml/min. Caution should be exercised when azithromycin is administered to patients with GFR < 10ml/min.

Hepatic impairment: Since azithromycin is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with azithromycin.

Method of administration:

Azithromycin suspension is for oral administration only. This medicine should be given as a single daily dose. Can be taken with food.

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 and cooled water into bottle. Shake well to form uniform suspension.

Azitma® 200mg/5ml suspension (30ml):

Shake bottle to loosen the mass. Add completely filled freshly boiled and cooled water by the provided measuring spoon (8ml) into bottle and shake well. Repeat

the procedure with an additional 8ml of freshly boiled and cooled water and shake well to form uniform suspension.

4.3. CONTRAINDICATIONS:

Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Hypersensitivity: As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalized exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity: Since 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. 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. 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.

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

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

Prolongation of the QT interval: Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de

pointes, have been seen in treatment with other macrolides, including azithromycin. The following situations may lead to an increased risk for ventricular arrhythmias (including torsades de pointes) which can lead to cardiac arrest (possibly fatal). Azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients with congenital or documented QT prolongation:

- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of Class IA (quinidine and procainamide) and III, (dofetilide, amiodarone and sotalol), cisapride and terfenadine, antipsychotic agents such as pimozide, antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval.

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

***Clostridium difficile* associated diarrhoea:** *Clostridium difficile* associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity form mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile. C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with 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.

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

Renal impairment: In patients with GFR < 10ml/min a 33% increase in systemic exposure to azithromycin was observed.

Myasthenia gravis: Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.

Paediatric population: Safety and efficacy for the prevention or treatment of Mycobacterium avium complex MAC in children have not been established.

Diabetes: Caution in diabetic patients as the suspension contains sugar. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltose insufficiency should not take this medicine. Azithromycin Suspension is for oral administration only.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Antacids: When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma fell by 24%. In patients receiving azithromycin and antacids, azithromycin should be taken at least 1 hour before or 2 hours after the antacid. Co-administration of azithromycin prolonged release granules for oral suspension with a single dose of 20ml co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Cetirizine: In healthy volunteers, co-administration of a 5-day regimen of azithromycin with 20mg cetirizine at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine): Co-administration of 1200mg/day azithromycin with 400mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady state pharmacokinetics of didanosine as compared with placebo.

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

Zidovudine: Single 1000mg doses and multiple 1200mg or 600mg 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: 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 (10mg daily) and azithromycin (500mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase-inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

Carbamazepine: In a pharmacokinetic interaction study in healthy volunteers, no significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single dose of 15mg warfarin administered to healthy volunteers. There have been reports received in the postmarketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500mg/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 AUC0-5 were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in AUC0-∞. 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 single dose of 600mg azithromycin and 400mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole: Co-administration of a single dose of 1200mg 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 1200mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800mg 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 500mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15mg dose of midazolam.

Nelfinavir: Co-administration of azithromycin (1200mg) and nelfinavir at steady state (750mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was 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 (500mg 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 500mg on Day 1 and 250mg on Day 2 with 0.125mg 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 (160mg/800mg) for 7 days with azithromycin 1200mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: In fertility studies conducted in rats, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

Pregnancy: There are no adequate data from the use of azithromycin in pregnant women. In reproduction toxicity studies in animals' azithromycin was shown to pass the placenta, but no teratogenic effects were observed. The

safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore, azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breast-feeding: Limited information available from published literature indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7mg/kg/day. No serious adverse effects of azithromycin on the breast-fed infants were observed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from azithromycin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

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

4.8. UNDESIRABLE EFFECTS:

Azithromycin is well tolerated with a low incidence of side effects. The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics.

The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥ 1/100 to < 1/10,000); Uncommon (≥1/1,000 to < 1/10,000) Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations: ***Uncommon:*** Candidiasis, vaginal infection, pneumonia, fungal infection, bacterial infection, pharyngitis, gastroenteritis respiratory disorder, rhinitis, oral candidiasis. ***Not known:*** Pseudomembranous colitis.

Blood and lymphatic system disorders: ***Uncommon:*** Leukopenia, neutropenia, eosinophilia. ***Not known:*** Thrombocytopenia, haemolytic anaemia.

Immune system disorders: ***Uncommon:*** Angioedema, hypersensitivity. ***Not known:*** Anaphylactic reaction.

