**1.3 Product Information**

**1.3.1 Summary of Product Characteristics (SmPC)**

**1- Name of the Medicinal Product:**

**1.1 Product Name**

**-Generic Name or International Non-Proprietary Name (INN)**

Azithromycin Tablet USP 500 mg

**-Brand Name**

PYTHROCIN

**1.2 Dosage Strength**

Each film coated tablet contains:

Azithromycin Dihydrate USP

Eq.to Azithromycin.....500mg

Excipients.....Q.S.

Colour: Titanium Dioxide

**1.3 Dosage Form**

Oral solid dosage form (Film Coated Tablet)

**2- Quality and Quantitative Composition:**

**2.1 Qualitative Declaration**

Each film coated tablet contains:

Azithromycin Dihydrate USP

Eq.to Azithromycin.....500mg

Excipients.....Q.S.

Colour: Titanium Dioxide

## 2.2 Quantitative Declaration

**Composition:**

Batch Size - 1, 00,000 Tablets

| Sr. No: | Ingredients | Spec. | Label Claim (mg) | Qty./Tab (mg) | Qty./ Batch 1 Lac Tab (kg) | Function |
|---|---|---|---|---|---|---|
| **SHIFTING/MIXING** | | | | | | |
| 1. | Azithromycin Dihydrate Eq. to Azithromycin | USP | 500 | 540.00 | 54.000 | Active |
| 2. | Maize Starch | BP | --- | 120.00 | 12.000 | Diluent |
| 3. | Calcium Hydrogen Phosphate Dihydrate | BP | --- | 80.00 | 8.000 | Diluent |
| 4. | Microcrystalline Cellulose (Plain) | BP | | 40.00 | 4.000 | Diluent |
| **PASTE PREPARATION** | | | | | | |
| 5. | Ethyl Cellulose | BP | --- | 14.00 | 1.400 | Binder |
| 6. | Isopropyl Alcohol* | BP | --- | 200.00 | 20.000 | Solvent |
| **LUBRICATION** | | | | | | |
| 7. | Colloidal Anhydrous Silica | BP | --- | 20.00 | 2.000 | Lubricant |
| 8. | Croscarmellose Sodium (Vivasol) | BP | --- | 14.00 | 1.400 | Super Disintegrant |
| 9. | Magnesium Stearate | BP | --- | 20.00 | 2.000 | Lubricant |
| 10. | Purified Talc (Talcum) | BP | --- | 12.00 | 1.200 | Glidant |
| **Average Wt. of Uncoated Tablet** | | | | **860 mg** | **Limit: 860.00 ± 5%** | |
| **COATING** | | | | | | |
| 11. | Hypromellose (H.P.M.C.E 15) | BP | --- | 7.00 | 0.700 | Film Forming Agent |
| 12. | Titanium Dioxide | BP | --- | 2.00 | 0.20 | Coloring Agent |
| 13. | Talcum (Purified Talc) | BP | --- | 1.00 | 0.100 | Glidant |
| 14. | Isopropyl Alcohol* | BP | --- | 150.00 | 15.000 | Coating Solvent |
| 15. | Methylene Chloride (Dichloromethane)* | BP | --- | 210.00 | 21.000 | Coating Solvent |
| | | | | | | |
| **Average wt. of Film Coated Tablet** | | | | **870 mg** | **Limit: 870.00 ± 5%** | |

**Note:** Active material was calculated on assay or Potency Basis.
USP = United states Pharmacopoeia
BP = British Pharmacopoeia
IHS= In-house Specification
*Does not found in finished product

**3- Pharmaceutical Form:**

PYTHROCIN, Azithromycin Tablet 500 mg available as White colored caplet shaped film coated tablets having break line on one side of the tablets

**4- Clinical Particulars:**

**4.1 Therapeutic indications**

Azithromycin tablets can be applied 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
- Skin and soft tissue infections
- Uncomplicated Chlamydia trachomatis urethritis and cervicitis

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

**4.2 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*

In uncomplicated *Chlamydia trachomatis* urethritis and cervicitis the dosage is 1,000 mg as a 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.

*Elderly people*

The same dose range as in adult patients may be used in the elderly. Since older elderly 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 film-coated 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 azithromycin, e.g. suspensions, may be used.

*Patients with renal impairment:*

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 30-80 ml/min).

*Patients with hepatic impairment:*

A dose adjustment is not necessary for patients with mild to moderately impaired liver function.

