1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. **Name of the medicinal product:** Azithromycin Tablets USP 500 mg
2. **Qualitative and Quantitative composition:**

Composition:

Each film coated tablet contains:

Azithromycin Dihydrate USP

Eq. to Anhydrous Azithromycin …….500 mg

Excipients……..q.s.

Colour: Tartrazine

Composition of the product

Sr. No.	Ingredients Chemical Name	Specification	Standard Quantity (mg/Tablet)	% Overage	Function
Dry Mixing					
1	Azithromycin Dihydrate Eq. to Anhydrous Azithromycin*	USP	500.0	--	Active
2	Maize Starch @	BP	132.0	5	Diluents
3	Microcrystalline cellulose**	BP	138.0	--	Diluents
4	Lactose	BP	40.0	--	Diluents
Wet Granulation					
5	Povidone K-30	BP	15.0	--	Binder
6	Isopropyl alcohol#	BP	0.200 ml	--	Solvent
Lubrication					
7	Croscarmellose Sodium	BP	15.0	--	Disintegrant
8	Sodium Starch Glycolate	BP	15.0	--	Diluents
9	Magnesium Stearate	BP	5.0	--	Lubricant
10	Purified Talc	BP	8.0	--	Glidant
11	Colloidal Anhydrous Silica	BP	4.0	--	Glidant
	Weight of uncoated tablet		**890.00**	--	-
Coating					
12	Color Tartrazine film coat	IHS	18.00	--	Coating agent
13	Isopropyl alcohol#	BP	0.144 ml	--	Solvent
14	Dichloromethane #	BP	0.216 ml	--	Solvent
	Weight of coated tablet		**908.00**	--	-

@5% extra starch taken to compensate loss during drying.
*qty to be calculated on basis of assay and LOD.
** qty to be compensate.
# Not Present in Finish Product

BP: British Pharmacopoeia, USP: United State Pharmacopoeia, IHS: In house Specification

3. **Pharmaceutical Form:** Oral Tablets

Clinical Particulars:

Therapeutic Indications: Azithromycin 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

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

• Uncomplicated Chlamydia trachomatis urethritis and cervicitis

3.1 Posology and method of administration:

Posology

Azithromycin tablets should be given as a single daily dose. The duration of treatment in each of the infectious diseases is given below.

Adults, elderly, children and adolescents over 45 kg body weight

The total dosage of azithromycin is 1500 mg which is spread over three days (500 mg once daily).

Alternatively, the dosage can be spread over five days (500 mg as a single dose on the first day and thereafter 250 mg once daily).

In uncomplicated Chlamydia trachomatis urethritis and cervicitis the dosage is 1000 mg as a single oral dose.

For sinusitis, treatment is indicated for adults and adolescents 16 years of age and over.

Children and adolescents 45 kg and under body weight

Tablets are not indicated for these patients. Other pharmaceutical forms of azithromycin, e.g. suspensions may be used.

Elderly

No dose adjustments are required for elderly patients. Since elderly 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.

Method of administration

Oral use.

3.2 Contraindications:

Hypersensitivity to the active substance, to erythromycin or any macrolide or ketolide antibiotic or to any of the Excipients.

3.3 Special warning and precaution for use:

Allergic reactions

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal) have been reported alongside dermatological reactions, including acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and DRESS syndrome (Drug Reaction with Eosinophilia and Systemic Symptoms).

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance > 40 ml/min).

Hepatic impairment

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.

Infantile hypertrophic pyloric stenosis

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported.

Ergot alkaloids and azithromycin

The concurrent use of ergot alkaloids and macrolide antibiotics has been found to accelerate the development of ergotism. The interactions between ergot alkaloids and azithromycin have not been studied.

QT prolongation

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

Myasthenia gravis and azithromycin

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

Superinfections

As with any antibiotic preparation, observation for signs of superinfection with non-susceptible organisms, including fungi is recommended.

Pharyngitis/tonsillitis

Azithromycin is not the substance of first choice for the treatment of pharyngitis and tonsillitis caused by Streptococcus pyogenes.

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.

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 administered with caution to patients suffering from neurological or psychiatric diseases.

Long-term use

There is no experience regarding the safety and efficacy of long-term use of azithromycin for the mentioned indications. In case of rapid recurrent infections, treatment with another antibiotic should be considered.

3.4 Interaction with other medicinal products and other forms of interaction:

Antacids

When studying the effect of simultaneously administered antacid on the pharmacokinetics of azithromycin, no overall change has been observed in the bioavailability, although the peak concentrations of azithromycin measured in the plasma reduced by approximately 25 %.

Didanosine (Dideoxyinosine)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine (P-gp substrates)

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.

Zidovudine

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. Azithromycin does not interact significantly with the hepatic cytochrome P450 system.

Ergot derivatives

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

Astemizole and alfentanil

No data are available on interactions with astemizole and alfentanil. Caution should be exercised with concomitant use of these agents and azithromycin in view of the described potentiation of its effect during concomitant use of the macrolide antibiotic erythromycin.

Atorvastatin

Coadministration 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).

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.

Cisapride

Cisapride is metabolised in the liver by the enzyme CYP 3A4.

