SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Medicinal Product

1.1 Product Name

AZGLO

Azithromycin Tablets USP 500 mg

1.2 Strength

Azithromycin Dihydrate USP 500 mg

1.3 Pharmaceutical Form

Tablet for Oral Administration

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Each film coated tablets contains:

Azithromycin Dihydrate USP

Equivalent to anhydrous Azithromycin ……. 500 mg

Excipients …….. q.s.

Colour: Yellow Oxide of Iron

2.2 Quantitative Declaration

Sr.	Ingredients	Specification	Qty./tablet (mg)	Qty./ batch (kg)
1.	Azithromycin Dihydrate	USP	530.0*	53.000
2.	Microcrystalline cellulose	USP	70.00	7.000
3.	Corn Starch	USP	34.83	3.831
4.	Povidone K-30	USP	16.00	1.600
5.	Ethylcellulose	USP	2.67	0.267
6.	Isopropyl alcohol@	USP	0.23	23.513
7.	Magnesium Stearate	USP	8.00	0.800
8.	Croscarmellose Sodium	USP	22.50	2.250
9.	Talc	USP	27.00	2.700
10.	Sodium Starch Glycolate	USP	10.00	1.000
11.	Colloidal Silicon Dioxide	USP	4.00	0.400
Average weight of the Uncoated Tablets 725.00 mg				
12.	Hypermellose	USP	7.00	1.400
13.	Titanium Dioxide	USP	0.40	0.080
14.	Talc	USP	2.00	0.400
15.	Colour : Yellow oxide of Iron	In-House	0.60	0.120
16.	Isopropyl alcohol@	USP	110.68	11.068
17.	Methylene Chloride@	USP	333.34	33.34
Average weight of the Coated Tablets 735.00 mg				

* The quantity of Azithromycin Dihydrate USP may vary with Assay and LOD.

** Overages in Corn starch have been added to compensate the drying loss.

*** Overages in coating materials have been added to compensate the process loss.

$ The quantity of Corn starch USP is to be calculated on the actual quantity of Azithromycin Dihydrate USP calculated on the basis of assay.

@ Does not remain in the finished product, removed during the process.

Note: Each 530 mg Azithromycin dihydrate = 500 mg of Azithromycin

3. Pharmaceutical Form

Description:

Yellow colour, elongated, biconvex, film coated tablets, having break line on one side and another side plain

Rational of break line

The break line is only to facilitate breaking for ease of swallowing and not to divide into equal doses, 'the tablet can be divided into equal halves'.

4. Clinical Particulars

4.1 Therapeutic indications

AZGLO (Azithromycin tablets USP 500 mg) 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

Considerations should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration

Posology

Adults

In uncomplicated Chlamydia trachomatis urethritis and cervicitis the dosage is 1000 mg as a single oral dose. For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Older people

The same dosage as in adult patients is used for older people. Since older people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.

Paediatric population

Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycine, e.g. suspensions, may be used.

In patients with renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min).

In patients with hepatic impairment: A dose adjustment is not necessary for patients with mild to moderately impaired liver function.

Method of administration

Azithromycin Tablets should be given as a single daily dose. The tablets may be taken with food.

4.3 Contraindications

The use of azithromycin is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

4.4 Special warning and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneuroticoedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

Since 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 . 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.

In patients receiving ergotamine derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered

Pharyngitis/ tonsilitis

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by Streptococcus pyogenes. For this and for the prophylaxis of acute rheumatic fever penicillin is the treatment of first choice.

Sinusitis

Often, azithromycin is not the substance of first choice for the treatment of sinusitis.

Acute otitis media

Often, azithromycin is not the substance of first choice for the treatment of acute otitis media.

Skin and soft tissue infections

The main causative agent of soft tissue infections, Staphylococcus aureus, is frequently resistant to azithromycin. Therefore, susceptibility testing is considered a precondition for treatment of soft tissue infections with azithromycin.

Infected burn wounds

Azithromycin is not indicated for the treatment of infected burn wounds.

Paediatric population

Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycine, e.g. suspensions, may be used.

In patients with renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min).

In patients with hepatic impairment: A dose adjustment is not necessary for patients with mild to moderately impaired liver function.

4.5 Interaction with other medicinal products and other forms of interactions

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids and azithromycin, no effect on overall bioavailability was seen, although the peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

Co-administration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Fluconazole

Coadministration 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 coadministration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Nelfinavir

Coadministration 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

Coadministration 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.

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.

Additional information on special populations

The same dosage as in adult patients is used for older people. Since older people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes

Paediatric population

Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycine, e.g. suspensions, may be used.

In patients with renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min).

4.6 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.

