1.5 Product Information

1.5.1 Summary of Product Characteristics

1. Name of the Medicinal Product

1.1 Trade Name : **AZITO SUSPENSION**
(Azithromycin for Oral Suspension USP 200 mg)

1.2 Strength : 200 mg/5 mL

1.3 Pharmaceutical Form : Powder for oral suspension

2. Qualitative and Quantitative Composition

S. No	**Name of Material**	**Quantity / 5 mL suspension (mg)**
Active Substance		
1	Azithromycin Dihydrate Eq. to Azithromycin	209.64 ≈200.00
Inactive Substance		
2	Sucrose	2152.1936
3	Cetostearyl Alcohol	8.6667
4	Polyoxyl 20 Cetostearyl Ether	0.8333
5	Simeticone	19.3333
6	Tribasic Sodium Phosphate Dodecahydrate	23.3333
7	Saccharin Sodium	23.3333
8	Sodium Chloride	20.0000
9	Carmellose Sodium	9.3333
10	Aspartame	33.3333
11	Banana D.C. Flavour (Powder)	100.0000
12	Sodium Carbonate (Anhydrous)	33.3333
13	Colloidal Anhydrous Silica	33.3333
14	Dichloromethane	Q.S.
15	Purified Water	Q.S.
	Total	**2666.67**

3. Pharmaceutical Form
Powder for oral suspension

White to off-white free flowing granular powder, after reconstitution it gives white to off-white color suspension having banana flavored taste.

4. Clinical Particulars

4.1 Therapeutic indications

Azithromycin 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.*

4.2 Posology and method of administration

Posology

Azithromycin should be given as a single daily dose.

Children over 45 kg body weight and adults, including elderly patients: The total dose of azithromycin is 1500 mg which should be given over three days (500 mg once daily).

In uncomplicated genital infections due to *Chlamydia trachomatis*, the dose is 1000 mg as a single oral dose. For susceptible *Neisseria gonorrhoeae* the recommended dose is 1000 mg or 2000 mg of azithromycin in combination with 250 mg or 500 mg ceftriaxone according to local clinical treatment guidelines. For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

Paediatric population:

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

Up to 15 kg (less than 3 years): Measure the dose as closely as possible using the 10 ml oral dosing.

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

15-25 kg (3-7 years): 5 ml (200 mg) given as 1 × 5 ml cap, once daily for 3 days.

26-35 kg (8-11 years): 7.5 ml (300 mg) given as 1 × 7.5 ml cap, once daily for 3 days.

36-45 kg (12-14 years): 10 ml (400 mg) given as 1 × 10 ml cap, once daily for 3 days.

***Over 45 kg: Dose as per adults*.**

The specially supplied measure should be used to administer Azithromycin suspension to children.

Renal impairment:

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

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.

Method of administration

For oral use.

Azithromycin Suspension can be taken with or without food.

Method of reconstitution

1. Tap the bottle to loosen the powder.
2. Slowly add boiled and cooled water up to the ring mark on bottle.
3. Shake vigorously to mix medicine properly.
4. Add water if necessary to adjust the volume up to the ring mark.
5. Not to be injected.
6. Shake well before each dose.

4.3 Contraindication

Azithromycin is contra-indicated in patients with a known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

4.4 Special warnings and special precautions for use

Hypersensitivity: As with erythromycin and other macrolides, serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), Acute Generalized Exanthematous Pustulosis (AGEP) 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.

Hepatotoxicity: The use of azithromycin should be undertaken with caution in patients with significant hepatic disease. 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: Because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administrated.

Prolongation of the QT interval: Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides. Caution is required when treating patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substance known to prolong QT interval such as antiarrhythmics of Classes Ia and III, cisapride and terfenadine
- With electrolyte disturbance, particularly in case 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 is recommended.

Clostridium difficile associated diarrhoea: Clostridium difficile associated diarrhoea (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 2 months after the administration of antibacterial agents. Discontinuation of therapy with azithromycin and the administration of specific treatment for C. difficile should be considered.

Renal impairment: In patients with severe renal impairment (GFR <10 ml/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.

Diabetes: Caution in diabetic patients as suspension contains sucrose.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This product also contains Aspartame which is the source of phenylalanine. May be harmful for people with phenylketonuria.

4.5 Interaction with other medicinal products and other forms of interaction
Digoxin and colchicine: Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, the 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.

Zidovudine: Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.
Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

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

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

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 anticoagulants.

Ciclosporin: If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Co-administration of Antacid, Cetirizine, Didanosine (Dideoxyinosine), Carbamazepine, Cimetidine, Efavirenz, Fluconazole, Indinavir, Methylprednisolone, Midazolam, Nelfinavir, Sildenafil, Terfenadine, Theophylline, Triazolam, Trimethoprim/sulfamethoxazole with Azithromycin does not show any interaction.

