1.3.1Summary of Product Characteristics (SmPC):

Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

AZISURE
Strength
Each film coated tablet contains:
Azithromycin Dihydrate U.S.P.
Eq. to Azithromycin 500mg
Excipients Q.S
Color: Titanium Dioxide BP

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SR. NO.	L.C.per Tab (mg)	O.A. (%)	INGREDIENTS	PHARMA-COPIAL STATUS	UNIT	A.Q.R/ B In Kg.	Function
Part- I Mixing							
1.	525.00	--	*Azithromycin Dihydrate eq to Azithromycin	USP	mg	52.5	Macrolide Antibacterial Drug
2.	62.350	--	#$Starch BP	BP	mg	6.23	Diluent
3.	82.350	--	Microcrystalline cellulose powder 102 BP	BP	mg	8.235	Diluent/disintegrate
Part – II Binding							
5.	20.00	--	Starch (Binding Agent)	BP	mg	2.00	Binding Agent
6.	0.940	--	Sodium Benzoate	BP	mg	0.094	Preservative
7.	16.00	--	Povidone PVP K-30	BP	--	1.6	Binding agent
Part III :- Lubrication							
8.	7.00	--	Talcum Powder	BP	mg	0.70	Glidant
9.	11.760	--	Sodium Starch Glycolate	BP	mg	1.176	Disintegrant
10.	11.760	--	Croscarmellose sodium	BP	mg	1.176	Disintegrant
11.	7.00	--	Magnesium Stearate	BP	mg	0.70	Lubricant
Total Material Weight per Tablet : 744.00 mg							
Part IV:- Coating							
14.	20.00	--	Titanium Dioxide	BP	--	2.00	Coating agent
15.	--	--	Purified Water	BP	--	8.00	Vehicle
Total Material Weight per Tablet : 764.00 mg							

Reference:

BP = British Pharmacopoeia
USP= United State Pharmacopoeia
* Quantity to be changed based on potency of API.

Quantity of starch is to be adjusted to keep the total mass.
$ Quantity of starch based on Moisture content

3. PHARMACEUTICAL FORM

Oral film-coated tablets
White colored, capsule shaped film coated tablets breakline on one side and plain on other side

4. Clinical particulars

4.1 Therapeutic indications

Azithromycin is indicated for infection caused by susceptible organisms;

- In lower respiratory tract infections including bronchitis and pneumonia,
- In odontostomatological infections,
- In skin and soft tissue infections,
- In acute otitis media and in upper respiratory tract infections including sinusitis and pharyngitis.
- 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 Haemophilusducreyi and uncomplicated genital infection due to non-multiresistance Neisseria gonorrhea, concurrent infection with Trepnemapallidum should be excluded.
- Azithromycin is indicated, either alone or in combination with rifabutin, for prophylaxis against mycobacterium avium-intracellulare complex (MAC) infection, an opportunist infection prevalent in patients with advanced human immune deficiency virus (HIV). Azythromycin is indicated in combination with ethambutol for the treatment of disseminated MAC (DMAC) infection in patients with advanced HIV infection.

4.2 Posology and method of administration

Oral azithromycin should be administered as single daily dose. The period of dosing with regard to infection is given below.
Administration of azithromycin tablets following a substantial meal reduces bioavailability by at least 50%. Therefore, in common with many other antibiotics, each dose of the tablet should be taken at least 1 hour before or 2 hours after food.
Azithromycin tablets can be taken with or without food.

In Adults For the treatment of sexually transmitted diseases caused by Chlamydia trachomatis, Haemophilusducreyl, or susceptible Niesseriagonorrhea, the dose is 1000 mg as a single oral dose.

For prophylaxis against MAC infections in patients infected with the human immunodeficiency Virus (HIV), the dose is 1200 mg once per week.

For the treatment of DMAC infections in patients with advanced HIV infections, the

recommended dose is 600 mg once a day. Azithromycin should be administered in combination with other antimycobacterial agents that have shown in vitro activity against MAC, such as ethambutol at the approved dose.
For all other indications in which the oral formulation is administered, the total dosage of 1500 mg should be given as 500 mg daily for 3 days. As an alternative, the same total dose can be given over 5 days with 500 mg given on day 1, then 250 mg daily on days 2 to 5.

In Children:
The maximum recommended total dose for any treatment is 1500 mg for children. In general, the total dose of 30 mg/kg. Treatment for pediatric streptococci 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 per day dose.
OR
As directed by Physician

4.3 Contraindications

The use of this product is contraindicated in patients with a history of allergic reactions to azithromycin or any of the macrolide antibiotics.