Cimetidine

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given 2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration of azithromycin pharmacokinetics was seen.

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.

Ciclosporin

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 ciclosporin, the resulting ciclosporin Cmax and AUC0-5 were found to be significantly elevated.

Efavirenz

Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz daily for 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole

Coadministration of a single dose of 1200 mg azithromycin did not alter the pharmacokinetics of a single dose of 800 mg fluconazole.

Indinavir

Coadministration of a single dose of 1200 mg azithromycin had no statistically significant effect on the pharmacokinetics of indinavir administered as 800 mg three times daily for 5 days.

Methylprednisolone

In a pharmacokinetic interaction study in healthy volunteers, azithromycin had no significant effect on the pharmacokinetics of methylprednisolone.

Midazolam

In healthy volunteers, coadministration of azithromycin 500 mg/day for 3 days did not cause clinically significant changes in the pharmacokinetics and pharmacodynamics of a single 15 mg dose of midazolam.

Nelfinavir

Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations.

Rifabutin

Coadministration of azithromycin and rifabutin did not affect the serum concentrations of either active.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin.

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 Cmax, of sildenafil or its major circulating metabolite.

Terfenadine

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine.

Theophylline

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam

In 14 healthy volunteers, coadministration of azithromycin 500 mg on Day 1 and 250 mg on Day 2 with 0.125 mg triazolam on Day 2 had no significant effect on any of the pharmacokinetic variables for triazolam compared to triazolam and placebo.

Trimethoprim/sulfamethoxazole

Coadministration of trimethoprim/sulfamethoxazole DS (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.

Protease inhibitors

There are no data available about a possible interaction with protease inhibitors.

Pregnancy and Lactation:

Pregnancy

There are no adequate data from 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 passes into human breast milk, but there are no adequate and well-controlled clinical studies in nursing women that have characterised 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. 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

3.5 Effects on the ability to drive and use machines: Not Applicable

3.6 Undesirable effects:

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
Immune System Disorders
Uncommon: Angioedema, hypersensitivity
Not Known: Anaphylactic reaction
Nervous System Disorders
Common: Headache, dizziness
Uncommon: Hypoaesthesia
Not Known: Syncope
Ear and Labyrinth Disorders
Common: Deafness
Uncommon: Ear disorder, vertigo
Cardiac Disorders
Uncommon: Palpitations
Not Known: Torsades de pointes
Vascular Disorders
Uncommon: Hot flushes
Not Known: Hypotension
Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea, epistaxis
Gastrointestinal Disorders
Common: Vomiting, dyspepsia
Uncommon: Constipation
Not Known: Pancreatitis
Hepatobiliary Disorders
Uncommon: Hepatitis**,** Abnormal hepatic function
Rare: Cholestatic jaundice
Not Known: Hepatic failure, hepatic necrosis

3.7 Overdose:

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. Characteristic symptoms of overdose with macrolide antibiotics include the following: reversible hearing loss, severe nausea, vomiting and diarrhoea.

4. Pharmacological Particulars:

4.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use; macrolides.
ATC code: J01FA10
MODE OF ACTION:
Azithromycin avoids the translocation of peptide chains from one side of the ribosome to the other by binding to the 50S ribosomal subunit. As a result, RNA-dependent protein synthesis in susceptible organisms is inhibited.

4.2 Pharmacokinetic properties

Absorption

Following oral administration the bio-availability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours. The mean maximum concentration observed (C_{max}) 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 shown considerably higher azithromycin concentrations in the tissues (up to 50 times the maximum concentration observed in the plasma). This indicates that the substance is extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). The mean maximum observed serum concentration (C_{max}) after a single dose of 500 mg is approx. 0.4 mg/mL, 2-3 hours after administration. With the recommended dosage no accumulation in the serum/plasma occurs.

Accumulation does occur in the tissues where the levels are much higher than in the serum/plasma.

Biotransformation and Excretion

The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 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, together with 10 metabolites (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the cladinose conjugate). Investigations suggests that the metabolites do not play a role in the micro-biological activity of azithromycin.

4.3 Preclinical safety data

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

Pharmaceutical Particulars:

4.4 List of Excipients:

- Maize Starch
- Microcrystalline cellulose
- Lactose
- Povidone K-30
- Isopropyl alcohol
- Croscarmellose Sodium
- Sodium Starch Glycolate
- Magnesium Stearate
- Purified Talc
- Colloidal Anhydrous Silica
- Color Tartrazine film coat
- Dichloromethane

4.5 Incompatibilities: None

4.6 Shelf Life: 36 months.

4.7 Special Precautions for storage:

Store below 30°C.

Protect from light & moisture.

4.8 Nature and contents of container:

03 Tablets are packed in Alu-PVC Blister. Such 1 blister is packed in carton with an insert.

4.9 Special precautions for disposal and other handling

Not Applicable

5. Marketing Authorization Holder:

Ratnatris Pharmaceuticals Pvt. Ltd.
Survey No. 416, At.- Indrad, Ta.- Kadi,
Dist.- Mehsana-382715, Gujarat, India

6. Marketing Authorization Number:

Not Applicable

7. Date of first Authorization /renewal of the authorization:

Not Applicable

8. Date of revision of text:

Not Applicable