*Method of administration*

Azithromycin 500 mg film-coated tablet should be administered as a daily single dose. Azithromycin 500 mg film-coated tablet may be taken with food.

**4.3 Contraindications**

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

**4.4 Special warnings and precautions 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). A certain number of these reactions resulted in recurring symptoms and required an extended period of observation and treatment.

If an allergic reaction occurs, use of this medicinal product must be discontinued and the appropriate treatment initiated. Doctors must be aware that allergic symptoms can recur if symptomatic treatment is discontinued.

*Renal impairment*

No dose adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance > 40 ml/min). In patients with severe renal function impairment (GFR < 10 mL/min), a 33% increase in systemic exposure to azithromycin has been observed

*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. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have, or have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

Liver function disorders, hepatitis, cholestatic jaundice, liver necrosis and renal failure have been reported and have been fatal in a number of cases. Discontinue the use of azithromycin if signs and symptoms of hepatitis occur.

Pseudomembranous colitis has been reported following use of macrolide antibiotics. This diagnosis should therefore be taken into consideration in patients who develop diarrhoea after starting treatment with azithromycin.

*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. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.

*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. The development of ergotism is however possible, so that azithromycin and ergot alkaloid derivatives should not be administered simultaneously.

*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.

Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing proarrhythmic conditions (especially women and elderly patients) such as:

• Patients with congenital or documented acquired QT prolongation.

• Patients currently receiving treatment with other active substances that prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin.

• Patients with a disrupted electrolyte balance, particularly in cases of hypokalaemia and hypomagnesaemia

• Patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

*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.

*Clostridium difficile associated diarrhoea*

*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*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

**The following should be considered before prescribing azithromycin:**

Azithromycin film-coated tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.

As for other macrolides, high resistance rates of *Streptococcus pneumoniae* have been reported for azithromycin in some European countries. This should be taken into account when treating infections caused by *Streptococcus pneumoniae*.

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.

*Pharyngitis/tonsillitis*

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.

*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.

Due to cross-resistance existing among macrolides, in areas with a high incidence of erythromycin resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other macrolides.

Azithromycin is not the first choice for the empirical treatment of infections in areas where the prevalence of resistant isolates is 10% or more.

*Paediatric population*

Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex in children have not been established.

*This medicinal product contains soya oil*

Azithromycin contains soya oil. Patients, who are allergic to peanut or soya, must not use this medicinal product.

Azithromycin contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

**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 azithromycin and antacids, the medicinal products should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

*Efavirenz*

Co-administration 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. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in $C_{max}$ (18%) of azithromycin was observed.

*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 medicinal product.

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.

*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.

*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. 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 $C_{max}$ and $AUC_{0-5}$ were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these drugs. If 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, co-administration 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.

*Didanosine (Dideoxyinosine)*

Co-administration 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*

Co-administration 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*

Co-administration 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 $C_{max}$ 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 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.

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.

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.

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 machine**

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**

The table below lists the adverse reactions identified through clinical trial experience and post marketing surveillance by system organ class and frequency.

The frequency grouping is defined using the following convention:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000) and Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Adverse reactions possibly or probably related to azithromycin based on clinical trial experience and post-marketing surveillance:**

| System Organ Class | Frequency | Adverse reaction |
|---|---|---|
| Infections and infestations | Uncommon | Candidiasis<br>Vaginal infection<br>Pneumonia<br>Fungal infection<br>Bacterial infection<br>Pharyngitis<br>Gastroenteritis<br>Respiratory disorder<br>Rhinitis<br>Oral candidiasis |
| | Not known | Pseudomembranous colitis |
| Blood and lymphatic system disorders | Uncommon | Leukopenia<br>Neutropenia<br>Eosinophilia |
| | Not known | Thrombocytopenia<br>Haemolytic anaemia |
| Immune system disorders | Uncommon | Angioedema Hypersensitivity |
| | Not known | Anaphylactic reaction |
| Metabolism and nutrition disorders | Uncommon | Anorexia |
| Psychiatric disorders | Uncommon | Nervousness<br>Insomnia |
| | Rare | Agitation<br>Depersonalisation |
| | Not known | Aggression<br>Anxiety<br>Delirium<br>Hallucination |
| Nervous system disorders | Common | Headache |
| | Uncommon | Dizziness<br>Somnolence<br>Dysgeusia<br>Paraesthesia |
| | Not known | Syncope, convulsion<br>Hypoaesthesia<br>Psychomotor hyperactivity<br>Anosmia<br>Ageusia<br>Parosmia<br>Myasthenia gravis |
| Eye disorders | Uncommon | Visual impairment |
| | Not known | Blurred vision |
| Ear and labyrinth disorders | Uncommon | Ear disorder<br>Vertigo |
| | Not known | Hearing impairment including deafness and/or tinnitus |
| Cardiac disorders | Uncommon | Palpitations |
| | Not known | Torsades de pointes<br>Arrhythmia including ventricular |

| | | |
|---|---|---|
| | | tachycardia electrocardiogram QT prolonged |
| Vascular disorders | Uncommon | Hot flush |
| | Not known | Hypotension |

**4.9 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.

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, 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-homo-erythromycin A. The molecular weight is 749.0.

