**1.3 Product Information**
**1.3.1 Summary of product characteristics (SmPC)**
**1. 3.1.1 Name of the medicinal product: AZITHROMYCIN 500 MG**
(Azithromycin Tablets USP 500mg)

**1.3. 1.2 Qualitative and quantitative composition:**
Each Film Coated Tablet Contains:
Azithromycin Dihydrate Equivalent to Azithromycin USP (500 mg)
Approved Colour Used. (- )
Excipients (QS)

| Sr. No. | Name of Ingredient | Specification | Label Claim | Over-ages added (In %) | Quantity/ Tablet in mg | Reason for Function |
|---|---|---|---|---|---|---|
| **a)** | **Dry Mixing** | | | | | |
| 1. | Azithromycin dihydrate | USP | Azithromycin dihydrate equivalent to Azithromycin 500mg | NA | 524.00 | Medicament |
| 2. | Calcium hydrogen phosphate dihydrate | BP | NA | NA | 23.42 | Diluent |
| 3. | Lactose monohydrate | BP | NA | NA | 15.00 | Diluent |
| 4. | Croscarmellose sodium | BP | NA | NA | 5.96 | Disintegrant |
| 5. | Povidone (K 30) | BP | NA | NA | 26.00 | Disintegrant |
| **b)** | **Binder Preparation** | | | | | |
| 6. | Maize starch | BP | NA | NA | 35.00 | Binder |
| 7. | Methyl hydroxybenzoate | BP | NA | NA | 0.42 | Preservative |
| 8. | Propyl hydroxybenzoate | BP | NA | NA | 0.22 | Preservative |
| 9. | Purified water | BP | NA | NA | -- | Vehicle |
| **c)** | **Lubrication** | | | | | |
| 10. | Sodium lauryl sulfate | BP | NA | NA | 2.98 | Lubricant |
| 11. | Magnesium stearate | BP | NA | NA | 7.00 | Lubricant |
| 12. | Croscarmellose sodium | BP | NA | NA | 20.00 | Disintegrant |
| | **Average weight of uncoated tablet (in mg)** | | | | **660.000** | |
| **d)** | **Film Coating** | | | | | |
| 13. | Hypromellose (15 CPS) | BP | NA | NA | 5.60 | Film Former |
| 14. | Macrogol-6000 | BP | NA | NA | 0.40 | Plasticizer |
| 15. | Titanium dioxide | BP | NA | NA | 1.00 | Colour |
| 16. | Purified talc | BP | NA | NA | 3.00 | Antiadherant |
| 17. | Purified water | BP | NA | NA | -- | Vehicle |
| | **Average weight of film coated tablet (in mg)** | | | | **670.000** | |

**1. 3.1.3 Pharmaceutical form:** Film coated Tablet

**Description:** White coloured, capsule shaped, biconvex, film coated tablet breakline on one side and plain on other side.

**1.3.1.4 Clinical Particulars**

**1.3.1.4.1 Therapeutic indications:**

**AZITHROMYCIN 500 MG (**Azithromycin Tablets USP 500mg) can be applied for the treatment of the following infections, when caused by microorganisms sensitive to azithromycin:

- acute bacterial sinusitis
- acute bacterial otitis media
- pharyngitis, tonsillitis
- acute exacerbation of chronic bronchitis
- mild to moderately severe community acquired pneumonia
- skin and soft tissue infections
- uncomplicated Chlamydia trachomatis urethritis and cervicitis

**1.3.1.4.2 Posology and method of administration**

~~Posology~~

**Adults**

In uncomplicated Chlamydia trachomatis urethritis and cervicitis the dose 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.

**Elderly people**

The same dose as in adult patients is used for elderly 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).

**In patients with hepatic impairment:** A dose adjustment is not necessary for patients with mild to moderately impaired liver function.

Method of administration

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

**1.3.1.4.3 Contraindications**

Hypersensitivity to the active substance, erythromycin, any macrolide or ketolide antibiotic, soya lecithin or to any of the excipients listed in section 1.3.1.6.1

**1.3.1.4.4 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.

If an allergic reaction occurs, the medicinal product should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

**Hepatoxicity**

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 had pre-existing hepatic diseaseor 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.

Abnormal liver function, hepatitis, cholestatic jaundice, hepatic necrosis, and hepatic failure have been reported, some of which have resulted in death. Discontinue azithromycin immediately if signs and symptoms of hepatitis occur.

**Infantile hypertrophic pyloric stenosis (IHPS)**

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.

**Pseudomembranous colitis**

Pseudomembranous colitis has been reported with the use of macrolide antibiotics. This diagnosis should therefore be considered in patients who get diarrhoea after starting treatment with azithromycin.

**Ergot derivatives**

In patients receiving ergotamine derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergotamine derivatives and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

**Cross resistance**

Cross-resistance exists between azithromycin and other macrolides (erythromycin, clarithromycin, roxithromycin), lincosamides and streptogramin B (MLSB phenotype). Concomitant use of several medicinal products from the same or related group of antibacterial agents is not recommended.

**Cardiovascular events**

Prolonged cardiac repolarisation and 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 arrhytmias (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 QT prolongation.
- Currently receiving treatment with other active substances known to 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

- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.

**~~Clostridoides difficile associated diarrhoea~~**

Clostridoides difficile associated diarrhoea (CDAD) has been reported with the 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 antimicrobial agents. In case of CDAD anti-peristaltics are contraindicated.

**~~Myasthenia gravis~~**

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

**~~Paediatric population~~**

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

**1.3.1.4.5 Interaction with other medicinal products and other forms of interaction 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 24%.

