1.4.1 PRESCRIBING INFORAMTION (SPC)
1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
Proprietary Name
AZITHROSAFE SUSPENSION

Approved Generic Name
Azithromycin Suspension 200 mg/5 ml

1.1 Strength
Each 5 ml contains:
Azithromycin Dihydrate
Eq to Azithromycin Anhydrous USP 200 mg
Flavoured Syrupy Base q.s
Approved colour used

1.2 Pharmaceutical form
Liquid Orals- Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 ml contains:
Azithromycin Dihydrate
Eq to Azithromycin Anhydrous USP 200 mg
Flavoured Syrupy Base q.s
Approved colour used

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:
Liquid Orals- Suspension
Yellow coloured homogeneous suspension with peppermint flavor.

4. CLINICAL PARTICULARS:
4.1 Therapeutic indications:
AZITHROSAFE suspension 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

Recommended route of administration: Oral

4.2 Posology and method of administration
Azithromycin should be taken at least one hour before or two hours after administration of food and antacid preparation.
In children under 45 kg body weight:
Azithrosafe 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 5ml measuring cap provided.
For children weighing more than 15 kg, Azithrosafe Suspension should be administered using the measuring cap provided according to the following guidance:
15-25 kg (3-7 years): 5 ml (200 mg) given as 1 x 5 ml capful, once daily for 3 days.
26-35 kg (8-11 years): 7.5 ml (300 mg) given as 7.5 ml capful, once daily for 3 days.
36-45 kg (12-14 years): 10 ml (400 mg) given as 10 ml capful, once daily for 3 days.
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: No dosage adjustment recommendations can be made; azithromycin has not been studied in patients with impaired hepatic function.

4.3 Method of administration:
Oral

Direction for use:
SHAKE WELL BEFORE USE. Replace cap tightly immediately after each use.

4.4 Contraindications:
Hypersensitivity to Azithromycin or any of the macrolide antibiotics.
Co–administration with ergot derivatives.

4.5 Special warning and 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
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 (see section 4.8). 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.

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. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation (see section 4.8); therefore 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) has been reported with the 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 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.

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 <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed (see section 5.2).

Myasthenia gravis
Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

Diabetes
Caution in diabetic patients: 5 ml of reconstituted suspension contains 3.87 g of sucrose.
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Azithrosafe Suspension is for oral administration only.

4.7 Interaction with other medicinal products and other forms of Interactions
-Caution is advised, when using azithromycin in conjuction with drugs like carbamazapine, corticosteroids, cyclosporin, digoxin, ergot alkaloids, Theophylline and warfarin.
-Azithromycin should be taken at least one hour before or two hours after administration of food and antacid preparation.

4.10 Pregnancy and lactation
Azithromycin is classified as FDA pregnancy risk category B. Animal data reveal no teratogenic effects. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Azithromycin has not been studied for use during labor and obstetric delivery. Treatment should be given only if clearly needed. Or as directed by physician
Breast-feeding
There are no data on secretion in breast milk. 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.

4.11 Effects on ability to drive and use machines
There is no evidence to suggest that Azithrosafe may have an effect on a patient's ability to drive or operate machinery.

4.12 Undesirable effects
Dizziness, headache, diarrhoea, nausea, flatulence, vomiting andrash.

4.13 Overdose and special antidotes
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

Mode of action:

Azithrosafe 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.

Breakpoints

Azithromycin susceptibility breakpoints for typical bacterial pathogens published by EUCAST are:

Organism	**MIC breakpoints (mg/L)**	
	Susceptible (S≤)	**Resistant (R>)**
Staphylococcus spp.	1	2
Streptococcus groups A, B, C and G	0.25	0.5
Streptococcus pneumoniae	0.25	0.5
Haemophilus influenzae	0.12	4
Moraxella catarrhalis	0.25	0.5
Neisseria gonorrhoeae	0.25	0.5

Susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Table: 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 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.

Paediatric population

Following the assessment of studies conducted in children, the use of azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

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. 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 to 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.

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:

Sucrose
Xanthan Gum (Plain)
Guar (Delca-P 225)
Sodium Benzoate
Bronopol
Colloidal Silicon Dioxide (Aerosil)
Kyron T-112
Colour Sunset Yellow
Coolen M 5366 Flavour
Pippermint Oil M-6509 Flavour
Spearmint M-7845 Flavour
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C. Protect from light and moisture.

6.5 Nature and contents of container:

15 ml suspension is packed in amber coloured pet bottle in carton along with product insert

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorization Holder:
Name: **Pharma Life Science Ltd,**
Address: P.O. Box: 38148-00623, Nairobi (Kenya)
Country: Kenya
Telephone No: --

Name and Address of Manufacturer:
Name: **Enicar Pharmaceuticals Pvt. Ltd.,**
Address: Plot No.J-214,215,216, MIDC Tarapur, Boisar,
Tal: Palghar Dist Thane,
Tarapur – 401506
Country: India

8. MARKETING AUTHORISATION NUMBER

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