National Agency for Food & Drug Administration & Control (NAFDAC)

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

[Instructions in this font/colour are from the World Health Organisation Public Assessment Report WHOPAR guidelines.]

1. NAME OF THE MEDICINAL PRODUCT

Azithromycin Capsules USP 250 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains:
Azithromycin (anhydrous) USP 250 mg
(as Azithromycin Dihydrate USP)
Colour: Approved colour used in capsule shell
Excipients: q. s.

Sr. No.	Ingredients	Spec.	Qty/ Tab (mg)	Ovg.	Function
1	Azithromycin Dihydrate	USP	275.000 ≡ 250.000	--	Active
2	Magnesium Stearate	BP	5.000	--	Lubricant
3	Lactose	BP	150.000	--	Diluent
4	Maize Starch (Dried)	BP	60.000	--	Diluent
5	Sodium Lauryl Sulphate	BP	10.000	--	Surfactant
6	*Maize Starch (Dried)	BP	6.000	--	Diluent
7	E.H.G Capsules Size '0' Blue/Blue	IHS	--	--	Capsule shell
		TOTAL	**500.000**		

USP : United State Pharmacopoeia
BP : British Pharmacopoeia
IHS: In-house

Average net content per capsules : 500.00 mg ± 7.5%
Average weight of filled capsules : 596.00 mg ± 7.5%

* Includes extra starch to compensate the loss on drying.

3. PHARMACEUTICAL FORM

Hard gelatin capsule

Hard gelatin capsule of size '0' having Blue coloured Cap & Blue coloured Body printed containing white coloured powder.

---

4. Clinical particulars

4.1 Therapeutic indications

Azithromycin is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated microorganisms in the specific conditions listed below. As recommended dosages, durations of therapy and applicable patient populations vary among these infections.

4.2 Posology and method of administration

Route of administration: Oral

Average dose and dose range for adults and children

Skin and soft tissue infections

Adult: 500 mg once daily for 3 days. Alternatively, 500 mg as a single dose on the 1st
day followed by 250 mg once daily for 4 days.
Child: >6 mth: 10 mg/kg; 15–25 kg: 200 mg; 26–35 kg: 300 mg; 36–45 kg: 400 mg.
Doses to be taken once daily for 3 days.

Respiratory tract infections

Adult: 500 mg once daily for 3 days. Alternatively, 500 mg as a single dose on the 1st
day followed by 250 mg once daily for 4 days.
Child: >6 mth: 10 mg/kg; 15–25 kg: 200 mg; 26–35 kg: 300 mg; 36–45 kg: 400 mg.
Doses to be taken once daily for 3 days

Uncomplicated genital infections due to Chlamydia trachomatis

Adult: 1 g as a single dose.

Uncomplicated gonorrhea

Adult: 2 g as a single dose.

Prophylaxis of disseminated Mycobacterium avium complex (MAC) infections
Adult: 1.2 g once every wk. For treatment or secondary prophylaxis: 500 mg once daily with other antimycobacterial.
Child: >6 mth: 10 mg/kg once daily for 3 days.

Granuloma inguinale

Adult: Initially, 1 g followed by 500 mg daily. Alternatively, 1 g once a wk for at least 3 wk, until all lesions have completely healed

Dosage interval

Usual oral dose: 500 mg x 1, then 250 mg po qd x 4 days.

Average duration of treatment

Childn >6 mth Pneumonia or otitis media 10 mg/kg on the 1st day, then 5 mg/kg daily for 4 days. Childn >2 yr Pharyngitis or tonsillitis 12 mg/kg once daily for 5 days.
Dosage in special situations e.g. renal, hepatic and cardiac insufficiency

Not Applicable

4.3 Contraindications

Azithromycin is contraindicated in patients with known hypersensitivity to Azithromycin, erythromycin, any macrolide or ketolide antibiotic.

4.4 Special warnings and precautions for use

Warnings

Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported rarely in patients on Azithromycin therapy. Although rare, fatalities have 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 unknown at present.

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.

Precautions

Azithromycin is principally eliminated via the liver caution should be exercised when Azithromycin is administered to patients with impaired hepatic function. Due to the limited data in subjects with GFR < 10 mL/min, caution should be exercised when prescribing Azithromycin in these patients.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsade's 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 repolarization.

Exacerbation of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving Azithromycin therapy.

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

4.5 Interaction with other medicinal products and other forms of interaction

Aluminum- and magnesium-containing antacids, digoxin, live vaccines, lovastatin, nelfinavir, warfarin. This medication may decrease the effectiveness of combination-type birth control pills. This can result in pregnancy. You may need to use an additional form of reliable birth control while using this medication.

Other drugs besides azithromycin which may affect the heart rhythm (QTc prolongation in the EKG) include dofetilide, pimozide, procainamide, quinidine, sotalol, and sparfloxacin among others. QTc prolongation can infrequently result in serious, rarely fatal, irregular heartbeats. Consult your doctor or pharmacist for details. Ask for instructions about whether you need to stop any other QTc-prolonging drugs you may be using in order to minimize the risk of this effect. Do not start or stop any medicine without doctor or pharmacist approval.

4.6 Pregnancy and Lactation

Pregnancy

Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in rats and mice at doses up to moderately maternally toxic dose concentrations (i.e., 200 mg/kg/day). These daily doses in rats and mice, based on body surface area, are estimated to be 4 and 2 times, respectively, an adult daily dose of 500 mg. In the animal studies, no evidence of harm to the fetus due to azithromycin was found. There are, however, 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.

