1.3.1 Summary of Product Characteristics (smpc)

1. Name of the medicinal product

1.1 (Invented) name of the medicinal product

AXEREM-250

INN (GENERIC NAME)

AZITHROMYCIN TABLETS USP 250MG

1.2 Strength:- 250MG

1.3 Pharmaceutical form:- Tablets.

AXEREM-250
(AZITHROMYCIN TABLETS USP 250

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AXEREM-250 (AZITHROMYCIN TABLETS USP 250MG)
Each film coated tablet contains:
Azithromycin (Dihydrate) USP Equivalent to Anhydrous Azithromycin (250 mg)
Approved colour used. (-)
Excipients: (- QS)

Batch Size: 100,000 Tablets

Sr. No.	Ingredients	Specification	% Overages	Quantity/ Tablets (mg)	Quantity/ Batch (kg)
ACTIVE					
1.	Azithromycin	USP	250	524	52.4
EXCIPIENTS					
2.	Sodium Lauryl Sulphate	BP	--	10	1.0
3.	Dibasic Calcium Phosphate	BP	--	31	3.10
4.	Maize Starch**	BP	8	28	3.044
5.	P.V.P.K.30	BP	--	3	0.30
6.	Isopropyl Alcohol	BP	--	--	11.0
LUBRICANTS					
7.	Purified Talc	BP	--	10	1.0
8.	Magnesium Stearate	BP	--	3	0.30
9.	Sodium Lauryl Sulphate	BP	--	7	0.70
10.	Sodium Starch Glycolate	BP	--	5	0.50
11.	Cros Carmellose Sodium	BP	--	9	0.90
COATING					
12.	Methylene Chloride	BP		--	14.0
13.	Isopropyl Alcohol	BP		--	14.0
14.	H.P.M.C.E 15CPS	BP		10.89	1.089
15.	Titanium Dioxide	BP		1.19	0.119
16.	Purified Talc	BP		2.18	0.218
17.	Polyethylene glycol 4000	BP		1.98	0.198
18.	Propylene Glycol	BP		1.98	0.198
19.	Colour Tartrazine Yellow Lake	IH		0.69	0.069

USP=United stated pharmacopeia
BP = British Pharmacopoeia
IH=In House specification.
*524 mg of azithromycin (as dihydrate) is equivalent to about 250 mg of anhydrous Azithromycin
** 8 % Maize starch extra added to compensate loss during production
# we are applying total 3.00% solution for weight gaining (2.38%) & 0.62% evaporation loss.
Note:-Solvents used during the manufacturing process will be evaporated completely.

3. PHARMACEUTICAL FORM. :

Yellow coloured, elongated, biconvex, film coated tablets, having a breakline on one side of each tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

For 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

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

The total dosage of azithromycin is 1250 mg which is spread over three days (250 mg once daily).

Alternatively, the dosage can be spread over five days (250 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.

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 30-80 ml/min/1.73 m^2).

Patients with hepatic impairment

A dose adjustment is not necessary for patients with mild to moderately impaired liver function (Child-Pugh class A or B).

4.3 Contraindications:

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.or to erythromycin or 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) and 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 m/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.

4.5 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 %. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin should be taken at least 1 hour before or 2 hours after the antacid.

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.

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. 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.

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.

Ergot

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

Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

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 (250 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 metabolised 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.

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. 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.

Ciclosporin

In a pharmacokinetic study with healthy volunteers that were administered a 250 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. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

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. Total exposure and half-life of azithromycin were unchanged by the coadministration of fluconazole, however, a clinically insignificant decrease in Cmax (18%) of azithromycin was observed.

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 250 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. 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.

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (250 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. 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.

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

Protease inhibitors

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

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.

Breastfeeding

Azithromycin has been reported to be secreted into human breast milk, but there are no adequate and well controlled clinical studies in nursing women that have characterized the pharmacokinetics of azithromycin excretion into human breast milk.