4.4 Special warnings and precautions for use

Hypersensitivity
Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson syndrome, and toxic epidermal necrolysis have been reported in patients on azithromycin therapy. Fatalities have been reported. Cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have also been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half-life of azithromycin and subsequent prolonged exposure to antigen is presently unknown.
If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that allergic symptoms may reappear when symptomatic therapy has been discontinued.
Hepatotoxicity

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

Infantile Hypertrophic

Pyloric Stenosis (IHPS) Following the use of azithromycin in neonates (treatment up to 42 days of life), IHPS has been reported. Direct parents and caregivers to contact their physician if vomiting or irritability with feeding occurs

Development of Drug-Resistant Bacteria

Prescribing Azithromycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

QT Prolongation

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen with treatment with macrolides, including azithromycin. Cases of torsades de pointes have been spontaneously reported during postmarketting surveillance in patients receiving azithromycin. Providers 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 known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmia or uncompensated heart failure
- Patients on drugs known to prolong the QT interval
- Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesaemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval.

4.5 Interaction with other medicinal products and other forms of interaction

Azithromyci can interact with the following drugs or groups of drugs:
Antacids, Ergot derivatives, Methylprednisolone, Digoxin and colchicine, Cetirizine, Zidovudine, Cimetidine, Coumarin-Type Oral Anticoagulants:, Nelfinavir etc.

4.6 Fertility, 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.
Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin.

4.7 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.

4.8 Undesirable effects

Blood and lymphatic system disorders: Leukopenia, Neutropenia, Eosinophilia, Thrombocytopenia,, Haemolytic anaemia
Immune system disorders: Angioedema Hypersensitivity, Anaphylactic reaction
Metabolism and nutrition disorders: Anorexia
Psychiatric disorders: Nervousness,Insomnia, Agitation, Aggression, Anxiety, Delirium, Hallucination
Cardiac disorders: Palpitations Torsades de pointes, Arrhythmia, including ventricular tachycardia, Electro-cardiogram QT prolonged

4.9 Overdose
Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

Symptoms

The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment

In the event of overdose, general symptomatic and supportive measures are indicated as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use, macrolides. ATC code: J01FA10.

Azithromycin is the first of a sub class of macrolide antibiotics known as azalides. The mode of action of azithromycin is inhibition of protein synthesis in bacteria by binding to the 50s ribozomal sub units and preventing translocation of peptides.
Azithromycin demonstrates activity invitro against a wide range of bacteria including;

- Gram-positive Aerobic Bacteria
- Gram-negative Aerobic Bacteria
- Anaerobic bacteria
- Organisms of Sexually transmitted Diseases
- Opportunistic Pathogens Associated with HIV infections

5.2 Pharmacokinetic properties

Absorption
Following oral administration in humans, azithromycin is widely distributed throughout the body; bioavailability is approximately 37%. **Administration of azithromycin tablets/suspension following a substantial meal reduces bioavailabilty by at least 50%. The time taken to peak plasma levels is 2-3 hours.**
Distribution
In animal studies, high azithromycin concentrations have been observed in phagocytes. In experimental models, higher concentrations of azithromycin are released during active phagocytes that form non-simulated phagocytes. In animal models, this results in high concentration of azithromycin being delivered to the site of infection.

Pharmacokinetic studies in humans have shown markedly higher azithromycin levels in tissues than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the drug is heavily tissue bound. Concentrations in target tissues, such as lung, tonsil and prostrate exceed the MIC_{90} for likely pathogens after a single dose of 500mg.

Elimination

Plasma terminal elimination Half-life closely reflects the tissue depletion half-life of 2 to 4 days. Approximately 12% of an intravenously administered dose is extracted in the urine over 3 days as the parent drug, the majority in the first 24 hours. Biliary excretion of azithromycin is a major route of elimination for unchanged drug following oral administration. Very high concentration of unchanged drug have been found in human bile, together with 10 metabolites, formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by cleavage of the cladinose conjugate. Comparison of HPLC and microbiological assays in tissues 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 relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

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 rat reproductive toxicity studies. In rats, azithromycin doses of 100 and 200 mg/kg body weight/ day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above.

6. Pharmaceutical particulars

6.1 List of excipients

#$Starch	BP
Microcrystalline cellulose powder 102	BP
Starch (Binding Agent)	BP
Sodium Benzoate	BP
Povidone PVP K-30	BP
Talcum Powder	BP
Sodium Starch Glycolate	BP
Croscarmellose sodium	BP

Magnesium Stearate	BP
Titanium Dioxide	BP
Purified water	BP

6.2 Incompatibilities
None

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store below 30° C. Protect from light.

6.5 Nature and contents of container
1 x 10 Tablets in Alu-Alu pack, in a mono-carton

6.6 Special precautions for disposal and other handling
KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. APPLICANT/MANUFACTURER

Exported by:
ROENTGEN IMPEX
NO. 2063/A, RABARI VAS, KHORAJ VILLAGE,
DIST. GANDHINAGAR-382735, GUJARAT, INDIA

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