Metabolism and nutrition disorders: ***Uncommon:*** Anorexia.

Psychiatric disorders: ***Uncommon:*** Nervousness, insomnia. ***Rare:*** Agitation. ***Not known:*** Aggression, anxiety, delirium, hallucination.

Nervous system disorders: ***Common:*** Headache. ***Uncommon:*** Dizziness, somnolence, dysgeusia, paraesthesia. ***Not known:*** Syncope, convulsion, hypoesthesia, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis.

Eye disorders: ***Uncommon:*** Visual impairment.

Ear and labyrinth disorders: ***Uncommon:*** Ear disorder, vertigo. ***Not known:*** Hearing impairment including deafness and/or, tinnitus.
Cardiac disorders: ***Uncommon:*** Palpitations. ***Not known:*** Torsades de pointes, arrhythmia including ventricular tachycardia, electrocardiogram QT prolonged.
Vascular disorders: ***Uncommon:*** Hot flush. ***Not known:*** Hypotension.
Respirator, thoracic and mediastina l disorders: ***Uncommon:*** Dyspnoea, epistaxis.
Gastrointestinal disorders: ***Very common:*** Diarrhoea. ***Common:*** Vomiting, abdominal pain, nausea. ***Uncommon:*** Gastritis, constipation, flatulence, dyspepsia, abdominal distension, dry mouth, eructation, mouth ulceration, salivary hypersecretion. ***Not known:*** Pancreatitis, tongue discoloration.
Hepatobiliary disorders: ***Rare:*** Hepatic function abnormal Jaundice cholestatic. ***Not known:*** Hepatic failure (which has rarely resulted in death), hepatitis fulminant, hepatic necrosis.
Skin and subcutaneous tissues disorders: ***Uncommon:*** Pruritis, rash, urticaria, dermatitis, dry skin, hyperhydrosis. ***Uncommon:*** Stevens-Johnson syndrome, photosensitivity reaction, urticaria. ***Rare:*** Photosensitivity reaction, acute generalized exanthematous pustulosis (AGEP). ***Not known:*** Toxic epidermal necrolysis, erythema multiforme, Steven John's syndrome.
Musculoskeletal and connective tissue disorders: ***Uncommon:*** Osteoarthritis, myalgia, back pain, neck pain. ***Not known:*** Arthralgia.
Renal and urinary disorders: ***Uncommon:*** Dysuria, renal pain. ***Not known:*** Renal failure acute, nephritis interstitial.
Reproductive system and breast disorders: ***Uncommon:*** Metrorrhagia, testicular disorder.
General disorders and administration site conditions: ***Uncommon:*** Chest pain, oedema, malaise, asthenia, fatigue, face oedema, pyrexia pain, peripheral oedema.
Investigations: ***Common:*** Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased, basophil increased, monocytes increased, neutrophils increased. ***Uncommon:*** Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal, blood alkaline phosphatase increased, chloride increased, glucose increased, platelets increased, hematocrit decreased, bicarbonate increased, abnormal sodium.

4.9. OVERDOSE:

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdose, general symptomatic supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.

ATC code: J01FA10

Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl9a-homoerythromycin A. The molecular weight is 749.0.

Mechanism of action: The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

5.2. PHARMACOKINETICS:

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

Distribution: Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues. Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5µg/ml up to 52% at 0.05µg azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

Elimination: The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days. Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O-demethylation, hydroxylation of desosamine – and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active. 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.

5.3. PRECLINICAL SAFETY DATA:

Phospholipids (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin.

Phospholipids has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The significance of the finding for animals and for humans is unknown.

Mutagenic potential: There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

Carcinogenic potential: Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

Reproductive toxicity: In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50mg/kg/day azithromycin and above was observed.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Sucrose
- Xanthan gum
- Hydroxypropyl cellulose
- Trisodium phosphate anhydrous
- Sucralose
- Silicon dioxide fumed
- Menthol powder flavor
- Blood orange flavor
- Apple green lake color

6.2. INCOMPATIBILITIES:

Not applicable

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat, light and moisture.

Improper storage may deteriorate the medicine.

The reconstituted suspension should be kept at room temperature (below 30°C), and used within 5 days.

Do not freeze.

Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Amber glass bottle with tamper-proof aluminium cap with conical plug, contains 8ml cylindrical measuring spoon. Pack sizes are 15ml and 30ml.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

074902

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

7th August, 2015

10. DATE OF REVISION OF THE TEXT

ایزِٹما® سسپینشن

(ایزی تھرومائی سن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہوجائیگی۔

تیار شدہ سسپینشن کو کمرے کے درجہ حرارت (۳۰ ڈگری سینٹی گریڈ سے کم) پر رکھیں

اور ۵ یوم کے اندر استعمال کرلیں۔

منجمد ہونے سے بچائیں۔

تجویز کردہ خوراک کے مکمل ہونے پر بچ جانے والے محلول کو ضائع کر دیں۔

Azitma®
(Azithromycin)

1. NAME OF THE PRODUCT
Azitma® (Azithromycin) 500mg Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Azitma® 500mg Injection
Each vial contains:
Sterile Powder of Azithromycin Dihydrate USP equivalent to Azithromycin.....500mg

3. PHARMACEUTICAL FORM
Powder for injection

Appearance: White to off white cake or powder.

4. CLINICAL PARTICULARS
4.1. THERAPEUTIC INDICATIONS:
- Azithromycin as powder for injection is indicated for the treatment of community-acquired pneumonia due to susceptible microorganisms, in adult patients where initial intravenous therapy is required.
- Azithromycin as powder for injection is indicated for the treatment of pelvic inflammatory disease (PID) due to susceptible microorganisms, in patients where initial intravenous therapy is required.
- Consideration should be given to official guidance regarding the appropriate use of antibacterial agents.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:
Posology:
The recommended dose of Azithromycin as powder for injection for the treatment of adult patients with community-acquired pneumonia due to the indicated susceptible microorganisms is of 500mg administered as a single intravenous daily dose for at least two consecutive days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 500mg up to 7 to 10 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the clinical response.
The recommended dose of Azithromycin as powder for injection for the treatment of adult patients with pelvic inflammatory disease (PID) due to the indicated susceptible microorganisms is of 500mg administered as a single

intravenous daily dose for one or two days. The intravenous therapy should be followed by the oral administration of azithromycin in a single daily dose of 250mg up to 7 days of treatment. Transition to oral therapy should be carried out when indicated by the doctor and according to the 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 - 80ml/min). Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10ml/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.

Method of administration:

Once Azithromycin as powder for injection is reconstituted and diluted is intended to be administered by intravenous infusion. It should not be administered as an intravenous bolus or an intramuscular injection. The concentration of the solution for infusion and the infusion rate of azithromycin as powder for injection should be 1mg/ml for 3 hours or 2mg/ml for 1 hour.

Preparation of the solution for intravenous administration:

Reconstitution: The initial solution of azithromycin is prepared by adding 4.8ml of sterile water for injections to the 500mg vial and shaking the vial until all the drug is dissolved. It is recommended that a standard 5ml (non-automated) syringe be used to ensure that the exact volume of 4.8ml of sterile water for injections is dispensed. Each ml of reconstituted solution contains azithromycin dihydrate equivalent to 100mg azithromycin (100mg/ml). Parenteral administration drugs should be inspected visually for particulate in suspension prior to administration. If particulate in suspension is evident in reconstituted solution, the drug solution should be discarded. The reconstituted solution must be further diluted 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 to the appropriate amount of any of the diluents listed under *Incompatibilities*.

Final infusion solution concentration (mg/ml)	Amount of diluent (ml)
1.0mg/ml	500ml
2.0mg/ml	250ml

It is recommended that a 500mg dose of azithromycin as powder for injection, diluted according to the instructions above, be administered as an intravenous infusion over at least 60 minutes.

4.3. CONTRAINDICATIONS:

Azithromycin is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin or any of the macrolide or ketolide antibiotics, or to any of the excipients. Azithromycin should not be co-administered with ergot derivatives because of the theoretical possibility of ergotism.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Hypersensitivity: As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatological reactions including acute generalized exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

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

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

Prolongation of the QT interval: Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation therefore, caution is required when treating patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA and III, cisapride and terfenadine.
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia.
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

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

***Clostridium difficile* associated diarrhoea:** *Clostridium difficile* associated diarrhoea (Pseudomembranous colitis - CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibiotics alters the normal flora of the colon allowing an overgrowth of *C. difficile.* Strains of *C. difficile* producing hypertoxin A and B contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile*
cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for *C. difficile* should be considered.