In patients receiving both azithromycin and antacids, the medicinal products should not be taken simultaneously, but with an interval of about 2 hours.

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

**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**

Co-administration of a single dose of 1,200 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 co-administration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

**Nelfinavir**

Co-administration of azithromycin (1,200 mg) and nelfinavir at steady state (750 mg three times daily) resulted in increased azithromycin concentrations. No clinically significant adverse effects ~~were obser~~ved and no dose adjustment is required.

**Rifabutin**

Co-administration 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:**

**~~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 co-administration 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.

**Zidovudine**

Single 1,000 mg doses and multiple 1,200 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.

**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.

**1.3.1.4.6 Pregnancy and Lactation Pregnancy**

There are no adequate and well-controlled studies on 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 is excreted in breast milk. Because of the long half-life, accumulation in the milk is possible. Information available from published literature indicates that, in short-term use, this does not lead to clinically relevant quantities in the milk. No serious side effects have been observed by azithromycin in breast-fed children.

A decision should be taken whether breastfeeding is discontinued or that treatment with azithromycin is discontinued/initiated or not, taking into account the benefit of breastfeeding for the child and the benefit of treatment for the woman.

**1.3.1.4.7 Effects on the 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.

**1.3.1.4.8 Undesirable effects**

The more common side effects of **AZITHROMYCIN 500 MG** (Azithromycin Tablets USP 500mg) can include Diarrhoea, nausea, stomach pain, vomiting.

Serious side effects can include:

- Liver problems. Symptoms can include: tiredness or weakness, loss of appetite, pain in your upper stomach, dark urine, yellowing of your skin or the whites of your eyes.
- QT prolongation. This can cause fast or irregular heart rhythm
- Allergic reactions. Symptoms can include: trouble breathing, swelling of your face, lips, tongue, or throat, hives
- Severe skin reactions, such as Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), or toxic epidermal necrolysis, which can cause symptoms such as red, blistering skin or skin sloughing (shedding dead skin cells)
- Infantile hypertrophic pyloric stenosis (in newborns). Symptoms can include: vomiting after eating, irritability with feeding, lack of weight gain.

**1.3.1.4.9 Overdoses**

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

**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 the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

**1.3.1.5 Pharmacological properties**

**1.3.1.5.1 Pharmacodynamic properties General properties**

Pharmacotherapeutic group: antibacterials for systemic use; macrolids; azithromycin, ATC code: J01FA10

Mode of action: 

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

**1.3.1.5.2 Pharmacokinetic properties**

**~~Absorption:~~** After oral administration the bioavailability of azithromycin is approximately 37%. Peak plasma levels are reached after 2-3 hours ($C_{max}$ 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 $MIC_{90}$ 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.

**~~Metabolism:~~** 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.

**~~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 unchanged form, is a major route of elimination.

**1.3.1.5.3 Preclinical safety Data:**

In high-dose animal studies, giving active substance concentrations 40 fold higher than those expected in clinical practice, azithromycin has been noted to cause reversible phospholipidosis, generally without discernible toxicological consequences. There is no evidence that this is of relevance to the normal use of azithromycin in humans.

*Carcinogenic potential:*

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

*Mutagenic potential:*

Azithromycin has shown no mutagenic potential in standard laboratory tests: mouse lymphoma assay, human lymphocyte clastogenic assay, and mouse bone marrow clastogenic assay.
*Reproductive toxicity:*
No teratogenic effects were observed in animal studies of embryotoxicity in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardations in foetal ossification and in maternal weight gain. In peri-/postnatal studies in rats, mild retardations following treatment with 50 mg/kg/day azithromycin and above were observed.

**1.3.1.6 Pharmaceutical particulars**

**1.3.1.6.1 List of excipients**
Calcium hydrogen phosphate dihydrate, Lactose monohydrate, Croscarmellose sodium, Maize starch, Povidone (K 30), Methyl hydroxybenzoate, Propyl hydroxybenzoate, Sodium Lauryl sulfate, Magnesium stearate, Hypromellose (15 CPS), Purified talc, Titanium dioxide, Macrogol-6000, Purified Water.

**1.3.1.6.2 Incompatibilities**
Not applicable

**1.3.1.6.3 Shelf life**
36 months

1.3.1.6.4 **Special precautions for storage** Store below 30°C in a dry & dark place. Keep all medicines out of reach of children.

**1.3.1.6.5 Nature and contents of container**
**Primary packing:** 10 Tablets in an ALU-ALU blister.
**Secondary packing:** 1 Blister is packed in an inner carton along with leaflet.
**Tertiary packing:** 10 Inner cartons are packed in an outer carton. Shrink individual outer carton. Such 100 Shrinks are packed in a 5 Ply shipper sealed with BOPP tape & strap with strapping roll.

**1.3.1.6.5 Special precautions for disposal and other handling**
None.

| | |
|---|---|
| **1.3.1.7 Applicant / Manufacturer** | |
| **Applicant** | |
| **Applicant name and address** | **M/s. AREPHARM AND AGROVET LTD.**<br>No 46/47 Haco House, Igbo Road, Kano |
| **Contact person's phone number** | |
| **Contact person's email** | |
| **Manufacturer** | |
| **Manufacturer name and address** | **M/s. IMPULSE PHARMA PVT. LTD.**<br>J-201, J-202/1 , MIDC Tarapur, Boisar,<br>Dist. Palghar - 401506, Maharashtra State, India. |
| **Contact person's phone number** | +91 7350864803 |
| **Contact person's email** | pravin.patil@kamlagroup.co.in |