AZIREN 100
Azithromycin Oral Suspension 100 mg/5 ml

COMPOSITION:
Each 5 ml Contains :
Azithromycin Dihydrate USP
Eq. to Anhydrous Azithromycin 100 mg
Flavour Syrup Base q.s.
Colour : Erythrosine

DESCRIPTION:
Azithromycin is a macrolide antibiotic belonging to the azalide group. By binding to the 50 S ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

INDICATION:
Aziren 100 is indicated for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin:
- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- Skin and soft tissue infections
- Uncomplicated *Chlamydia trachomatis* urethritis and cervicitis

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

PHARMACOKINETICS:
Absorption
Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (Cmax) after a single dose of 500 mg is approximately 0.4 µg/ml.
Distribution
After oral administration, azithromycin is distributed throughout the entire body. Pharmacokinetic studies have shown clearly higher azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities.
Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.
The protein binding of azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.
Excretion
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 is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml azithromycin, 2 days after a 5-day course of treatment, have been found in human bile. Ten metabolites have been identified (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggest that the metabolites do not play a role in the microbiological activity of azithromycin.

PHARMACODYNAMICS:
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-methyl-9a-homoerythromycin A. The molecular weight is 749.0.
Mode of action:
Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50 S ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.
PK/PD relationship:
For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.
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.
Complete cross resistance exists among *Streptococcus pneumoniae,* betahaemolytic *streptococcus* of group *A, Enterococcus faecalis* and *Staphylococcus aureus,* including methicillin resistant *S. aureus* (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

POSOLOGY AND METHOD OF ADMINISTRATION:
Azic Oral Suspension can be taken with or without food. Shake the bottle well before you use the Suspension.

PEDIATRIC DOSAGE GUIDELINES FOR OTITIS MEDIA, ACUTE BACTERIAL SINUSITIS, AND COMMUNITY-ACQUIRED PNEUMONIA:
Age 6 months and above: Based on Body Weight

OTITIS MEDIA AND COMMUNITY-ACQUIRED PNEUMONIA: (5-Day Regimen)*

Dosing Calculated on 10 mg/kg/day Day 1 and 5 mg/kg/day Days 2 to 5.

Weight	100 mg/5 ml		200 mg/5 ml		Total ml per Treatment Course	Total mg per Treatment Course
Kg	**Day 1**	**Day 2-5**	**Day 1**	**Day 2-5**		
5	2.5ml; (½ tsp)	1.25 ml; (¼ tsp)			7.5 ml	150 mg
10	5 ml; (1 tsp)	2.5 ml; (½ tsp)			15 ml	300 mg
20			5 ml; (1 tsp)	2.5 ml; (½ tsp)	15 ml	600 mg
30			7.5 ml; (1½ tsp)	3.75 ml; (¾ tsp)	22.5 ml	900 mg
40			10 ml; (2 tsp)	5 ml; (1 tsp)	30 ml	1200 mg
50 & Above			12.5 ml; (2½ tsp)	6.25 ml; (1¼ tsp)	37.5 ml	1500 mg

*Effectiveness of the 3-day or 1-day regimen in pediatric patients with community-acquired pneumonia has not been established.

OTITIS MEDIA AND ACUTE BACTERIAL SINUSITIS: (3-Day Regimen)

Dosing Calculated on 10 mg/kg/day

Weight	100 mg/5 ml	200 mg/5 ml	Total ml per Treatment Course	Total mg per Treatment Course
Kg	Days 1-3	Days 1-3		
5	2.5 mL; (½ tsp)		7.5 ml	150 mg
10	5 mL; (1 tsp)		15 ml	300 mg
20		5 ml; (1 tsp)	15 ml	600 mg
30		7.5 ml; (1½ tsp)	22.5 ml	900 mg
40		10 ml; (2 tsp)	30 ml	1200 mg
50 & Above		12.5 ml; (2½ tsp)	37.5 ml	1500 mg

*Effectiveness of the 5-day or 1-day regimen in pediatric patients with acute bacterial sinusitis has not been established.

Amount of water to be added	**Total volume after constitution (azithromycin content)**	**Azithromycin concentration after constitution**
9 mL (300 mg)	15 mL (300 mg)	100 mg/5 mL
9 mL (600 mg)	15 mL (600 mg)	200 mg/5 mL

PEDIATRIC DOSAGE GUIDELINES FOR PHARYNGITIS/ TONSILLITIS:
(Age 2 years and above) Based on Body Weight
Constituting instructions for Azithromycin Oral Suspension 300, 600, 900, 1200 mg bottles. The table below indicates the volume of water to be used for constitution:
Shake well before each use. Oversized bottle provides shake space. Keep tightly closed.

Method of administration
Oral

CONTRAINDICATION:
Azithromycin for oral suspension is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic.

SPECIAL WARNING AND PRECAUTION FOR USE:
As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
Since 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.
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.
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 ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.
Superinfections:
As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with non-susceptible micro-organisms like fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.
Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from 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 two months after the administration of antibacterial agents.
In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.
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, including azithromycin. Therefore as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as patients: - With congenital or documented acquired QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class 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.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.
Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex (MAC) in children have not been established.

INTERACTION WITH OTHER MEDICINE AND CONCOMITANT USE:
Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with azithromycin, no effect on overall bioavailability was seen, although peak serum levels were reduced by approximately 25%. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.
Cetirizine: In healthy volunteers, 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.
Didanosins (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 as compared with placebo.
Digoxin (P-gp substrates):
Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.
Zidovudine: Single 1000 mg doses and multiple doses of 600 mg or 1200 mg 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.
Ergotamine 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.
Astemizole, alfentanil:
There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with Azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid antibiotic erythromycin.
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). 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.
Fluconazole: Coadministration 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 coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.
Indinavir: Coadministration 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.

PREGNANCY AND LACTATION:
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.
Lactation:
Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.
Fertility:
In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
No data are available regarding the influence of azithromycin on a patient's ability to drive or operate machinery.

ADVERSE REACTION:
The table below lists the adverse reactions. 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:

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

INCOMPATIBILITY:
Not applicable.

SHELF LIFE:
3 Years

PACKAGING:
15 ml HDPE bottle packed in a carton along with pack insert and two sided spoon.

STORAGE CONDITION:
Store in dry place below 30^0C. Protect from light & moisture.
Keep the cap tightly close after use.
Keep the medicine out of reach of children.
SHAKE WELL BEFORE USE.

MARKETED AND DISTRIBUTED BY:
HTAT THIHA PAING CO. LTD.
No.(19) ,1st Floor, Nat Sin Street, Kyauk Myaung,
Tamwe Township, Yangon Region, Myanmar

MANUFACTURED BY:
CIAN HEALTHCARE LTD.
(An ISO 9001:2015 & WHO-GMP Certified Co.)
Khasra No. 248, Vill. Sisona, Bhagwanpur,
Roorkee, Distt. Haridwar, Uttarakhand - 247661, India.