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

Renal impairment: In patients with severe renal impairment (GFR <10ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Myasthenia gravis: Exacerbation of the symptoms of myasthenia and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy. Safety and efficacy of azithromycin intravenous infusion for treatment of infections in children have not been established. Safety and efficacy for prevention or treatment of MAC in children have not been established. Azithromycin should be reconstituted and diluted according to the instructions and should be administered as an intravenous infusion over at least 60 minutes. It should not be administered as an intravenous bolus or an intramuscular injection.

Sodium: This medicinal product contains 6.65mg (0.23mmol) sodium per vial, equivalent to approximately 0.33% of the WHO recommended maximum daily intake of 2g sodium for an adult.

Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS

Antacids: The effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 24%. In patients taking azithromycin by oral administration, azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

Cetirizine: Azithromycin with 20mg cetirizine at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine): Co-administration of 1200mg/day azithromycin with 400mg/day didanosine in six HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared to placebo.

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

Zidovudine: Single 1000mg doses and multiple 1200mg or 600mg 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.

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

Carbamazepine: No significant effect was observed on the plasma levels of carbamazepine or its active metabolite in patients receiving concomitant azithromycin.

Cimetidine: 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: There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin: 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: Coadministration of a single dose of 600mg azithromycin and 400mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole: Co-administration of a single dose of 1200mg azithromycin did not alter the pharmacokinetics of a single dose of 800mg 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 1200mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800mg three times daily for 5 days.

Methylprednisolone: Azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

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

Nelfinavir: Co-administration of azithromycin (1200mg) and nelfinavir at steady state (750mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment was 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: There was no evidence of an effect of azithromycin (500mg daily for 3 days) on the AUC and C_{max}, of sildenafil or its major circulating metabolite.
Terfenadine: 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: No significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.
Trimethoprim/ sulfamethoxazole: Co-administration of trimethoprim/ sulfamethoxazole DS (160mg/800mg) for 7 days with azithromycin 1200mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole.
Hydroxychloroquine and chloroquine: Co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Carefully consider the balance of benefits and risks before prescribing azithromycin for any patients taking hydroxychloroquine. Similar careful consideration of the balance of benefits and risk should also be undertaken before prescribing azithromycin for any patients taking chloroquine, because of the potential for a similar risk with chloroquine.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: Animal data do not suggest an effect of the treatment of azithromycin on male and female fertility. Human data are lacking.
Pregnancy: There are no adequate and well-controlled studies in pregnant women. Azithromycin as powder for Injection should not be used during pregnancy unless the expected benefit to the mother outweighs any potential risk to the foetus.
Breast-feeding: Azithromycin passes into breast milk. Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with Azithromycin. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

There is no evidence to suggest that Azithromycin may have an effect on a patients ability to drive or operate machinery.

4.8. UNDESIRABLE EFFECTS:

Below is the list of adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. The frequency grouping is defined using the following convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥ 1/10,000 to <1/1,000); Very Rare (< 1/10,000); and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations:

Uncommon: Candidiasis, oral candidiasis, vaginal infection.

Not known: Pseudomembranous colitis.

Blood and lymphatic system disorders:

Uncommon: Leukopenia, neutropenia

Not known: Thrombocytopenia, haemolytic anaemia

Immune system disorders:

Uncommon: Angioedema, hypersensitivity

Not known: Anaphylactic reactions

Metabolism and nutrition disorders:

Common: Anorexia

Psychiatric disorders:

Uncommon: Nervousness

Rare: Agitation

Not known: Aggression, anxiety

Nervous system disorders:

Common: Dizziness, headache, paraesthesia, dysgeusia

Uncommon: Hypoaesthesia, somnolence, insomnia

Not known: Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, myasthenia gravis

Eye disorders:

Common: Visual impairment

Ear and labyrinth disorders:

Common: Deafness

Uncommon: Hearing impaired, tinnitus

Rare: Vertigo

Cardiac disorders:

Uncommon: Palpitations

Not known: Torsades de pointes, arrhythmia including ventricular tachycardia.

