SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

a. Product Name

AZITHRAA 500 (Azithromycin Tablets USP)

b. Strength

500 mg

c. Pharmaceutical dosage form

Tablet for oral administration

2. Quality and Quantitative Composition

Label claim

Each film coated tablet contains:

Azithromycin (as Dihydrate)

eq. to Azithromycin .....500 mg

For the full list of excipients, see section 6.1

3. Pharmaceutical Form: Tablet

Visual Description: Yellow coloured, caplet shape biconvex, film coated tablets having central break line on one side & plain on other side

4. Clinical Particulars

4.1 Therapeutic indication

Azithromycin is indicated for the following bacterial infections induced by micro-organisms susceptible 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

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method administration

Azithromycin film-coated tablets should be given as a single daily dose.

Adults

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

For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Older people

The same dosage as in adult patients is used for older people. Since older people can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes

Paediatric population

Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycine, e.g. suspensions, may be used.

In patients with renal impairment: No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min) .

Method of administration

Azithromycin Tablets should be given as a single daily dose. The tablets may be taken with food.

4.3. Contraindication

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 Warning and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

4.5. Interaction with other medicinal products and other forms of interactions

Effects of other medicinal products on azithromycin:

Antacids

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids and azithromycin, no effect on overall bioavailability was seen, although the peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

Co-administration of azithromycin prolonged-release granules for oral suspension with a single 20 ml dose of co-magaldrox (aluminium hydroxide and magnesium hydroxide) did not affect the rate and extent of azithromycin absorption.

Fluconazole Nelfinavir

Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects were observed and no dose adjustment is required.

Rifabutin

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

Neutropenia was observed in subjects receiving concomitant treatment of azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with azithromycin has not been established (see section 4.8).

Terfenadine

Pharmacokinetic studies have reported no evidence of an interaction between azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

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.

Effect of azithromycin on other medicinal products:

Ergotamine derivatives

Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended (see section 4.4).

Digoxin (P-gp substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with Pglycoprotein substrates such as digoxin, 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.

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. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

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 AUC0-5were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

Theophylline

There is no evidence of a clinically significant pharmacokinetic interaction when azithromycin and theophylline are co-administered to healthy volunteers. As interactions of other macrolides with theophylline have been reported, alertness to signs that indicate a rise in theophylline levels is advised.

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. Azithromycin serum concentrations were similar to those seen in other studies.

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. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients. Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advised in the co-administration of these medicines with azithromycin because of the known enhancing effect of these medicines when used concurrently with the macrolid 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). 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.

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.

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.

Didanosins (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.

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.

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.

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 聽 of sildenafil or its major circulating metabolite.

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.

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.

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.

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 the ability to drive and use machines

No information

4.8 Undesirable effects

About 13% of patients included in clinical trials reported adverse events most commonly gastrointestinal disorders.

System organ class	Common >1/100, <1/10	Uncommon >1/1000, <1/100	Rare >1/10000, <1/1000
Blood and lymphatic - system disorders			• thrombocytopenia • haemolytic anaemia • transient mild reductions in neutrophil counts have occasionally been observed in clinical trials for which a causal relationship with Azithromycin treatment has not been confirmed
Psychiatric disorders			• aggression • agitation • anxiety • nervousness • depersonalisation, in elderly patients delirium may occur.
Nervous system disorders		• dizziness/vertigo • somnolence • headache • convulsions • disruption to the patient's sense of smell and taste	• paraesthesia, syncope and asthenia • insomnia • hyperactivity
Ear and labyrinth disorders			• macrolide antibiotics have been reported to have caused hearing damage. In some patients receiving azithromycin, impaired hearing, deafness and ringing in the ears have been reported. Many of these cases relate to experimental studies in which Azithromycin was used in large doses over prolonged periods. According to available follow-up reports, the majority of these problems, however, were reversible
Cardiac disorders			• palpitations • arrhythmia including associated ventricular

			tachycardia. • there is a potential risk of QT prolongation and torsade de pointes, particularly in patients who are susceptible to these conditions
Gastrointestinal disorders	• nausea/vomiting • diarrhoea • abdominal discomfort (pain/cramps)	• loose stools (as a result of infrequent dehydration) • flatulence • anorexia • digestive disorders	• constipation • tongue discolouration • pancreatitis • discolouration of the teeth • pseudomembranous colitis
Hepatobiliary disorders			• abnormal liver function test values • hepatitis • cholestatic jaundice • rare cases of hepatic necrosis and hepatic failure which have rarely resulted in death
Skin and subcutaneous tissue disorders		• allergic reactions including pruritus and rash	• allergic reactions including angioneurotic oedema, urticaria and photosensitivity; serious skin reactions including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis
Musculoskeletal, connective tissue and bone disorders		• arthralgia	
Renal and urinary tract disorders			• interstitial nephritis • acute renal failure
Reproductive system and breast disorders		• vaginitis	
General disorders and administration site conditions			• anaphylaxis including oedema (rarely fatal) • asthenia • candidiasis

h. Overdose and special antidotes

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. In the event of overdosage, general symptomatic and supportive measures are indicatedas required.

