1. Name of the medicinal product

AZITHROMYCIN FOR ORAL SUSPENSION USP 200 MG/5 ML

2. Qualitative and quantitative composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIAL SPECIFICATION	LABEL CLAIM	OVERAGES %	QTY. / 5 ML*	PURPOSE
ACTIVE INGREDIENTS						
1.	Azithromycin Dihydrate** Eq. to Azithromycin base	USP	209.62 mg (200.00 mg)	25.18 %	262.4 mg	API
INACTIVE INGREDIENTS						
2.	Sodium Propyl paraben	BP	-	0.00 %	2.975 mg	Preservative
3.	Aspartam	BP	-	0.00 %	44.625 mg	Sweetener
4.	Sodium Carboxyl methyl Cellulose	BP	-	0.00 %	23.800 mg	Polymer
5.	Colloidal silicon dioxide	BP	-	0.00 %	14.875 mg	Glidant
6.	Sodium Methyl paraben	BP	-	0.00 %	5.950 mg	Preservative
7.	Sucrose	BP	-	0.00 %	2545.425 mg	Sweetener
8.	Sucralose	BP	-	0.00 %	14.875 mg	Sweetener
9.	Tartrazine Yellow	IN HOUSE	-	0.00 %	0.600 mg	Colour
10.	Essence Lemon Premium dry powder	IN HOUSE	-	0.00 %	59.500 mg	Flavour

*5 ml is equivalent to 2.975 gm of powder.
** 25.18 % Overages are added on label claim.

3. Pharmaceutical form

Oral Suspension.

4. Clinical particulars

4.1 Therapeutic indications

This Product is a macrolide antibacterial drug indicated for mild to moderate infections caused by designated, susceptible bacteria:

- Acute bacterial exacerbations of chronic bronchitis in adults
- Acute bacterial sinusitis in adults
- Uncomplicated skin and skin structure infections in adults
- Urethritis and cervicitis in adults
- Genital ulcer disease in men
- Acute otitis media in pediatric patients
- Community-acquired pneumonia in adults and pediatric patients
- Pharyngitis/tonsillitis in adults and pediatric patients

4.2 Posology and method of administration

Adults
In uncomplicated Chlamydia trachomatis urethritis and cervicitis, the dose is 1,000 mg in one single oral dose.
For all other indications the dose is 1,500 mg, to be administered as 500 mg per day for three consecutive days. Alternatively the same total dose (1,500 mg) can also be given over a period of 5 days with 500 mg on the first day and then 250 mg on days 2 to 5.
To treat these patients other pharmaceutical forms are also available.
Elderly people
The same dose as in adult patients is used in the older people. Since older patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes.
Children and adolescents (< 18 years)
The total dose in children aged 1 year and older is 30 mg/kg administered as 10 mg/kg once daily for three days, or over a period of five days starting with a single dose of 10 mg/kg on the first day, followed by doses of 5 mg/kg per day for the following 4 days,There are limited data on use in children younger than 1 year.
Patients with renal impairment:
No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min).
Patients with hepatic impairment:
A dose adjustment is not necessary for patients with mild to moderately impaired liver function.
Method of administration
Before use the powder should be reconstituted with water into a white to off white, homogenous suspension, After reconstitution the drug can be administered using a PE/PP syringe for oral use.
After taking the suspension a bitter after-taste can be avoided by drinking fruit juice directly after swallowing. Azithromycin powder for oral suspension should be given in a single daily dose. The suspension may be taken together with food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hypersensitivity
As with erythromycin and other macrolides, rare serious allergic reactions, including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with Azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.
Cardiovascular Events
Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including Azithromycin
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.

Sexually transmitted disease

In case of sexually transmitted diseases a concomitant infection by T. pallidum should be excluded.

Neurological or psychiatric diseases

Azithromycin should be used with caution in patients with neurological or psychiatric disorders.
Caution in diabetic patients: 5 ml of reconstituted suspension contain 3.70 g of sucrose.

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 25%. In patients receiving both Azithromycin and antacids, the medicinal products should not be taken simultaneously.

Cetirizine: In healthy volunteers, coadministration 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

Digoxin and colchicine: Concomitant administration of macrolide antibiotics, including Azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if Azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered**.**

Ergot: Due to the theoretical possibility of ergotism, the concurrent use of Azithromycin with ergot derivatives is not recommended

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). However, post-marketing cases of rhabdomyolysis in patients receiving Azithromycin with statins have been reported.

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.

Cyclosporin: 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 cyclosporin, the resulting cyclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

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 C_{max} of sildenafil or its major circulating metabolite.