Breast feeding

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. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is

recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

Fertility

In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of Azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and use machine

AZGLO (Azithromycin Tablets USP 500 mg) has no influence on ability to drive or use machines.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical 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); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ Class	Frequency	Adverse reaction
Infections and infestations	Uncommon	Candidiasis Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis
	Not known	Pseudomembranous colitis
Blood and lymphatic system disorders	Uncommon	Leukopenia Neutropenia Eosinophilia
	Not known	Thrombocytopenia Haemolytic anaemia
Immune system disorders	Uncommon	Angioedema Hypersensitivity

	Not known	Anaphylactic reaction
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Uncommon	Nervousness Insomnia
	Rare	Agitation Depersonalisation
	Not known	Aggression Anxiety Delirium Hallucination
Nervous system disorders	Common	Headache
	Uncommon	Dizziness Somnolence Dysgeusia Paraesthesia
	Not known	Syncope, convulsion Hypoaesthesia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Ear disorder Vertigo
	Not known	Hearing impairment including deafness and/or tinnitus

4.9 Overdose

AZGLO (Azithromycin Tablets USP 500 mg) adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage genaral symptomatic and general supportive measures are indicated as required.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolids; azithromycin, ATC code:

ATC Classification

Pharmacotherapeutic group: antibacterials.

ATC Code: J01FA10

a) **Mechanism of action:**

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By binding to the 50S-ribosomal sub-unit, azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other. As a consequence of this, RNA-dependent protein synthesis in sensitive organisms is prevented.

b) **Pharmacodynamics effects:**

For azithromycin the AUC/MIC is the major PK/PD parameter correlating best with the efficacy of azithromycin.

c) **Clinical efficacy and safety :**

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.

Complete cross resistance exists among Streptococcus pneumoniae, betahaemolytic streptococcus of group A, Enterococcus faecalis and Staphylococcus aureus, including methicillin resistant S. aureus (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Paediatric population:

Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycin, e.g. suspensions, may be used.

5.2 Pharmacokinetic Properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (C_{max} after a single dose of 500 mg orally was approximately 0.4 mg/l).

Distribution

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500 mg.

In experimental in vitro and in vivo studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.

In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Metabolism:

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

Elimination

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24 hours. Biliary excretion of azithromycin, predominantly in unchanged form, is a major route of elimination.

The identified metabolites (formed by N- and O-demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

Special Population

Renal Insufficiency

Azithromycin pharmacokinetics was investigated in 42 adults (21 to 85 years of age) with varying degrees of renal impairment. Following the oral administration of a single 1.0 g dose of azithromycin (2 x 500 mg tablets), the mean Cmax and AUC0-120 increased by 5.1% and 4.2%, respectively, in subjects with GFR 10 to 80 mL/min compared to subjects with normal renal function (GFR > 80 mL/min). The mean Cmax and AUC0-120 increased 61% and 35%, respectively, in subjects with end-stage renal disease (GFR < 10 mL/min) compared to subjects with normal renal function (GFR > 80 mL/min).

Hepatic Insufficiency

The pharmacokinetics of azithromycin in subjects with hepatic impairment has not been established.

Gender

There are no significant differences in the disposition of azithromycin between male and female subjects. No dosage adjustment is recommended on the basis of gender.

Geriatric Patients

Pharmacokinetic parameters in older volunteers (65 to 85 years old) were similar to those in younger volunteers (18 to 40 years old) for the 5-day therapeutic regimen. Dosage adjustment does not appear to be necessary for older patients with normal renal and hepatic function receiving treatment with this dosage regimen. [see Geriatric Use]

Pediatric Patients

No data available

5.3 Preclinical Safety Data

In animal studies using exposures 40 times those achieved at the clinical therapeutic dosages, azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. 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

No teratogenic effects were observed in embryotoxicity studies in rats after oral administration of azithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline cellulose, Corn Starch, Povidone K-30, Ethylcellulose, Magnesium Stearate, Croscarmellose Sodium, Talc, Sodium Starch Glycolate, ColloidalSilicon Dioxide, Hypermellose, Titanium Dioxide, Polyethylene glycol 4000, Colour: Yellow oxide of Iron

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for storage

Store at a temperature not exceeding 30^0C. Store in a dark and dry place.

6.5 Nature and Contents of Container

1 X 3 Tablets in PVC-Alu blister pack

1 X 10 Tablets in Alu-Alu blister pack

Note: All pack sizes may not marketed

6.6 Special precautions for disposal

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

7. Marketing Authorization Holder/ Manufacture

GLOBAL ORGANICS LTD.
PLOT-868, KM-34,
Lagos Abeokuta express way,
Lagos state,
NIGERIA

Marketing Authorization Numbers

NA

8. Date of revision of text

SEP .2018