Vascular disorders:

Not known: Hypotension

Gastrointestinal disorders:

Very common: Diarrhoea, abdominal pain, nausea, flatulence

Common: Vomiting, dyspepsia

Uncommon: Gastritits, constipation

Not known: Pancreatitis, tongue discoloration.
Hepatobiliary disorders:
Uncommon: Hepatitis
Rare: Hepatic function abnormal
Not known: Hepatic failure**, hepatitis fulminant, hepatic necrosis, jaundice cholestatic.
Skin and subcutaneous tissues disorders:
Common: Pruritus and rash
Uncommon: Stevens-Johnson syndrome (SJS), photosensitivity reaction, urticaria
Rare: Acute Generalized Exanthematous Pustulosis (AGEP)
Very rare: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Not known: Toxic epidermal necrolysis (TEN), erythema multiforme
Musculoskeletal and connective tissue disorders
Common: Arthralgia
Renal and urinary disorders:
Not known: Renal failure acute, nephritis interstitial
General disorders and administration site conditions:
Common: Fatigue, pain and inflammation on the local injection site*
Uncommon: Chest pain, oedema, malaise, asthenia
Investigations:
Common: Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased.
Uncommon: Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal.
Not known: Electrocardiogram QT prolonged
* Have been reported with the intravenous administration of azithromycin.
** which has rarely resulted in death

4.9. 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 reversible loss of hearing, severe nausea, vomiting and diarrhoea. In the event of overdose, general symptomatic treatment and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES
5.1. PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.
ATC code: J01FA10

Mechanism of action: Azithromycin is a macrolide antibiotic belonging to the azalide group. The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl9a-homoerythromycin A. The molecular weight is 749.0. The mechanism of action of azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

5.2. PHARMACOKINETICS:

Absorption: Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2 to 3 hours after taking the medicinal product. The administration of azithromycin capsules after a substantial meal reduces bioavailability. In patients hospitalized with community-acquired pneumonia treated with a single daily intravenous infusion of 500mg azithromycin, over one hour, in a solution with a concentration of 2mg/ml.

Distribution: Orally administered azithromycin is widely distributed throughout the body. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogen agents after a single dose of 500mg. High azithromycin concentrations were detected in gynecological tissue 96 hours after a single dose of 500mg azithromycin.

Biotransformation/Elimination: The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 days. The amount of administered azithromycin dose excreted in urine in 24 hours was about 11% after the 1st dose and 14% after the 5th dose. These values are higher than the reported 6% as being excreted unchanged in urine after oral administration of azithromycin.

5.3. PRECLINICAL SAFETY DATA:

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

Mutagenic potential: There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

Carcinogenic potential: Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

Reproductive toxicity: In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats,

azithromycin doses of 100 and 200mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50mg/kg/day azithromycin and above was observed.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Citric acid anhydrous
- Sodium hydroxide
- Water for Injection

6.2. INCOMPATIBILITIES:

This medicinal solution must not be mixed with other medicinal product except following:

- 0.9% sodium chloride
- 0.45% sodium chloride
- 5% dextrose in water
- Lactated Ringer's solution
- 5% dextrose in 0.3% sodium chloride
- 5% dextrose in 0.45% sodium chloride

Other intravenous substances, additives or other medications should not be added or infused simultaneously through the same intravenous line.

6.3. SHELF LIFE:

Unopened vial: See expiry on the pack.

Reconstituted vial: The reconstituted solution is stable for 24 hours at room temperature or for 7 days in refrigerator.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless the reconstitution / dilution has taken place in controlled and validated aseptic conditions.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Avoid exposure to heat, light and humidity. Store between 15 to 30°C.

Improper storage may deteriorate the medicine.

Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Powder for Injection: 8ml clear colorless glass vial USP Type-I, with bromobutyl rubber stopper with flip off seal.

Sterile Water for Injection: Clear 5ml ampoule (USP Type-I).

Pack size is 1 vial & 1 ampoule.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Azithromycin as powder for injection is supplied in single dose vials. Parenteral administration drugs should be inspected visually for particulate in suspension prior to administration. If particulate in suspension is evident in the reconstituted solution, it should be discarded. It is recommended that the 500mg dose of azithromycin as powder for solution for infusion, diluted as described above, be administered as an intravenous infusion over at least 60 minutes. Azithromycin should not be administered as an intravenous bolus or an intramuscular injection. Any unused product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

USP Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

079591

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

4th November, 2015

10. DATE OF REVISION OF THE TEXT

ایزِٹما® ۵۰۰ ملی گرام انجکشن

(ایزی تھرومائی سن)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت 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 انجکشن کمرے کے درجہ حرارت پر ۲۴ گھنٹے یا ریفریجریٹر میں ۷ دن تک رکھنے کی صورت میں قابل استعمال رہتا ہے۔