ZIM LABORATORIES LIMITED B-21/22, MIDC Area, Kalmeshwar - 441501, Dist. Nagpur, Maharashtra, India	**Rev.00**

Product Name : Leaflet of KIDIMAC

(Azithromycin for Oral Suspension USP 200 mg)

Malaysia

Size : (L) 300 x (W) 280 (After fold (L) 75 x (W) 35 mm	Date of Preparation : 25/06/2020
Material : 60 GSM, Maplitho Paper (Export quality)	Artwork Code : *P6372/X/XX/XX
Other Instruction : Not Applicable	Language : English
Colours : Black ■ Black	Folding : Six Folds (Three Vertical and Three Horizontal)

*P6372/X/XX/XX Where X is variable and it will be change at the time of commercialised.

KIDIMAC

Azithromycin for Oral Suspension USP 200 mg/5 ml

Product Name:
Brand Name : KIDIMAC
Generic Name : Azithromycin for Oral Suspension USP 200 mg/5ml

Name and Strength of Active ingredients(s):
Each 5 ml of reconstituted suspension contains:

Azithromycin Dihydrate	USP
Eq. to Azithromycin	200 mg

Product Description:
White to off-white free flowing granular powder, after reconstitution it get white to off white color suspension having flavored sweet taste.
Odour of Powder: The odour of powder is like a banana.

Pharmacodynamics:
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 here because they are rarely susceptible to azithromycin.

Pharmacokinetics:
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. 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. Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following 3 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.

Indication:
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.

Recommended Dose:
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. 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	5 Day Regimen
<15	10 mg/kg once daily on days 1-3	10 mg/kg on day 1, then 5 mg/kg once daily on days 2-5.
15-25	200 mg (5 ml) once daily on days 1-3	200 mg (5 ml) on day 1, then 100 mg (2.5 ml) once daily on days 2-5.
26-35	300 mg (7.5 ml) once daily on days 1-3.	300 mg (7.5 ml) on day 1, then 150 mg (3.75 ml) once daily on days 2-5
36-45	400 mg (10 ml) once daily on days 1-3.	400 mg (10 ml) on day 1, then 200 mg (5 ml) once daily on days 2-5.
>45	Dose as per adults	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.

Mode 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.

Contraindications:
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.

Warnings and precautions for use:
Hypersensitivity
In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalised exanthematous pustulosis (AGEP)], KIDIMAC should be discontinued immediately and appropriate treatment should be urgently initiated.

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.

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-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, including azithromycin. Prescriber 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 substance known to prolong QT interval such as antiarrhytmics of classes IA and III, antipsychotic agents, antidepressants and fluoroquinolones.
- Patients with electrolyte disturbance, particularly in case of hypokalaemia and hypomagnesemia.
- Patients 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.

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

Clostridium difficile associated diarrhoea (CDAD):
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. 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.

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

Diabetes
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), glucosegalactose malabsorption or saccharase-isomaltase deficiency.
This product contains the Aspartame which is unsuitable for phenylketonurics.

Interaction with other Medicaments
Antacids: No effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 24%. In patients receiving both oral 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 patients did not appear to affect the steady-state pharmacokinetics of didanosine.
Digoxin: Azithromycin concomitant with digoxin the possibility of raised digoxin levels should be borne in mind.
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.
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 C max (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 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.
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.

Pregnancy and lactation
Pregnancy: Azithromycin should be used during pregnancy only if clearly needed.
Breast feeding: 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.

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

Undesirable Effects:
The following undesirable effects have been reported.
Blood and Lymphatic System Disorders:
Transient episodes of mild neutropenia, Leukopenia, haemolytic anaemia.
Ear, Eye and Labyrinth Disorders:
Hearing impairment (including hearing loss, deafness and/or tinnitus), Visual impairment.
Gastrointestinal Disorders:
Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps), and flatulence.
Hepatobiliary Disorders:
Abnormal liver function.
Skin and Subcutaneous Tissue Disorders:
Frequency not known: Severe cutaneous adverse reaction (SCARs) including Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), Drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalized exanthematous pustulosis (AGEP).

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.

Post marketing Experience:
Cardiac Disorders: Palpitations and arrhythmias including ventricular tachycardia have been reported. There have been rare reports of QT prolongation and torsades de pointes (see Warnings and Precautions).
Gastrointestinal Disorders: infantile hypertrophic pyloric stenosis.

Overdose and Treatment:
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.

Instructions for Use:
For 30 ml:
Tap the bottle to loosen the powder. Slowly add boiled and cooled water upto the ring of mark on bottle. Shake vigorously to mix medicine properly. Add water if necessary to adjust the volume upto the ring mark. Not to be injected.
Do not use the tap water for reconstitution

For 15 ml:
Tap the bottle to loosen the powder. Add 10ml of boiled and cooled water in bottle. Shake vigorously to mix medicine properly. Not to be injected.
Do not use the tap water for reconstitution.

Storage Conditions
Before reconstitution store below 30 °C. After reconstitution store the suspension at 25°C to 30 °C. Reconstituted suspension should be used within 10 days. Discard the reconstituted suspension if more than 10 days. Do not freeze. Shake well before use.

Dosage forms and Packaging Available:
Dosage Form : Powder for Oral Suspension
Packaging : 30 mL HDPE Bottle
15 mL HDPE Bottle

Manufactured by :
ZIM LABORATORIES LIMITED
B-21/22, MIDC Area,
Kalmeshwar, Nagpur,
Maharashtra State, 441501,
India

Zeal & Innovation in Medicine

Product registration holder:
Healol Pharmaceuticals Sdn Bhd
74-3, Jalan Wangsa Delima 6,
KLSC Wangsa Maju,
53300 Kuala Lumpur, Malaysia.

Date of Revision : 27 June 2020

*P6372/X/XX/XX