1.3.1
Summary Of Product Characteristics (SPC)

1.3.1 Product information for health professionals 1.

1.0 NAME OF THE MEDICINAL PRODUCT

1.1 Invented Name of the Medicinal Product

GREMAX 250

Azithromycin Capsules USP 250 mg

1.2 Strength

Each hard gelatin capsule contains :

Azithromycin Dihydrate USP

Eq. to Azithromycin (Anhydrous) 250 mg.

Excipients q.s.

Approved colures used in empty capsule shells.

1.3 Pharmaceutical Form

Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains :

Azithromycin Dihydrate USP

Eq. to Azithromycin (Anhydrous) 250 mg.

Excipients q.s.

Approved colours used in empty capsule shells.

3. PHARMACEUTICAL FORM

Hard Gelatin Capsule .

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gremax (Azithromycin) is indicated for the treatment of the following:

Infections of upper respiratory tracts (bacterial pharyngitis, laryngitis, tonsilitis, sinusitis etc.)

Infections of lower respiratory tracts (bacterial bronchitis, alveolar & krupps pneumoniae, chronicle obstructive lung disease) nose, ear throat infections (otitis, rhinitis, tonsilitis etc.)

Skin & skin reproductive infections: furunculosis of varied origin, pyodermy & impedigo.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Method of administration:

Azithromycin Capsules are for oral administration only.

Rout of administration: By orally.

Treatment and prophylaxis of susceptible infections including M. Avium Complex (MAC) infection: prophylaxis of endocarditis in high-risk penicillin-allergic patients:

Adult: Initially, 500 mg followed by 250 mg daily for 4 days or 500 mg daily as a single dose for 3 days.

Treatment of uncomplicated, genital infections due to chlamydia trachomatis.

Adult: 1 g as a single dose.

Treatment of uncomplicated gonorrhoea:

Adult: 2 g as a single dose.

Prophylaxis of disseminated mac infections: Adult: As dihydrate: 1.2 g once every week.

Child: >6 months: 10 mg/kg body weight once daily for 3 days.

4.3 CONTRAINDICATIONS

Azithromycin capsules are contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide antibiotic.

4.4 WARNING AND PRECAUTIONS

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.

In the treatment of pneumonia, azithromycin has only been shown to be safe and effective in the treatment of community-acquired pneumonia due to Chlamydia pneumoniae, Haemophilusinfluenzae, Mycoplasma pneumoniae, or Streptococcus pneumoniae in patients appropriate for oral therapy. Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: patients with cystic fibrosis, patients with nosocomially acquired infections, patients with known or suspected bacteremia, patients requiring hospitalization, elderly or debilitated patients, or patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea 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 diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Antacids: In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 24%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

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.

Didanosine *(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: Some of the macrolide antibiotics have been reported to impair the microbial metabolism of digoxin in the gut in some patients. In patients receiving concomitant azithromycin, a related azalide antibiotic, and 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 have been conducted 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 (based on a HMG CoA-reductase inhibition assay).

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.

Cimetidine: In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

Coumarin-Type Oral Anticoagulants: In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15 mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period 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.

Ciclosporin: In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in $AUC_{0-\infty}$. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin 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 Cmax (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: In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam*:* In healthy volunteers, 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 subjects 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: In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for 3 days) on the AUC and Cmax, of sildenafil or its major circulating metabolite.

Terfenadine: Pharmacokinetic studies have reported 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 to healthy volunteers.

Triazolam*:* In 14 healthy volunteers, co-administration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

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. Azithromycin serum concentrations were similar to those seen in other studies.

4.6 PREGNANCY AND LACTATION

Pregnancy

Animal reproduction studies have been performed at doses up to moderately maternally toxic dose concentrations. In these studies, no evidence of harm to the foetus 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.

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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 UNDESIRABLE EFFECTS

The table below lists the adverse reactions identified through clinical trial experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. 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.