Nursing Mothers:

Azithromycin has been reported to be excreted in human breast milk in small amounts. Caution should be exercised when azithromycin is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

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

4.7 Undesirable effects

Mild to moderate nausea, vomiting, abdominal pain, dyspepsia, flatulence, diarrhea, cramping; angioedema, cholestatic jaundice; dizziness, headache, vertigo, somnolence; transient elevations of liver enzyme values.

4.9 Overdose

Brief clinical description of symptoms

Overdose symptoms may include nausea, vomiting, diarrhea, and stomach discomfort.

Treatment of over dosage

Symptomatic therapy and general supportive measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolides

ATC code: J01FA10.

Mechanism of action:

Azithromycin blocks transpeptidation by binding to 50s ribosomal subunit of susceptible organisms and disrupting RNA-dependent protein synthesis at the chain elongation step.

5.2 Pharmacokinetic properties

Absorption

The absolute bioavailability of Azithromycin 250 mg capsules is 38%.
In a two-way crossover study in which 12 healthy subjects received a single 500 mg dose of Azithromycin (two 250 mg tablets) with or without a high fat meal, food was shown to increase Cmax by 23% but had no effect on AUC.

When Azithromycin suspension was administered with food to 28 adult healthy male subjects, Cmax increased by 56% and AUC was unchanged.

The AUC of Azithromycin was unaffected by co-administration of an antacid containing aluminum and magnesium hydroxide with Azithromycin capsules; however, the Cmax was reduced by 24%. Administration of Cimetidine (800 mg) two hours prior to azithromycin had no effect on Azithromycin absorption.

Distribution

The serum protein binding of Azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 µg/mL to 7% at 2 µg/mL.

Following oral administration, Azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg. Greater Azithromycin concentrations in tissues than in plasma or serum were observed. High tissue concentrations should not be interpreted to be quantitatively related to clinical efficacy. The antimicrobial activity of Azithromycin is pH related and appears to be reduced with decreasing pH. However, the extensive distribution of drug to tissues may be relevant to clinical activity.

Selected tissue (or fluid) concentration and tissue (or fluid) to plasma/serum concentration ratios are shown in the following table:

AZITHROMYCIN CONCENTRATIONS FOLLOWING A 500 mg DOSE (TWO 250mg CAPSULES) IN ADULTS[1]

TISSUE OR FLUID	TIME AFTER DOSE (h)	TISSUE OR FLUID CONCENTRATION (µg/g or µg/mL)	CORRESPONDING PLASMA OR SERUM LEVEL (µg/mL)	TISSUE (FLUID) PLASMA (SERUM) RATIO
SKIN	72-96	0.4	0.012	35
LUNG	72-96	4.0	0.012	> 100
SPUTUM*	2-4	1.0	0.64	2
SPUTUM**	10-12	2.9	0.1	30
TONSIL***	9-18	4.5	0.03	> 100
TONSIL***	180	0.9	0.006	> 100
CERVIX****	19	2.8	0.04	70

[1] Azithromycin tissue concentrations were originally determined using 250 mg capsules.
* Sample was obtained 2-4 hours after the first dose.
** Sample was obtained 10-12 hours after the first dose.
*** Dosing regimen of two doses of 250 mg each, separated by 12 hours.
**** Sample was obtained 19 hours after a single 500 mg dose.

The extensive tissue distribution was confirmed by examination of additional tissues and fluids (bone, ejaculum, prostate, ovary, uterus, salpinx, stomach, liver, and gallbladder). As there are no data from adequate and well-controlled studies of Azithromycin treatment of infections in these additional body sites, the clinical importance of these tissue concentration data is unknown.

Following a regimen of 500 mg on the first day and 250 mg daily for 4 days, only very low concentrations were noted in cerebrospinal fluid (less than 0.01 µg/mL) in the presence of non-inflamed meninges.

Metabolism

In vitro and in vivo studies to assess the metabolism of Azithromycin have not been performed.

Excretion

Plasma concentrations of Azithromycin following single 500 mg oral and i.v. doses declined in a polyphasic pattern with a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hours. The prolonged terminal half-life is thought to be due to extensive uptake and subsequent release of drug from tissues. Biliary excretion of Azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine.

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

S.No.	Excipients	Specifications
1	Magnesium Stearate	As per BP
2	Lactose	As per BP
3	*Maize Starch (Dried)	As per BP
4	Sodium Lauryl Sulphate	As per BP
5	E.H.G Capsules Size '0' Blue/Blue	As per IHS

BP : British Pharmacopoeia
IHS : In-house Specification

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months (3 years)

6.4 Special precautions for storage

Do not store above 30°C. Protect from light and moisture.

6.5 Nature and contents of container <and special equipment for use, administration, or implantation>

Sr. No.	**Container closure system / Blister pack of 6 capsules**
Primary Packing	
1.	Printed aluminium foil
2.	Non-toxic, clear transparent PVC film
Secondary Packing	
3.	Printed carton
4.	Leaflet
5.	7 ply corrugated shipper

6.6 Special precautions for disposal <and other handling>

No special requirements.

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

7. APPLICANT/MANUFACTURER

Name and Address of Manufacturer

Manufactured by:
Fredun Pharmaceuticals Ltd.
14,15,16, Zorabian Industrial Complex,
Veoor, Palghar (E) - 401 404. INDIA

Name and Address of Applicant

Manufactured for:
PREFERRED DRUGS NIGERIA LTD.
20 Erhuvwa Club Street,
Asaba Delta State, Nigeria &
Preferred Groups LLC, Maryland U.S.A.
www.preferred-drugs.com