3. Pharmaceutical Form

Powder for Oral Suspension

White to off white free flowing granular powder after reconstitution it gets a white to off white colour suspension having flavoured sweet taste.

4. Clinical Particulars

4.1 Therapeutic indications

Azithromycin is indicated for infections caused by susceptible organisms; in lower respiratory tract infections including bronchitis and pneumonia, in skin and soft tissue infections, in acute otitis media and in upper respiratory tract infections including sinusitis and pharyngitis/tonsillitis. (Penicillin is the usual drug of choice in the treatment of *Streptococcus pyogenes* pharyngitis, including the prophylaxis of rheumatic fever. Azithromycin is generally effective in the eradication of streptococci from the oropharynx, however, data establishing the efficacy of azithromycin and the subsequent prevention of rheumatic fever are not available at present.)

In sexually transmitted diseases in men and women, azithromycin is indicated in the treatment of uncomplicated genital infections due to *Chlamydia trachomatis*. It is also indicated in the treatment of chancroid due to *Haemophilus ducreyi* and uncomplicated genital infection due to non-multiresistant *Neisseria gonorrhoea*; concurrent infection with *Treponema pallidum* should be excluded.

4.2 Posology and method of administration

Posology

Azithromycin Oral

Oral azithromycin should be administered as a single daily dose. The period of dosing with regard to infection is given below.

Azithromycin powder for oral suspension can be taken with or without food.

In adults

For the treatment of sexually transmitted diseases caused by *Chlamydia trachomatis* and *Haemophilus ducreyi*, the dose is 1000 mg as a single oral dose. For susceptible *Neisseria gonorrhoeae*, the 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.

In children

The maximum recommended total dose for any treatment is 1500 mg for children.

In general, the total dose in children is 30 mg/kg. Treatment for pediatric streptococcal pharyngitis should be dosed at a different regimen.

The total dose of 30 mg/kg should be given as a single daily dose of 10 mg/kg daily for 3 days, or given over 5 days with a single daily dose of 10 mg/kg on Day 1, then 5 mg/kg on Days 2-5.

As an alternative to the above dosing, treatment for children with acute otitis media can be given as a single dose of 30 mg/kg.

For pediatric streptococcal pharyngitis, azithromycin given as a single dose of 10 mg/kg or 20 mg/kg for 3 days has been shown to be effective; however, a daily dose of 500 mg must not be

exceeded. In clinical trials comparing these two dosage regimens, similar clinical efficacy was observed but greater bacteriologic eradication was evident at the 20 mg/kg/day dose. However, penicillin is the usual drug of choice for the treatment of Streptococcus pyogenes pharyngitis, including prophylaxis of rheumatic fever. For children weighing less than 15 kg, azithromycin suspension should be measured as closely as possible. For children weighing 15 kg or more, azithromycin suspension should be administered according to the guide provided below.

Azithromycin Suspension 30 mg/kg Total Treatment Dose	
Weight (kg)	**3 Day Regimen**
<15	10 mg/kg once daily on days 1-3.
15-25	200 mg (5 ml) once daily on days 1-3.
26-35	300 mg (7.5 ml) once daily on days 1-3.
36-45	400 mg (10 ml) once daily on days 1-3.
>45	Dose as per adults.

Special populations:
In the Elderly
The same dosage as in adult patients is used in the elderly. Elderly patients may be more susceptible to the development of torsades de pointes arrhythmia than younger patients.
In Patients with 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)
In Patients with Hepatic Impairment: The same dosage as in patients with normal hepatic function may be used in patients with mild to moderate hepatic impairment.

Method of administration
For Oral use.
Before use the powder should be reconstituted with water, after reconstitution it gets white to off-white color suspension having flavored sweet taste.

Method of reconstitution
1. Tap the bottle to loosen the powder.
2. Add 10 mL of boiled and cooled water in bottle.
3. Shake vigorously to mix medicine properly.
4. Not to be injected.
5. Shake well before each dose.

4.3 Contraindication
The use of Azithromycin Suspension is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any excipient used in the formulation.

4.4 Special warnings and special precautions for use
Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema 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 liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease.
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.

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.

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.

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

***Clostridium difficile*-associated diarrhea**
Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of C. difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. Hypertoxin-producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

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

Diabetes
Azithromycin 200 mg/5ml powder for oral suspension:
Caution in diabetic patients: 5 ml of reconstituted suspension contains 2.14 g of sucrose.
Due to the sucrose content this medicinal product is not indicated for persons with fructose intolerance (hereditary fructose intolerance), glucose-galactose malabsorption or saccharase-isomaltase deficiency.

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 macrolides, including azithromycin. Prescribers should consider the risk of QT prolongation, which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:

- Patients with congenital or documented QT prolongation.
- Patients currently receiving treatment with other active substances known to prolong QT interval, such as antiarrhythmics of Classes IA and III, antipsychotic agents, antidepressants, and fluoroquinolones.
- Patients with electrolyte disturbance, particularly in cases of hypokalemia and hypomagnesemia.
- Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency.
- Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval.

Myasthenia gravis
Exacerbations of the symptoms of myasthenia gravis have been reported in patients receiving azithromycin therapy.

