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

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)

1. Name of the Medical Product

1.1 Product Name:

ZAHA 500 (Azithromycin Tablets BP 500 mg)

1.2 Strength:

Each film coated tablet contains:
Azithromycin Dihydrate BP equivalent to Azithromycin 500 mg
Colour : Titanium Dioxide
Excipients……....q.s

1.3 Pharmaceutical Dosage Form:

Film coated tablet

2. Qualitative & Quantitative Composition

Each film coated tablet contains:
Azithromycin Dihydrate BP equivalent to Azithromycin 500 mg
Colour : Titanium Dioxide
Excipients……....q.s
For a full list of excipients, see section 6.1 of SmPC

3. Pharmaceutical Form

Film coated tablet
White to off white coloured, capsule shaped, film coated tablets, with breakline on one side.

4. Clinical Particulars

4.1 Therapeutic Indications:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of azithromycin and other antibacterial drugs, azithromycin should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.
Azithromycin is a macrolide antibacterial drug 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. Recommended dosages and durations of therapy in adult and pediatric patient populations vary in these indications.

Adult Patients

- Acute bacterial exacerbations of chronic bronchitis due to *Haemophilus influenzae, Moraxella catarrhalis,* or *Streptococcus pneumoniae.*
- Acute bacterial sinusitis due to *Haemophilus influenzae*, *Moraxella catarrhalis* or *Streptococcus pneumoniae.*
- Community-acquired pneumonia due to *Chlamydophila pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae,* or *Streptococcus pneumoniae* in patients appropriate for oral therapy.
- Pharyngitis/tonsillitis caused by *Streptococcus pyogenes* as an alternative to first-line therapy in individuals who cannot use first-line therapy.
- Uncomplicated skin and skin structure infections due to *Staphylococcus aureus*, *Streptococcus pyogenes,* or *Streptococcus agalactiae.*
- Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.
- Genital ulcer disease in men due to *Haemophilus ducreyi* (chancroid). Due to the small number of women included in clinical trials, the efficacy of azithromycin in the treatment of chancroid in women has not been established

4.2 Posology and Method of administration:
Adult Patients

Infection*	**Recommended Dose/Duration of Therapy**
Community-acquired pneumonia Pharyngitis/tonsillitis (second-line therapy) Skin/skin structure (uncomplicated)	500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5
Acute bacterial exacerbations of chronic obstructive pulmonary disease	500 mg once daily for 3 days OR 500 mg as a single dose on Day 1, followed by 250 mg once daily on Days 2 through 5
Acute bacterial sinusitis	500 mg once daily for 3 days
Genital ulcer disease (chancroid)	One single 1 gram dose
Non-gonococcal urethritis and cervicitis	One single 1 gram dose
Gonococcal urethritis and cervicitis	One single 2 gram dose

*Due to the indicated organisms

Method of administration
Azithromycin Tablets BP 500mg tablets can be taken with or without food.

4.3 Contraindications:
Hypersensitivity
Azithromycin is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide drug.

Hepatic Dysfunction
Azithromycin is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin.

4.4 Special warning and precautions for use:
Hypersensitivity
Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including 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. 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.

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 postmarketing 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, bradyarrhythmias or uncompensated heart failure
- Patients on drugs known to prolong the QT interval
- Patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, 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.

***Clostridium difficile*-Associated Diarrhea (CDAD)**

Clostridium difficile-associated diarrhea 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 antibacterial 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.

Exacerbation of Myasthenia Gravis

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

Use in Sexually Transmitted Infections

Azithromycin, at the recommended dose, should not be relied upon to treat syphilis. Antibacterial agents used to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis.

All patients with sexually transmitted urethritis or cervicitis should have a serologic test for syphilis and appropriate testing for gonorrhea performed at the time of diagnosis. Appropriate antibacterial therapy and follow-up tests for these diseases should be initiated if infection is confirmed.

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.

Additional information on special populations
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.
Breastfeeding
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.
Pediatric Use
Azithromycin Tablets BP 50mg are not indicated for pediatric use.
Geriatric Use
In multiple-dose clinical trials of oral azithromycin, 9% of patients were at least 65 years of age (458/4949) and 3% of patients (144/4949) were at least 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Elderly patients may be more susceptible to development of torsades de pointes arrhythmias than younger patients.

4.5 Interactions with other medicinal products and other forms of Interactions:
Nelfinavir
Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.

Warfarin
Spontaneous postmarketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin.

Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.

Potential Drug-Drug Interactions with Macrolides
Interactions with digoxin or phenytoin have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interactions. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin or phenytoin are used concomitantly with azithromycin careful monitoring of patients is advised.