*Mechanism 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.

*Cardiac electrophysiology*:

QTc interval prolongation was studied in a randomised, placebo-controlled parallel trial in 116 healthy subjects, who received chloroquine (1000 mg), either alone or in combination with azithromycin (500 mg, 1000 mg and 1500 mg once daily). Concomitant administration of azithromycin increased the QTc interval in a dose and concentration-dependent manner. Compared to chloroquine alone, the maximum mean (95% upper confidence bound) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with concomitant administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.

**5.2 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. Three days after administration of 500 mg as a single dose or in split doses, concentrations of 1.3 to 4.8 mg/g, 0.6 to 2.3 mg/g, 2.0 to 2.8 mg/g and 0 to 0.3 mg/mL were detected in lung, prostate, tonsil and serum respectively. Concentrations in these target tissues exceed the MIC90 for likely pathogens.

In experimental *in vitro* and *in vivo* studies, azithromycin accumulates in phagocytes; release is promoted by active phagocytosis. In animal models this process appears to contribute to the accumulation of azithromycin in tissue.

The binding of azithromycin to plasma proteins is variable and varies from 52% at 0.005 μg/ml to 18% at 0.5 μg/ml, depending on the serum concentration.

*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.

*Pharmacokinetics in special populations*

*Renal impairment*

Following a single oral dose of azithromycin 1g, mean $C_{max}$ and $AUC_{0-120}$ increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 30-80 ml/min/1.73m$^2$) compared with normal renal function (GFR > 80

ml/min). In subjects with severe renal impairment (GFR < 30 ml/min/1.73m$^2$), the mean $C_{max}$ and $AUC_{0-120}$ increased 61% and 35% respectively compared to normal.

*Hepatic impairment*

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. There are no data on azithromycin use in cases of more severe hepatic impairment.

*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 were always observed after a 5-day course than in younger volunteers (<45 years). However, these differences are not considered to be clinically relevant; no dose adjustment is therefore recommended.

*Paediatric population*

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 $C_{max}$ achieved is slightly lower than 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 $t_{1/2}$ of 36h 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

No teratogenic effects were observed in embryotoxicity studies in rats after oral administration of azithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg body

weight/day led to mild retardations in fetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

**6- Pharmaceutical Particulars :**

**6.1 List of Excipients**

Maize Starch

Dibasic Calcium Phosphate

Microcrysatlline Cellulose (Plain)

Ethyl Cellulose

Colloidal Silicon Dioxide (Light)

Croscarmellose Sodium (Vivasol)

Magnesium Stearate

Talcum (Purified Talc)

H.P.M.C.E 15 (Hypromellose)

Talcum (Purified Talc)

Titanium Dioxide

**6.2 Incompatibilities**

None known

**6.3 Shelf life**

36 months from the date of manufacture.

**6.4 Special precautions for storage**

Store below 30°C. Protect from moisture.

**6.5 Nature and contents of container**

10 Tablets packed in one Alu-Alu Blister. Such 1 Alu-Alu Blisters packed in unit printed duplex board carton along with its package insert. Such cartons packed in export worthy shipper.

**Multipack style**: 1x3 Alu-PVC Blister, 10 x10 Alu Alu Blister/Strip

**Note**: All pack style may not be marketed

**7- Marketing Authorization Holder:** Globela Pharma Pvt. Ltd.

**8- Marketing Authorization Number (s):** G/28/1231

**-Product license / registration Number (s)**

**9- Manufacturer Name:**

**- Name :** **GLOBELA PHARMA PVT. LTD.**

**- Address :** 357-358, G.I.D.C,
Sachin, Surat – 394 230,
Gujarat, India

**- Phone :** +91– 261–6158000

**- E-mail :** Sales@globelapharma.com

**10- Date of first authorization/renewal of the authorization:**

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**11- Date of revision of the text:**

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