Because it is not known whether azithromycin may have adverse effects on the breast-fed infant, nursing should be discontinued during treatment with azithromycin. Among other things diarrhoea, fungus infection of the mucous membrane as well as sensitisation is possible in the nursed infant. It is recommended to discard the milk during treatment and up until 2 days after discontinuation of treatment. Nursing may be resumed thereafter.

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 machines:

Tablets has no or negligible influence on the ability to drive and use machines. As dizziness and convulsions were reported with azithromycin, patients should be aware of how they react to this medicine before driving or operating machinery.

4.8 Undesirable Effects:

Multiple-dose regimens: Overall, the most common treatment-related adverse reactions in adult patients receiving multiple-dose regimens of Azithromycin were related to the gastrointestinal system with diarrhea/loose stools (4 to 5%), nausea (3%), and abdominal pain (2 to 3%) being the most frequently reported.

No other adverse reactions occurred in patients on the multiple-dose regimens of Azithromycin with a frequency greater than 1%. Adverse reactions that occurred with a frequency of 1% or less included the following:

Cardiovascular: Palpitations, chest pain
Gastrointestinal: Dyspepsia, flatulence, vomiting, melena, and cholestatic jaundice.
Genitourinary: Monilia, vaginitis, and nephritis.
Nervous System: Dizziness, headache, vertigo, and somnolence.
General: Fatigue.
Allergic: Rash, pruritus, photosensitivity, and angioedema.
Single 1gram dose regimen:
Overall, the most common adverse reactions in patients receiving a single-dose regimen of 1 gram of Azithromycin were related to the gastrointestinal system and were more frequently reported than in patients receiving the multiple-dose regimen.
Adverse reactions that occurred in patients on the single 1-gram dosing regimen of Azithromycin with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%), dyspepsia (1%), and vaginitis (1%).
Single 2-gram dose regimen:
Overall, the most common adverse reactions in patients receiving a single 2-gram dose of Azithromycin were related to the gastrointestinal system. Adverse reactions that occurred in patients in this study with a frequency of 1% or greater included nausea (18%), diarrhea/loose stools (14%), vomiting (7%), abdominal pain (7%), vaginitis (2%), dyspepsia (1%), and dizziness (1%). The majority of these complaints were mild in nature.
Pediatric Patients
Single and Multiple-dose regimens: The types of adverse reactions in pediatric patients were comparable to those seen in adults, with different incidence rates for the dosage regimens recommended in pediatric patients.
Acute Otitis Media: For the recommended total dosage regimen of 30 mg/kg, the most frequent adverse reactions (≥1%) attributed to treatment were diarrhea, abdominal pain, vomiting, nausea, and rash.

4.9 OVERDOSE:

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses.

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

Treatment-In cases of overdose the administration of medicinal charcoal and general symptomatic treatment and measures to support vital functions 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 Iactone 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

The action mechanism of azithromycin is based upon the suppression of bacterial protein synthesis, by binding to the 50 S subunit and thus inhibiting the translocation of peptides.

Mechanism of resistance

Generally, the resistance of different bacterial species to macrolides has been reported to occur by three mechanisms associated with target site alteration, antibiotic modification, or altered antibiotic transport (efflux). The efflux in streptococci is conferred by the mef genes and results in a macrolide-restricted resistance (M phenotype). Target modification is controlled by erm encoded methylases.

A complete cross-resistance exists among erythromycin, azithromycin, other macrolides and lincosamides for Streptococcus pneumoniae, beta-haemolytic streptococci of group A, Enterococcus spp. and Staphylococcus aureus, including methicillin-resistant S. aureus (MRSA).

Penicillin-sensitive S. pneumoniae are more likely to be susceptible to azithromycin than are penicillin-resistant strains of S. pneumoniae. Methicillin-resistant S. aureus (MRSA) is less likely to be susceptible to azithromycin than methicillin-sensitive S. aureus (MSSA).

The induction of significant resistance in both in vitro and in vivo models is ≤1 dilution rise in MICs for S. pyogenes, H. influenzaeand Enterobacterciae after nine sub-lethal passages of active substance and three dilution increase for S. aureus and development of in vitro resistance due to mutation is rare.