4.6 Fertility, 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.

Breastfeeding
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 machine:
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:
Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, most of the reported side effects were mild to moderate in severity and were reversible upon discontinuation of the drug. Potentially serious adverse reactions of angioedema and cholestatic jaundice were reported. Approximately 0.7% of the patients (adults and pediatric patients) from the 5-day multiple-dose clinical trials discontinued azithromycin therapy because of treatment-related adverse reactions. In adults given 500 mg/day for 3 days, the discontinuation rate due to treatment-related adverse reactions was

0.6%. In clinical trials in pediatric patients given 30 mg/kg, either as a single dose or over 3 days, discontinuation from the trials due to treatment-related adverse reactions was approximately 1%. Most of the adverse reactions leading to discontinuation were related to the gastrointestinal tract, e.g., nausea, vomiting, diarrhea, or abdominal pain.

Adults
Multiple-dose regimens: Overall, the most common treatment-related adverse reactions in adult patients receiving multiple-dose regimens of azithromycin were related to the gastrointestinal system with diarrhea/loose stools (4 to 5%), nausea (3%), and abdominal pain (2 to 3%) being the most frequently reported.

No other adverse reactions occurred in patients on the multiple-dose regimens of azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:
Cardiovascular: Palpitations, chest pain.

Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.

Genitourinary: Monilia, vaginitis, and nephritis.

Nervous System: Dizziness, headache, vertigo, and somnolence.

General: Fatigue.

Allergic: Rash, pruritus, photosensitivity, and angioedema.

Single 1-gram dose regimen:
Overall, the most common adverse reactions in patients receiving a single-dose regimen of 1 gram of Azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen. Adverse reactions that occurred in patients on the single 1-gram dosing regimen of azithromycin with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).

Single 2-gram dose regimen:
Overall, the most common adverse reactions in patients receiving a single 2-gram dose of azithromycin were related to the gastrointestinal system. Adverse reactions that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of azithromycin. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Adverse reactions reported with azithromycin during the postmarketing period in adult and/or pediatric patients for which a causal relationship may not be established include:

Allergic: Arthralgia, edema, urticaria, and angioedema.

Cardiovascular: Arrhythmias including ventricular tachycardia and hypotension. There have been reports of QT prolongation and torsades de pointes.

Gastrointestinal: Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.

General: Asthenia, paresthesia, fatigue, malaise, and anaphylaxis

Genitourinary: Interstitial nephritis and acute renal failure and vaginitis.

Hematopoietic: Thrombocytopenia.

Liver/Biliary: Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure.

Nervous System: Convulsions, dizziness/vertigo, headache, somnolence, hyperactivity, nervousness, agitation, and syncope.

Psychiatric: Aggressive reaction and anxiety.

Skin/Appendages: Pruritusserious skin reactions including erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and DRESS.

Special Senses: Hearing disturbances including hearing loss, deafness and/or tinnitus, and reports of taste/smell perversion and/or loss.

Laboratory Abnormalities

Adults:

Clinically significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows: with an incidence of greater than 1%: decreased hemoglobin, hematocrit, lymphocytes, neutrophils, and blood glucose; elevated

serum creatine phosphokinase, potassium, ALT, GGT, AST, BUN, creatinine, blood glucose, platelet count, lymphocytes, neutrophils, and eosinophils; with an incidence of less than 1%: leukopenia, neutropenia, decreased sodium, potassium, platelet count, elevated monocytes, basophils, bicarbonate, serum alkaline phosphatase, bilirubin, LDH, and phosphate. The majority of subjects with elevated serum creatinine also had abnormal values at baseline. When follow-up was provided, changes in laboratory tests appeared to be reversible.

In multiple-dose clinical trials involving more than 5000 patients, four patients discontinued therapy because of treatment-related liver enzyme abnormalities and one because of a renal function abnormality.

4.9 Overdose:
Adverse reactions experienced at higher than recommended doses were similar to those seen at normal doses particularly nausea, diarrhea, and vomiting. In the event of overdosage, general symptomatic and supportive measures are indicated as required.

5. Pharmacological Particulars

5.1 Pharmacodynamic properties:
Mechanism of action
Azithromycin is a macrolide antibacterial drug. Azithromycin acts by binding to the 50S ribosomal subunit of susceptible microorganisms and interferes with bacterial protein synthesis.
Nucleic acid synthesis is not affected.

Cross Resistance
Azithromycin demonstrates cross resistance with erythromycin resistant Gram positive isolates.
Azithromycin has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical.