Reporting of suspected adverse reactions:

Healthcare professionals are requested to report any suspected adverse reactions via the national Pharmacovigilance Electronic Reporting Systems to the respective national regulatory authorities.

5 Pharmacological Properties Clinical Particulars

5.1. Pharmacodynamic Properties

The mechanism of action of azithromycin is based on the suppression of bacterial protein synthesis, that is to say that it binds to the ribosomal 50s subunit and inhibits the translocation of peptides. Azithromycin acts bacteriostatic.

5.2. Pharmacokinetic properties

Absorption

After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours (Cmax after a single dose of 500 mg orally was approximately

0.4 mg/l).

Distribution

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50 times the maximum observed concentration in plasma) indicating that the active substance is heavily tissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 500 mg.

In experimental *in vitro* and *in vivo* studies azithromycin accumulates in the phagocytes, freeing is stimulated by active phagocytosis. In animal studies this process appeared to contribute to the accumulation of azithromycin in the tissue.

In serum the protein binding of azithromycin is variable and depending on the serum concentration varies from 50% in 0.05 mg/l to 12% in 0.5 mg/l.

Excretion

Plasma terminal elimination half-life closely reflects the tissue depletion half-life of 2 to 4 days. About 12% of an intravenously administered dose is excreted in the urine unchanged over a period of 3 days; the majority in the first 24

hours. Biliary excretion of azithromycin, predominantly in unchangedform, is a major route of elimination.

The identified metabolites (formed by N- and O- demethylising, by hydroxylising of the desosamine and aglycone rings, and by the splitting of the cladinose conjugate) are microbiologically inactive.

After a 5 day treatment slightly higher (29%) AUC values were seen in the elderly volunteers (>65 years of age) compared to the younger volunteers (< 45 years of age). However these differences are not regarded as clinically relevant; therefore a dose adjustment is not recommended.

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 > 80 ml/min). In subjects with severe renal impairment, the mean Cmax and AUC0-120 increased 61% and 33% 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.

Infants, toddlers, children and adolescents

Pharmacokinetics have 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 adults with 224 ug/l in children aged 0.6-5 years and after 3 days dosing and 383 ug/l in those aged 6-15 years. The t1/2 of 36 h in the older children was within the expected range for adults.

c. Pre clinical safety data

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6 Pharmaceutical Particulars

6.1. List of Excipients

Corn Starch USP
Microcrystalline Cellulose USP
Polyvidone (K-30) BP
Isopropyl alcohol BP
Sodium Starch Glycolate USP
Purified Water BP
Magnesium Stearate USP
Talc USP
Colloidal Silicon Dioxide USP
Cross Carmellose Sodium US(NF)
Insta coat EHP A10D00009 Yellow $

6.2. Incompatibilities

None

6.3. Shelf Life

24 months

Shelf life after dilution or reconstitution according to directions.

Not applicable

Shelf-life first opening the container.

Not applicable.

6.4. Special precaution for storage

Do not store above 25^0C. Protect from light.

6.5. Nature and content of container

PVC blister of 3 tablets.

1 such PVC blister is packed in a printed carton along with the pack insert.

6.6. No special requirements.

7 Marketing Authorization Holder

Pinnacle Life Science Pvt. Ltd.
Mahendra Industrial Estate, Ground Floor
Plot no .109-D, Rd no 29
Sion (East), Mumbai 400 022, INDIA

Manufacturer Name:
Pinnacle Life Science Pvt. Ltd.

Khasra No. 1328-1330, Village Manpura, Tehsil-Baddi, Distt. Solan, Himachal Pradesh (H.P.) - 174101, India.

8. Marketing Authorization Number:

H2022/CTD7238/14257

9. Date of first authorization/ renewal of the authorization

01 December 2022

10. Date of the revision of the text

01 December 2022