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

Registration & Regulatory Affairs (R & R) Directorate

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) TEMPLATE

1. NAME OF THE MEDICINAL PRODUCT

AZITHROMYCIN FOR ORAL SUSPENSION USP 200MG/5ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azithromycin Dihydrate USP	
Eq. to Azithromycin Anhydrous	200mg

Each 5ml (after reconstitution) contains:

Azithromycin Dihydrate USP	
Eq. to Azithromycin Anhydrous	200mg
Excipients	Q.S.
Colour: Tartrazine	

3. PHARMACEUTICAL FORM

Oral powder for Suspension

4. Clinical particulars

4.1 Therapeutic indications

Azithromycin is indicated for the treatment of the following infections when known or likely to be due to one or more susceptible microorganisms:

- Bronchitis
- Community-acquired pneumonia
- Sinusitis
- Pharyngitis/tonsillitis
- Otitis media
- Skin and soft tissue infections
- Uncomplicated genital infections due to Chlamydia trachomatis.

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

4.2 Posology and method ofadministration

Method of administration: Oral

Shake the dry powder loose. Add the 7.5 ml of water shake well until a light yellow coloured suspension, homogenous suspension is achieved.

Azithromycin for Oral Suspension USP should be given as a single daily dose.

Azithromycin for Oral Suspension USP can be taken with food.

Adults and adolescents - 1 gram (25ml) taken once as a single dose.

For gonococcal infections:

Adults and adolescents - 2 grams (50 ml) taken once as a single dose.

For otitis media and pneumonia:

Children 6 months to 12 years of age - 10 milligrams (mg) per kilogram (kg) (4.5 mg per pound) of body weight once a day on the first day, then 5 mg per kg (2.2 mg per pound) of body weight once a day on days two through five.

For strep throat:

Children 2 to 12 years of age - 12 mg per kg (5.4 mg per pound) of body weight once a day or five days.

Children up to 2 years of age - Use and dose must be determined by your doctor.

For bronchitis, strep throat, pneumonia, and skin infections:

Adults and adolescents 16 years of age and older - 500 mg (10ml) on the first day, then 250 mg(5ml)

once a day on days two through five.
Children up to 16 years of age - Use and dose must be determined by your doctor.
For chlamydia infections:
Adults and adolescents 16 years of age and older - 1000 mg (25 ml) taken once as a single dose.
Children up to 16 years of age - Use and dose must be determined by your doctor.
For prevention of Mycobacterium avium complex (MAC) disease:
Adults and adolescents 16 years of age and older - 1200 mg (30ml) once a week. Children up to 16 years of age - use and dose must be determined by your doctor.
For Sinusitis:
Adults and adolescents - 500 mg a day for 3 days
Children up to 16 years of age - Use and dose must be determined by your doctor

4.3 Contraindications

Azithromycin Tablets USP is contra-indicated in patients with a known hypersensitivity to azithromycin or any macrolide or ketolide antibiotics, erythromycin, or to any of the excipients used in manufacture of the product.

4.4 Special warnings and precautions for use

Azithromycin powder for oral solution is not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.
Azithromycin is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more.
In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.

Paediatric population
For otitis media and pneumonia:
Children 6 months to 12 years of age - 10 milligrams (mg) per kilogram (kg) (4.5 mg per pound) of body weight once a day on the first day, then 5 mg per kg (2.2 mg per pound) of body weight once a day on days two through five.
For strep throat:
Children 2 to 12 years of age - 12 mg per kg (5.4 mg per pound) of body weight once a day or five days.
Children up to 2 years of age - Use and dose must be determined by your doctor.
For bronchitis, strep throat, pneumonia, and skin infections:
Children up to 16 years of age - Use and dose must be determined by your doctor.
For chlamydia infections:
Children up to 16 years of age - Use and dose must be determined by your doctor.
For Sinusitis:
Children up to 16 years of age - Use and dose must be determined by your doctor

4.5 Interaction with other medicinal products and other forms of interaction

Nelfinavir: side effects of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.
Azithromycin did not affect the prothrombin time response to a single dose of warfarin. However, prudent medical practice dictates careful monitoring of prothrombin time in all patients treated with azithromycin and warfarin concomitantly. Concurrent use of macrolides and warfarin in clinical practice has been associated with increased anticoagulant effects.
Drug interaction studies were performed with azithromycin and other drugs likely to be co-administered. When used in therapeutic doses, azithromycin had a modest effect on the pharmacokinetics of atorvastatin, carbamazepine, cetirizine, didanosine, efavirenz, fluconazole, indinavir, midazolam, rifabutin, sildenafil, theophylline (intravenous and oral), triazolam, trimethoprim/sulfamethoxazole or zidovudine. Co-administration with efavirenz or fluconazole had a modest effect on the pharmacokinetics of azithromycin. No dosage adjustment of either drug is recommended when azithromycin is co administered with any of the above agents. Interactions with the drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug-drug interaction. Nonetheless, they have been observed with macrolide products. Until further data are developed regarding drug interactions when azithromycin and these drugs are used concomitantly, careful

monitoring of patients is advised:
Digoxinelevated digoxin concentrations.
Ergotamine or dihydroergotamine acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia. Cyclosporine, hexobarbital and phenytoin concentrations.