Theophylline: There is no evidence of a clinically significant pharmacokinetic interaction when Azithromycin and theophylline are co-administered to healthy volunteers.
Trimethoprim/sulfamethoxazole: Co-administration of trimethoprim/sulfamethoxazole (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: 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.
Breastfeeding: Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well-controlled clinical studies in breastfeeding women that have characterized the pharmacokinetics of Azithromycin excretion into human breast milk.
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 machines

There is no evidence to suggest that Azithromycin may have an effect on a patient's ability to drive or operate machinery. Visual impairment and vision blurred may have an effect on a patient's ability to drive or operate machinery.

4.8 Undesirable effects

Metabolism and Nutrition Disorders: Anorexia
Nervous System Disorders: Dizziness, Headache, Paraesthesia, Dysgeusia
Eye Disorders: Visual impairment
Ear and Labyrinth Disorders: Deafness**,** Hearing impaired**,** Tinnitus
Cardiac Disorders: Palpitations
Gastrointestinal Disorders: Diarrhea, Abdominal pain, Nausea, Flatulence, Abdominal discomfort, Loose stools
Hepatobiliary Disorders: Hepatitis
Skin and Subcutaneous Tissue Disorders: Rash, Pruritus, Stevens-Johnson syndrome, Photosensitivity reaction
Musculoskeletal and Connective Tissue Disorders: Arthralgia
General Disorders and Administration Site Conditions: Fatigue**,** Asthenia**,** Malaise

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 over dosage, general symptomatic and supportive measures are indicated as required.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use; macrolides; Azithromycin, ATC code: J01FA10

Mode of action

Azithromycin is an azalide, a sub-class of the macrolide 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.

PK/PD relationship

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

Following the assessment of studies conducted in children, the use of Azithromycin is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

Mechanism of 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.

5.2 Pharmacokinetic properties

Absorption

The biological availability of Azithromycin after oral administration is approximately 37%. Peak plasma levels are achieved 2-3 hours after taking the medicinal product.

Distribution

After oral administration, Azithromycin is distributed throughout the entire body. Pharmacokinetic studies have shown clearly higher Azithromycin levels in the tissues than in the plasma (up to 50 times the maximum observed concentration in plasma). This indicates that the substance is bound in the tissues in considerable quantities.

Concentrations in the infected tissues, such as lungs, tonsil and prostate are higher than the MRC90 of the most frequently occurring pathogens after a single dose of 500 mg.

The protein binding of Azithromycin in serum is variable and varies, depending on the serum concentration, from 52% at 0.05 mg/l to 12% at 0.5 mg/l. The steady state distribution volume is 31.1 l/kg.

Elimination

The terminal plasma-elimination half-life closely follows the tissue depletion half-life from 2 to 4 days.

Approximately 12% of an intravenously administered dose of Azithromycin is, over a period of 3 days, excreted unchanged in the urine. High concentrations of unchanged Azithromycin were found in human bile. In this, ten metabolites were also detected (formed by N- and O- desmethylation, by hydroxylation of the desosamin and aglycon rings and by splitting the cladinose conjugate). A comparison of fluid chromatography and microbiological assessment methods shows that the metabolites are microbiologically inactive.

In animal models high concentrations of Azithromycin were found in phagocytes. Also it has been shown that during active phagocytosis higher concentrations of Azithromycin are released than during inactive phagocytosis. In animal models this process was shown to contribute to the accumulation of Azithromycin in infectious tissue.

5.3 Preclinical safety data

In animal tests in which the doses used amounted to 40 times the clinical therapeutic doses, Azithromycin was found to have caused reversible phospholipidosis, but as a rule no true toxicological consequences were observed which were associated with this. 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.
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 embryotoxicity studies in mice and rats no teratogenic effects were observed. In rats, Azithromycin dosages of 100 and 200 mg/kg bodyweight/day led to slight retardations in fetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, slight retardations in physical development and delay in reflex development were observed following treatment with 50 mg/kg/day Azithromycin and above.

6. Pharmaceutical particulars

6.1 List of excipients

- Sodium Propyl paraben
- Aspartam
- Sodium Carboxyl methyl Cellulose
- Colloidal silicon dioxide
- Sodium Methyl paraben
- Sucrose
- Sucralose
- Tartrazine Yellow
- Essence Lemon Premium dry powder

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place at a temperature below 30°C.

6.5 Nature and contents of container

20 ml HDPE bottle with measuring cap, Packed in printed and laminated carton.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing authorization holder

West Coast Pharmaceuticals Works Ltd.

8. Marketing authorization number(s)

Not Applicable

9. Date of first authorization/renewal of the authorization

Not Applicable

10. Date of revision of the text

November 2019