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	not known frequency cannot be estimated from available data
Infections and infestations					
		Candidiasis Oral candidiasis Vaginal infection Pneumonia			Pseudomem-branous colitis

		Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis			
Blood and lymphatic system disorders					
		Leukopenia Neutropenia Eosinophilia			Thrombocytopenia, Haemolytic anaemia
Immune system disorders					
		Angioedema Hypersensitivity			Anaphylactic reaction (see section 4.4.)
Metabolism and nutrition disorders					
		Anorexia			
Psychiatric disorders					
		Nervousness Insomnia	Agitation .		Aggression Anxiety Delirium Hallucination
Eye disorders					
		Visual impairment			
Ear and labyrinth disorders					
		Vertigo Ear disorder			Hearing impairment including deafness and/or tinnitus
Vascular disorders					
		Hot flush			Hypotension
Respiratory, thoracic and mediastinal disorders					
		Dyspnoea Epistaxis			
Gastrointestinal disorders					
Diarrhoea ,	Vomiting Abdominal pain Nausea	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominal distension Dry mouth Eructation			Pancreatitis Tongue discoloration

		Mouth ulceration Salivary hypersecretion			
Hepatobiliary disorders					
		Hepatitis	Hepatic function abnormal Jaundice cholestatic		Hepatic failure (see section 4.4), which has rarely resulted in death Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders					
		Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis	Photosensitivity reaction, Acute generalised exanthematous pustulosis (AGEP)		Stevens-Johnson syndrome Toxic epidermal necrolysis, Erythema multi-forme
Musculoskeletal and connective tissue disorders					
		Osteoarthritis Myalgia Back pain Neck pain			Arthralgia
Renal and urinary disorders					
		Dysuria Renal pain			Renal failure acute Nephritis interstitial
Reproductive system and breast disorders					
		Metrorrhagia Testicular disorder			
Injury and poisoning					
		Post-procedural complication			

4.9 OVERDOSE

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.

ATC code: J01FA10

MECHANISM OF ACTION:
Azithromycin is a semi-synthetic macrolide antibiotic of the azalide class. Like other macrolide antibiotics, azithromycin inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit of the bacterial 70S ribosome. Binding inhibits peptidyltransferase activity and interferes with amino acid translocation during the process of translation. Its effects may be bacteriostatic or bactericidal depending of the organism and the drug concentration. Its long half life, which enables once daily dosing and shorter administration durations, is a property distinct from other macrolides.

5.2 Pharmacokinetic properties

Absorption:
Following oral administration, the bioavailability of azithromycin is approximately 37 %. Peak plasma levels are reached after 2-3 hours. The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4 μg/ml.

Distribution:
Orally administered azithromycin is widely distributed over the whole body.
Pharmacokinetic studies have shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma) than in the plasma. This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg).

In experimental *in-vitro* and *in-vivo* studies, azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appeared to contribute to the accumulation of azithromycin in tissue. The binding of azithromycin to plasma proteins is variable, and varies from 52 % at 0.05 μg/ml to 18 % at 0.5 μg/ml, depending on the serum concentration.

Metabolism and Excretion: The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 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.

Pharmacokinetics in Special populations:

Renal Insufficiency:
Following a single oral dose of azithromycin 1 g, mean C_{max} and AUC_{0-120} increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 10-80 ml/min) compared with normal renal function (GFR>80ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 35% respectively compared to normal.

Hepatic insufficiency:
In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly:
The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.
In elderly volunteers (>65 years), higher (29 %) AUC values were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

Infants, toddlers, children and adolescents:
Pharmacokinetics has been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than in adults, with 224 µg/l in children aged 0.6-5 years and after 3 days dosing, and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

5.3 Preclinical safety data

Relevant information on the preclinical safety of **Azithromycin Capsules USP 250 mg** is included in previous sections of this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Azithromycin Dihydrate
Microcrystalline cellulose phosphate
Crosscarmelose sodium
Sodium Lauryl sulphate
Purified Talc
Aerosil
White/white E.H.G. capsules size '0',printed GREMAX on capsules Shell.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 30°C. Protected from light.

6.5 Nature and contents of container

PVC/Alu Blister pack of 6's capsules.

6.6 Special precautions for disposal and other Special handling

None

7. Marketed by:

GREENLIFE PHARMACEUTICALS LTD.

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Illupeju, Lagos, Nigeria.