4.6 Pregnancy and Lactation

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 definitely indicated.
Azithromycin passes into 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.

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.
However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

4.8 Undesirable effects

The following side-effects have been reported:
Infections and Infestations:
Uncommon: Candidiasis, oral candidiasis, vaginal infection
Not known: Pseudomembranous colitis
Blood and Lymphatic System Disorders:
Uncommon: Leukopenia, neutropenia
Not known: Thrombocytopenia, haemolytic anaemia
Immune System Disorders:
Uncommon: Angioedema, hypersensitivity
Not known: Anaphylactic reaction
Metabolism and Nutrition Disorders:
Common: Anorexia
Psychiatric Disorders:
Uncommon: Nervousness
Rare: Agitation
Not known: Aggression, anxiety
Nervous System Disorders:
Common: Dizziness, headache, paraesthesia, dysgeusia
Uncommon: Hypoaesethesia, somnolence, insomnia
Not known: Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, and Myasthenia gravis.
Eye Disorders:
Common: Visual impairment
Ear and Labyrinth Disorders:
Common: Deafness
Uncommon: Hearing impaired, tinnitus
Rare: Vertigo
Cardiac Disorders:
Uncommon: Palpitations
Not known: Torsades de pointes, arrhythmia including ventricular tachycardia
Vascular Disorders:
Not known: Hypotension
Gastrointestinal Disorders:
Very common: Diarrhoea, abdominal pain, nausea, flatulence
Common: Vomiting, dyspepsia

Uncommon: Gastritis, constipation
Not known: Pancreatitis, tongue discolouration

Hepatobiliary Disorders:
Uncommon: Hepatitis
Rare: Hepatic function abnormal
Not known: Hepatic failure, which has rarely resulted in death, hepatitis fulminant, hepatic necrosis, jaundice cholestatic

Skin and Subcutaneous Tissue Disorders:
Common: Pruritus and rash
Uncommon: Stevens-Johnson syndrome, photosensitivity reaction, urticaria
Not known: Toxic epidermal necrolysis, erythema multiforme.

Musculoskeletal, Connective Tissue Disorders:
Common: Arthralgia

Renal and Urinary Disorders:
Not known: Renal failure acute, nephritis interstitial

General disorders and Administration Site Conditions:
Common: Fatigue
Uncommon: Chest pain, oedema, malaise, asthenia

Investigations:
Common: Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased
Uncommon: Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal.

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 Pharmacodynamics properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolides.
ATC code: J01FA10.
Azithromycin is a macrolide antibiotic belonging to the azalide group.
The molecule is constructed by adding a nitrogen atom to the lactone ring of erythromycin A. The chemical name of azithromycin is 9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin A. The molecular weight is 749.0.
Mode of action
Azithromycin is an azalide, a sub-class of the macrolide antibiotics. By binding to the 50Sribosomal 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.

5.2 Pharmacokinetic properties

Absorption
Bioavailability after oral administration is approximately 37%. Peak plasma concentrations are attained 2 to 3 hours after taking the medicinal product.

Distribution
Orally administered azithromycin is widely distributed throughout the body. In pharmacokinetic studies it has been demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues.
Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram azithromycin/ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

Elimination

The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2 to 4 days.
Approximately 12% of an intravenously administered dose of azithromycin is excreted unchanged in urine within the following three days. Particularly high concentrations of unchanged azithromycin have been found in human bile. Also in bile, ten metabolites were detected, which were formed through N- and O- demethylation, hydroxylation of desosamine and aglycone rings and cleavage of cladinose conjugate. Comparison of the results of liquid chromatography and microbiological analyses has shown that the metabolites of azithromycin are not microbiologically active.
In animal tests, high concentrations of azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of azithromycin are released from inactive phagocytes. In animal models this results in high concentrations of azithromycin being delivered to the site of infection.

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 significance of the finding for animals and humans is unknown.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

Mutagenic potential:

There was no evidence of a potential for genetic and chromosome mutations in in-vivo and in-vitro test models.

Reproductive toxicity:

In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Kyron T-134
Xanthan Gum
Sodium Methyl Paraben
Sodium Propyl Paraben
Colloidal Anhydrous Silica
Essence Dry Pineapple
Aspartame
Menthol
Bronopol
Colour Tartrazine

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened bottle with dry powder: 24 months.

Reconstituted suspension: 5 days.

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children. After reconstitution, the suspension may be kept for 5 days either at room temperature, without significant loss of potency. Keep tightly closed. Shake well before using. Discard unused portion after 5 days.

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

implantation>

15 ml milky white bottle HDPE 30ml marking

6.6 Special precautions for disposal <and other handling>

There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

7. <APPLICANT/MANUFACTURER>

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