Gram-Positive Bacteria
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-Negative Bacteria
Haemophilus ducreyi
Haemophilus influenzae
Moraxella catarrhalis
Neisseria gonorrhoeae

Other Bacteria
Chlamydophila pneumonia
Chlamydia trachomatis
Mycoplasma pneumoniae
The following *in vitro* data are available, but their clinical significance is unknown. Azithromycin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 4.0 mcg/ml or less against most (≥90%) isolates of the following bacteria; however, the safety and effectiveness of azithromycin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

Gram-Positive Bacteria
Beta-hemolytic streptococci (Groups C, F, G)
Viridans group streptococci

Gram-Negative Bacteria
Bordetella pertussis
Legionella pneumophila

Anaerobic Bacteria
Prevotella bivia
Peptostreptococcus species

Other Bacteria
Ureaplasma urealyticum

5.2 Pharmacokinetics Properties:
Following oral administration of a single 500 mg dose (two 250 mg tablets) to 36 fasted healthy male volunteers, the mean (SD) pharmacokinetic parameters were AUC0-72 =4.3 (1.2) mcg·hr/mL; Cmax =0.5 (0.2) mcg/mL; Tmax =2.2 (0.9) hours. Two azithromycin 250 mg tablets are bioequivalent to a single 500 mg tablet.

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

Distribution:
The serum protein binding of azithromycin is variable in the concentration range approximating human exposure, decreasing from 51% at 0.02 mcg/mL to 7% at 2 mcg/mL.
The antibacterial 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.

Azithromycin has been shown to penetrate into human tissues, including skin, lung, tonsil, and cervix. 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 significance of these tissue concentration data is unknown.

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

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

Elimination:
Plasma concentrations of azithromycin following single 500 mg oral and IV doses declined in a polyphasic pattern resulting in a mean apparent plasma clearance of 630 mL/min and terminal elimination half-life of 68 hr. 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:
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate carcinogenic potential.

Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.

No evidence of impaired fertility due to azithromycin was found in rats given daily doses up to 10 mg/kg (approximately 0.2 times an adult daily dose of 500 mg based on body surface area).

Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) has been observed in some tissues of mice, rats, and dogs given multiple doses of azithromycin. It has been demonstrated in numerous organ systems (e.g., eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) in dogs and rats treated with azithromycin at doses which, expressed on the basis of body surface area, are similar to or less than the highest recommended adult human dose. This effect has been shown to be reversible after cessation of azithromycin treatment. Based on the pharmacokinetic data, phospholipidosis has been seen in the rat (50 mg/kg/day dose) at the observed maximal plasma concentration of 1.3 mcg/mL (1.6 times the observed C of 0.821 mcg/mL at the adult dose of 2 g). Similarly, it has been shown in the dog (10 mg/kg/day dose) at the observed maximal serum concentration of 1 mcg/mL (1.2 times the observed C of 0.821 mcg/mL at the adult dose of 2 g). Phospholipidosis was also observed in neonatal rats dosed for 18 days at 30 mg/kg/day, which is less than the pediatric dose of 60 mg/kg based on the surface area. It was not observed in neonatal rats treated for 10 days at 40 mg/kg/day with mean maximal serum concentrations of 1.86 mcg/mL, approximately 1.5 times the Cmax of 1.27 mcg/mL at the pediatric dose. Phospholipidosis has been observed in neonatal dogs (10 mg/kg/day) at maximum mean whole blood concentrations of 3.54 mcg/mL, approximately 3 times the pediatric dose Cmax. The significance of these findings for animals and for humans is unknown.

6. Pharmaceutical particulars

6.1 List of Excipients:

Lactose, Calcium Hydrogen Phosphate Dihydrate, Sodium Lauryl Sulphate, Povidone (P.V.P.K.30), Isopropyl alcohol, Sodium Starch Glycolate Type A, Croscarmellose Sodium, Colloidal Silicon Dioxide, Magnesium Stearate, Instacoat Aqua-III (IA-III-40001) (White).

Instacoat Aqua-III (IA-III-40001) (White) comprises of Hypromellose, Polyethylene Glycol, Lactose Monohydrate, Talc, Titanium Dioxide.

6.2 Incompatibilities:

Not applicable

6.3 Shelf life:

24 months

6.4 Special Precautions for storage:

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

6.5 Nature and contents of container:
3 tablets are packed into one blister pack. Such 1 blister is packed in a carton along with pack insert

6.6 Special precautions for disposal and other handling:
Not applicable

7. Marketing authorization holder and manufacturing site addresses:
Market Authorization Holder
Ajanta Pharma Limited
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067,
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Manufacturing site address:
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8. Marketing authorization number : A4-8829

9. Date of first registration/ renewal of the registration: Jan 10, 2013

10. Date of revision of text: Dec 12, 2017