4.6 Fertility, pregnancy and lactation
Pregnancy: Azithromycin should be used during pregnancy only if clearly needed.

Breast feeding: 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
The frequencies of adverse reactions are ranked according to the following convention. 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).

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 reaction

Metabolism and nutrition disorder
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 : Gastritis, constipation
Not known : Pancreatitis, tongue discolouration

Hepatobiliary disorders
Uncommon : Hepatitis
Rare : Hepatic function abnormal
Not known : Hepatic failure, hepatitis fulminant, hepatic necrosis, jaundice cholestatic

Skin and subcutaneous tissue disorders
Common : Pruritus and rash
Uncommon : SJS, photosensitivity reaction, urticaria
Rare : Acute Generalized Exanthematous Pustulosis (AGEP)
Not known : TEN, erythema multiforme

Musculoskeletal and connective tissue disorders
Common : Arthralgia

Renal and urinary disorders
Not known : Renal failure acute, nephritis interstitial

General disorders and adverse reaction related to administration site.
Common : Fatigue
Uncommon : Chest pain, oedema, malaise, asthenia

Diagnostic 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
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 Pharmacodynamics properties
Pharmacotherapeutic group : Antibacterial for systemic use.
ATC code : J01FA10
Mode 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-methyl-9a-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.

Mechanism of resistance: Resistance to azithromycin may be inherent or acquired. There are three main mechanisms of resistance in bacteria: target site alteration, alteration in antibiotic transport and modification of the antibiotic.

Azithromycin demonstrates cross resistance with erythromycin resistant gram positive isolates. A decrease in macrolide susceptibility over time has been noted particularly in Streptococcus pneumoniae and Staphylococcus aureus. Similarly, decreased susceptibility has been observed among Streptococcus viridans and Streptococcus agalactiae (Group B) streptococcus against other macrolides and lincosamides.

Azithromycin is susceptible against following microorganisms:

Aerobic Gram-positive microorganisms
Staphylococcus aureus: Methycillin-susceptible
Streptococcus pneumoniae: Penicillin-susceptible
Streptococcus pyogenes (Group A)

Aerobic Gram-negative microorganisms
Haemophilus influenzae, Haemophilus parainfluenzae, Legionella pneumophila, Moraxella catarrhalis, Neisseria gonorrhoeae, Pasteurella multocida

Anaerobic microorganisms
Clostridium perfringens, Fusobacterium spp., Prevotella spp., Porphyromonas spp.
Other microorganisms

Chlamydia trachomatis

Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Streptococcus pneumoniae, Penicillin-intermediate, Penicillin-resistant
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Enterococcus faecalis, Staphylococci MRSA, MRSE*

Anaerobic microorganisms
Bacteroides fragilis group
*Methycillin-resistant staphylococci have a very high prevalence of acquired resistance to macrolides and have been placed here because they are rarely susceptible to azithromycin.

5.2 Pharmacokinetic Properties
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. 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 0.5 microgram/ml up to 52% at 0.05 microgram 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 to 4 days.

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.
Carcinogenic potential:
Long-term studies in animals have not been performed to evaluate carcinogenic potential.
Mutagenic potential:
There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.
Reproductive toxicity:
Teratogenic effects were not observed in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/ day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above.

6. Pharmaceutical Particulars
6.1 List of excipients

Sucrose
Cetostearyl Alcohol
Polyoxyl 20 Cetostearyl Ether
Simeticone
Tribasic Sodium Phosphate Dodecahydrate
Saccharin Sodium
Sodium Chloride
Carmellose Sodium
Aspartame
Banana D.C. Flavour (Powder)
Sodium Carbonate (Anhydrous)
Colloidal Anhydrous Silica

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 Months from the date of manufacture.

6.4 Special precautions for storage
Before reconstitution store below 30°C.
After reconstitution store the suspension at 5°C to 30°C.
After reconstitution use within 7 days.
Do not freeze.
Keep out of reach and sight of children.

6.5 Nature and contents of container
200 mg powder for oral suspension packed in 30 mL HDPE Bottle.

6.6 Special precautions for disposal and other handling
No special requirement.

7. Marketing Authorization Holder
ZIM Laboratories Limited
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441 501,
Maharashtra State, India

Manufacturing Site Addresses:
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 4401501,
Maharashtra State,
India.

8. Marketing Authorization Number
TAN 22 HM 0346

9. Date of First Registration / Renewal of the Registration
21/09/2022

10. Date of Revision of the Text

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