4.5 Interaction with other medicinal products and other forms of interaction
Antacids: 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: Co-administration of a 5-day regimen of azithromycin with cetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.
Didanosine (Dideoxyinosine): Co-administration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine.
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.
Ergot derivatives:
There is a theoretical possibility of interaction between azithromycin and ergot derivatives.

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.

The Pharmacokinetic studies between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

*Atorvastatin***:** Co-administration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin.

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

Cimetidine: Administration of a single dose of cimetidine given 2 hours before azithromycin no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants: There have been reports 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.

Cyclosporin: Caution should be exercised before considering concurrent administration of cyclosporin and azithromycin. If co-administration of these drugs is necessary, Cyclosporin levels should be monitored and the dose adjusted accordingly.

*Efavirenz**:*** Co-administration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole: Co-administration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life of azithromycin were unchanged by the co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Indinavir: Co-administration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

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

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

Nelfinavir: Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.
Rifabutin: Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.
Neutropenia was observed in patients 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 (500 mg daily for 3 days) on the AUC and Cmax, 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.
Trimethoprim/sulfamethoxazole: Co-administration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole.

4.6 Pregnancy and lactation

No evidence of harm to the fetus due to azithromycin was found. However there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, azithromycin should be used during pregnancy only if clearly needed.
Lactation
Limited information indicates that azithromycin is present in human milk at an estimated highest median daily dose of 0.1 to 0.7 mg/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.
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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following undesirable effects have been reported.
Blood and Lymphatic System Disorders:
Transient episodes of mild neutropenia.

Ear and Labyrinth Disorders:
Hearing impairment (including hearing loss, deafness and/or tinnitus).
Gastrointestinal Disorders:
Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps), and flatulence.
Hepatobiliary Disorders:
Abnormal liver function.
Skin and Subcutaneous Tissue Disorders:
Allergic reactions including rash and angioedema.

In post-marketing experience:
Infections and Infestations:
Moniliasis and vaginitis.
Blood and Lymphatic System Disorders:
Thrombocytopenia.
Immune System Disorders:
Anaphylaxis (rarely fatal).
Metabolism and Nutrition Disorders:
Anorexia.
Psychiatric Disorders:
Aggressive reaction, nervousness, agitation and anxiety.
Nervous System Disorders:
Dizziness, convulsions, headache, hyperactivity, hypoesthesia, paresthesia, somnolence, and syncope.
There have been rare reports of taste/smell perversion and/or loss.
Ear and Labyrinth Disorders:
Deafness, tinnitus, hearing impaired and vertigo.
Cardiac Disorders:
Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongations and torsades de pointes.
Vascular Disorders:
Hypotension.
Gastrointestinal Disorders:
Vomiting/diarrhea (rarely resulting in dehydration), dyspepsia, constipation, pseudomembranous colitis, pancreatitis, and rare reports of tongue discoloration.
Hepatobiliary Disorders:
Hepatitis and cholestatic jaundice have been reported, as well as rare cases of hepatic necrosis and hepatic failure, which have resulted in death.
Skin and Subcutaneous Tissue Disorders:
Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious cutaneous adverse reactions including erythema multiforme, AGEP, SJS, TEN and DRESS.
Musculoskeletal and Connective Tissue Disorders:
Arthralgia.
Renal and Urinary Disorders:
Interstitial nephritis and acute renal failure.
General Disorders and Administration Site Conditions:
Asthenia, fatigue, and malaise.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group : Antibacterials for systemic use

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 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.

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.

Antibacterial spectrum of Azithromycin:

Commonly susceptible species

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:

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 ere because they are rarely susceptible to azithromycin.

5.2 Pharmacokinetic Properties

Absorption: Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2-3 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 0.5 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 2-4 days. Very high concentrations of unchanged azithromycin have been found in human bile together with in metabolites, formed by N- and O-demethylation, by hydroxylation of desosamine and aglycone rings and by cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses suggests that metabolites play no part in the microbiological activity 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.
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.
Mutagenic potential:
There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.
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 200 mg/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 50 mg/kg/day azithromycin and above was observed.

6. Pharmaceutical Particulars

6.1 List of excipients

Simethicone
Cetostearyl Alcohol
Sucrose
Polyoxyl 20 Cetostearyl Ether
Trisodium Phosphate Dodecahydrate
Sodium Chloride
Saccharin Sodium
Colloidal Anhydrous Silica
Carmellose Sodium
Methyl Hydroxybenzoate
Propyl Hydroxybenzoate
Aspartame
Sodium Carbonate (Anhydrous)
Banana D.C. Flavour

6.2 Incompatibilities

None

6.3 Shelf life

3 years from the date of manufacture

6.4 Special precautions for storage

Before reconstitution store below 30 °C.
After reconstitution store the suspension at 25°C to 30 °C.
Discard the reconstituted suspension if more than 10 days.
Do not freeze.
Shake will before use.

6.5 Nature and contents of container

15 ml HDPE Bottle.

6.6 Special precautions for disposal and other handling

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

7. Marketing Authorization Holder

ZIM Laboratories Limited
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441501
Maharashtra State,
India.

8. Number(S) In the National Register of Finished pharmaceutical products
NA

9. Date of First Authorization/Renewal of the Authorization
NA

10. Date of Revision of the Text
19 May 2019