Breakpoints:

Azithromycin susceptibility breakpoints for typical bacterial pathogens.

EUCAST (European Committee on Antimicrobial Susceptibility Testing, version 3.1, 11-02-2013)

	MIC breakpoint (mg/L)

Pathogens	**Susceptible (mg/L)**	**Resistant (mg/L)**
Staphylococcus spp.	≤ 1	> 2
Streptococcus spp. (Group A, B, C, G)	≤ 0.25	> 0.5
Streptococcus pneumoniae	≤ 0.25	> 0.5
Haemophilus influenzae	≤ 0.12	> 4
Moraxella catarrhalis	≤ 0.25	> 0.5
Neisseria gonorrhoeae	≤ 0.25	> 0.5

Susceptibility

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

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

Table 1: Antibacterial spectrum of azithromycin

Species
Commonly susceptible species
Aerobic Gram-positive
Corynebacterium diphteriae
Streptococcus pneumoniae
Erythromycin-sensitive
Penicillin-sensitive
Streptococcus pyogenes
Erythromycin-sensitive
Aerobic Gram-negative
Bordetella pertussis
Escherichia coli-ETEC
Escherichia coli-EAEC
Haemophilus influenzae Haemophilus ducreyi
Legionella spp.
Moraxella catarrhalis
Erythromycin-sensitive
Erythromycin-intermediate
Pasteurella multocida
Anaerobic

Fusobacterium nucleatum Fusobacterium necrophorum
Prevotella spp.
Porphyromonas spp.
Propionibacterium spp.
Other micro-organisms
Chlamydia pneumoniae
Chlamydia trachomatis
Listeria spp.
Mycobacterium avium Complex
Mycoplasma pneumoniae
Species for which acquired resistance may be a problem
Aerobic Gram-positive
Staphylococcus aureus
Methicillin-susceptible
Coagulase-neg. staphylococci
Methicillin-susceptible^{+}
Streptococcus pneumoniae
Penicillin-intermediate
Penicillin-resistant
Erythromycin-intermediate
Streptococcus pyogenes
Erythromycin-intermediate
Streptococci viridans group
Penicillin-intermediate
Aerobic Gram-negative
Moraxella catarrhalis Erythromycin-resistant
Anaerobic
Peptostreptococcus spp.
Inherently resistant organisms
Aerobic Gram positive
Corynebacterium spp.
Enterococcus spp.
Staphylococci MRSA, MRSE
Streptococcus pneumoniae
Erythromycin-resistant

Penicillin & Erythromycin resistant
Streptococcus pyogenes
Erythromycin-resistant
Streptococci viridans group
Penicillin-resistant
Erythromycin-resistant
Aerobic Gram-negative
Pseudomonas aeruginosa
Anaerobic
Bacteroides fragilis group

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 (Cmax) after a single dose of 250 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). 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. Concentrations in target tissues such as lung, tonsil, and prostate exceed the MIC90 for likely pathogens after a single dose of 250 mg.

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.

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 Cmax and AUC0-120 increased by 5.1% and 4.2% respectively, in subjects with mild to moderate renal impairment (glomerular filtration rate of 30-80 ml/min/1.73m2) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment (GFR < 30 ml/min/1.73m2), the mean Cmax and AUC0-120 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 Cmax 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 t1/2 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.

Sodium Lauryl Sulphate BP, Dibasic calcium Phosphate BP, Maize Starch BP, P.V.P. K. 30 BP, Isopropyl Alcohol BP, Purified Talc BP, Magnesium Stearate BP, Sodium Lauryl Sulphate BP, Sodium Starch Glycolate BP, Cross Carmellose Sodium BP, Methylene Chloride BP, Hydroxypropyl Methyl Cellulose BP, Titanium dioxide BP, Polyethylene glycol 4000 BP, Propylene Glycol BP, Colour Tartrazine Yellow Lake IH .

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

Store in cool & dry place

6.5 Nature and contents of container

ALU-ALU Blister Pack of 10 Tablets (10 X1X10).