1.6.1 Prescribing information (Summary of products characteristics)

1. Name of the Finished Pharmaceutical Product

1.1 Product name:
AZAL-500
(AZITHROMYCIN TABLETS USP 500MG)

1.2 Strength:
Each Film coated Tablet Contains:
Azithromycin Dihydrate USP
Eq. to Azithromycin (Anhydrous) 500 mg
Excipients Q.S.
Colour: Yellow Oxide of Iron

1.3 Pharmaceutical dosage forms:
Oral-Film Coated Tablet

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Label Claim (mg)	Req. Qty/Tablet (mg)	Req. Qty/Batch (Kg)	Functions
Dry Mixing					
1.	Azithromycin Dihydrate USP Eq. to Azithromycin Anhydrous*	500.00	524.05	52.405	Antibiotic
2.	Maize Starch BP	-	168.00	16.800	Diluent
3.	Dibasic calcium Phosphate Anhydrous BP	-	118.00	11.800	Diluent
Binding					
4.	Povidone BP	-	20.00	2.000	Binder
5.	Maize Starch BP	-	40.00	4.000	Binder
6.	Sodium Benzoate BP	-	2.000	0.200	Preservative
7.	Purified Water BP **	-	Q.S.	Q.S. to Batch	Vehicle
Lubrication					
8.	Purified Talc BP	-	32.00	3.200	Glidant
9.	Sodium Starch Glycolate BP	-	14.00	1.400	Disintegrant
10.	Magnesium Stearate BP	-	20.00	2.000	Lubricant
11.	Colloidal anhydrous silica BP	-	14.00	1.400	Glidant
12.	Maize Starch BP	-	8.000	0.800	Disintegrant
Weight of Uncoated Tablets			**960.00 mg**	**96.00 Kg**	

Film Coating					
13.	Colorezy White IH	-	22.00	2.200	Film Former
14.	Yellow Oxide of Iron IH	-	2.000	0.200	Colouring agent
15.	Isopropyl Alcohol BP**	-	0.220 ml	22.00 Ltr.	Solvent
16.	Methylene Chloride BP**	-	0.320 ml	32.00 Ltr.	Solvent
Weight of Film Coated Tablets			**984.00 mg**	**98.40 kg**	

*Quantity to be calculated on the basis of its potency
**The materials that will not remain in the final product.

Calculation:

Azithromycin Dihydrate USP Eq. to Azithromycin (Anhydrous) 500 mg

$$\text{Calculated By} = \frac{\text{Label Claim X Molecular weight of Azithromycin Dihydrate}}{\text{Molecular weight of Azithromycin anhydrous}}$$

$$= \frac{500 \times 785.02}{748.98}$$

= 524.05 mg

3. Pharmaceutical forms

Yellow coloured oblong shaped, biconvex film coated tablet having break line on one side and plain on other side.

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:

- 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
- Infections of the skin and soft tissues of mild to moderate severity e.g. Folliculitis, cellulitis, erysipelas

4.2 Posology and Method of administration

Children and adolescents with a body weight above 45 kg, adults and the elderly:

The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5.

Elderly patients:

For elderly patients the same dose as for adults can be applied.

Patients with renal impairment:

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min).

Patients with hepatic impairment:

Dose adjustment is not required for patients with mild to moderate hepatic dysfunction.

Rout of Administration:

For oral administration only

4.3 Method of administration

Oral use only.

4.4 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 excipient used in manufacture of the product.

4.5 Special warning and precaution for use

Warnings

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), have been reported. Use of azithromycin should be undertaken with caution in patients with significant hepatic disease. However, because of the possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

As with any antibiotic preparation, it is recommended to pay attention to signs of superinfection with non-susceptible micro-organisms like fungi. A superinfection may require an interruption of the azithromycin treatment and initiation of adequate measures.Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with other macrolides, including Azithromycin.

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

4.6 Paediatric population

Safety and efficacy of Azithromycin in children under 12 years of age have not been established.

4.7 Interaction with other medicinal products and other forms of interactions

Antacids: Peak serum levels were reduced by approximately 25%. Azithromycin must be taken at least 1 hour before or 2 hours after antacids.
Digoxin (P-gp substrates): Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate.
Zidovudine: Single doses and multiple doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of Zidovudine or its glucuronide metabolite.
Ergotamine derivatives: Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.
Cisapride: Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsades de pointes.
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.
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 Cmax and AUC0-5 were found to be significantly elevated.
Fluconazole: Clinically insignificant decrease in Cmax (18%) of azithromycin was observed.
Nelfinavir: Coad ministration of azithromycin and nelfinavir at steady resulted in increased azithromycin concentrations.
Rifabutin: Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin.

4.8 Additional information on special populations
Not Applicable

4.9 Paediatric population
Safety and efficacy of Azithromycin in children under 12 years of age have not been established.

4.10 Fertility, 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.

Lactation:

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.

4.11 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.

4.12 Undesirable effects

Candidiasis, oral candidiasis, vaginal infection, Pseudomembranous colitis, Leukopenia, neutropenia, Thrombocytopenia, hemolytic anaemia, Angioedema, hypersensitivity, Anaphylactic reaction, Anorexia, Nervousness, Agitation, Aggression, anxiety, Dizziness, headache, paraesthesia, dysgeusia, Hypoaesethesia, somnolence, insomnia, Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, and Myasthenia gravis, Visual impairment, Deafness, Hearing impaired, tinnitus, Vertigo, Palpitations, Torsades de pointes, arrhythmia including ventricular tachycardia, Hypotension, Diarrhoea, abdominal pain, nausea,

flatulence, Vomiting, dyspepsia, Gastritis, constipation, Pancreatitis, tongue discolouration, Hepatitis, Hepatic function abnormal, Hepatic failure, which has rarely resulted in death, hepatitis fulminant, hepatic necrosis, jaundice cholestatic, Pruritus, rash, Stevens-Johnson syndrome, photosensitivity reaction, urticaria, Toxic epidermal necrolysis, erythema multiforme, Arthralgia, Renal failure acute, nephritis interstitial, Fatigue, Chest pain, oedema, malaise, asthenia

4.13 Overdose

Symptoms:

The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhoea.

Treatment:

In the event of overdose, general symptomatic and supportive measures are indicated as required.

5. Pharmacological properties

5.1 Pharmacodynamic 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.

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

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 pneumonia, betahaemolytic streptococcus of group A, Enterococcus faecalis and Staphylococcus aureus, including methicillin resistant S. aureus (MRSA) to erythromycin, azithromycin, other macrolides and lincosamides.

Susceptibility:
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Pathogens for which resistance may be a problem: prevalence of resistance is equal to or greater than 10% in at least one country in the European Union.

5.2 Pharmacokinetic Properties

Absorption:
Bioavailability of azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (Cmax) after a single dose of 500 mg is approximately 0.4 µg/ml.

Distribution:

Orally administered azithromycin is widely distributed throughout the body.

Pharmacokinetic studies have demonstrated that the concentrations of azithromycin measured in tissues are noticeably higher (up to 50 times the maximum observed concentration in plasma) than those measured in plasma. This indicates that the agent strongly binds to tissues (steady-state distribution volume approx. 31 l/kg).
At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 µg/g, 0,6-2,3 µg/g, 2,0-2,8 µg/g and 0-0,3 µg/ml have been measured in resp. lung, prostate, tonsil and serum.
In experimental in vitro and in vivo studies azithromycin accumulates in phagocytes. Release is stimulated by active phagocytosis. In animal models this process contributes to the accumulation of azithromycin in tissue.
Binding of azithromycin to serum proteins is variable and varies from 52% at 0.05 mg/l to 18% at 0,5 mg/l, depending on the serum concentration.

Excretion:
The terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4 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 Cmax and AUC0-120 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 Cmax and AUC0-120 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 have been measured after a 5 day treatment than in younger volunteers (< 45 years). These differences are not regarded as clinically relevant; dose adjustment is therefore not 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 Cmax 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

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:
Teratogenic effects were not observed in rat reproductive toxicity studies. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/ day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above.

6. Pharmaceutical Particulars

6.1 List of Excipients

Maize Starch
Dibasic calcium Phosphate Anhydrous
Povidone

Sodium Benzoate
Purified Water
Purified Talc
Sodium Starch Glycolate
Magnesium Stearate
Colloidal anhydrous silica
Colorezy White
Yellow Oxide of Iron
Methylene Chloride
Isopropyl Alcohol

6.2 Incompatibilities

None known.

6.3 Shelf Life

36 months from the date of manufacturing

6.4 Special precautions for storage

Store at a temperature not exceeding 30˚C in dry place, Protected from light. Keep out of reach of children.

6.5 Nature and contents of container

Packing: 10 X 3 Tablets Alu-PVC Blister Pack

Primary Packing:
3 Tablets are packed in printed aluminium foil on one side and plain aluminium foil on other side

Secondary Packing:
Such 10 Blister is packed in printed carton along with package insert.

6.6 Special precautions for disposal and other handling

None

7. Marketing authorisation holder and manufacturing site addresses

STALLION LABORATORIES PVT.LTD.
817, 8TH FLOOR, DEVPATH, OFF C. G. ROAD,
B/H LAL BUNGLOW, NR. SUPERMALL,
AHMEDABAD –380 006,
GUJARAT, INDIA.

8. Marketing authorisation numbers

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9. Date of First Registration/Renewal of the Registration

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10. Date of revision of Text

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11. Dosimetry (If Applicable)

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12. Instructions for Preparation of Radiopharmaceuticals (If Applicable)
