Product Name: P-AZITH-250	
Generic Name: Azithromycin Tablets USP 250 mg	
SUMMARY PRODUCT CHARACTERISTICS	

PRESCRIBING INFORMATION

Product information for Health Professionals

1. NAME OF THE MEDICINAL PRODUCT

P-AZITH-250

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Azithromycin Dihydrate USP equivalent to
Azithromycin (Anhydrous) 250mg
Excipients q.s.
Colour : Lake of Tartrazine

3. PHARMACEUTICAL FORM

Film coated Tablets
White coloured, Oblong Shaped, Biconvex, Film coated tablets with break line on one side.

4. CLINICAL PARTICULARS

Therapeutic indications

For the treatment of the following infections when caused by micro-organisms sensitive to azithromycin (see sections 4.4 and 5.1):

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis
- Acute exarcebation 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

Posology and method of administration

Posology

The duration of treatment in each of the infectious diseases is given below

Paediatric population over 45 kg body weight, adults

The total dosage of azithromycin is 1500 mg which is spread over three days (500 mg once daily). Alternatively, the dosage can be spread over five days (500 mg as a single dose on the first day and thereafter 250 mg once daily).

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

For sinusitis, treatment is aimed at adults and adolescents over 16 years of age.

Paediatric population under 45 kg body weight

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

Older people

The same dosage as in adult patients is used in the 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. (see Section 4.4 Special warnings and precautions for use).

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10- 80 ml/min) (see section 4.4).

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) (see section 4.4).

Method of administration

Azithromycin tablets should be given as a single daily dose. The tablets can be taken with or without food.

Contraindications

Hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic or to any of the excipients.

Special warnings and precautions for use

Azithromycin is not the first choice for the empirical treatment of infections in areas where the prevalence of resistant isolates is 10% or more (see section 5.1).

Allergic reactions

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.

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 (see Section 4.8). Some patients may 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.

Ergot alkaloids and azithromycin

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

Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment (GFR 10-80 ml/min. Caution is advised in patients with severe renal impairment (GFR < 10 ml/min) because in these patients a 33 % increase in systemic exposure of azithromycin was observed (see Section 5.2 Pharmacokinetic properties).

QT prolongation

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 (See Section Undesirable effects). 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 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 hypomagnesemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

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.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to azithromycin and other antibiotics.
As for other macrolides, high resistance rates of Streptococcus pneumoniae (> 30 %) have been reported for azithromycin in some European countries (see section 5.1). 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.

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

Neurological or psychiatric diseases
Azithromycin should be administered with caution to patients suffering from neurological or psychiatric diseases.

Myasthenia gravis
Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin (see section 4.8).

Clostridium difficile-associated diarrhoea
Clostridium 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. A careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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.
The safety and efficacy of azithromycin for the prevention or treatment of Mycobacterium avium complex (MAC) infection in children have not been established.

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 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. 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.

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)

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 (P-gp substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein 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.

Zidovudine

Single 1000 mg dose 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 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 (see Section 4.4 Special warnings and special precautions for use).

Pharmacokinetic studies have been conducted between azithromycin and the following

agents known to undergo significant cytochrome P450-mediated metabolism.

Atorvastatin

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentration 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.

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 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 prothrombin time monitoring when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin C_{max} and AUC_{0-5} were found to be significantly elevated. Consequently, caution should be exercised before considering concurrent administration of these agents. If combination treatment is necessary, the ciclosporin levels should be carefully monitored and the dosage 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

Co-administration 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.

Indinavir

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

Methylprednisolone

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

Midazolam

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

Nelfinavir

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

Sildenafil

In normal healthy male volunteers, there was no evidence of an effect of azithromycin (500 mg daily for three 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.

Azithromycin should be administered with caution in combination with terfenadine.

Theophylline

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

Triazolam

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

Trimethoprim/sulphamethoxazole

Coadministration of trimethoprim/sulphamethoxazole 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 sulphamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP3A4. Because macrolides inhibit this enzyme, concomitant administration of cisapride may cause the increase of QT interval prolongation, ventricular arrhythmias and torsade de pointes.

CYP3A4 substrates
Even though azithromycin does not appear to inhibit the enzyme CYP3A4, caution is advised when combining the medicinal product with quinidine, cyclosporine, cisapride, astemizole, terfenadine, ergot alkaloids, pimozide or other medicinal products with a

narrow therapeutic index predominantly metabolised by CYP3A4.

Astemizole, 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.

Substances that prolong the QT interval

Azithromycin should not be used concurrently with other active substances that prolong the QT interval (see section 4.4).

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 passes into 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.

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.

Effects on 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.

Undesirable effects

Like all medicines P-AZITH-250 can cause side effects although not everybody gets them. Tell your doctor immediately if you experience any of the following symptoms

after takingthis medicine as the symptoms can be severe.

- sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching(especially affecting the whole body)
- severe or prolonged diarrhoea, which may have blood or mucus in it, during or after treatmentwith P-AZITH-250 as this may be a sign of serious bowel inflammation

- severe skin rash causing redness and flaking
- rapid or irregular heartbeat
- low blood pressure

The most common side effects that occur when taking P-AZITH-250 are listed below. These may goaway during treatment as your body adjusts to the medicine. Tell your doctor if any of these sideeffects continue to bother you.

Very common side effects (may affect more than 1 in 10 people):

- stomach cramps, feeling sick, diarrhoea, wind

Common side effects (may affect up to 1 in 10 people):

- dizziness, headache
- numbness or pins and needles
- being sick, indigestion
- loss of appetite, taste disturbance
- visual disturbances, deafness
- skin rash and /or itching
- joint pain
- low numbers of lymphocytes (type of white blood cells), higher number of eosinophils (type ofwhite blood cells)
- low blood bicarbonate
- tiredness or weakness

Uncommon side effects (may affect up to 1 in 100 people):

- yeast infections of the mouth and vagina (thrush)
- low numbers of leukocytes (type of white blood cells), low number of neutrophils (type of whiteblood cells)
- allergic reactions of various severity
- blistering of the skin, mouth, eyes and genitals
- skin more sensitive to sunlight than normal
- feeling nervous
- reduced sense of touch or sensation (hypoesthesia)
- sleepiness or sleeplessness (insomnia)
- poor hearing or ringing in the ears

• heart palpitations, chest pain
• constipation, stomach pain associated with diarrhoea and fever
• inflammation of the liver (hepatitis), changes in liver enzymes
• general loss of strength
• swelling
• general discomfort
• abnormal laboratory test values (e.g. blood or liver tests).

Rare side effects (may affect up to 1 in 1,000 people):
• agitation
• vertigo
• changes in liver function

Other side effects that have been reported, but frequency cannot be estimated from theavailable data:
• fits or fainting
• aggression or anxiety
• feeling hyperactive
• localised muscle weakness
• loss of smell or altered sense of smell, loss of taste
• tongue discolouration
• inflammation of the pancreas (pancreatitis)
• inflammation of the kidney or kidney failure
• yellowing of the skin or eyes (jaundice) or liver failure (rarely life-threatening)
• bruising or prolonged bleeding after injury
• blistering of the skin, severe skin reaction
• abnormal electrocardiogram (ECG)

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

Pharmacotherapeutic group: Antibacterials for systemic use; macrolides.
ATC code: J01FA10.

Pharmacodynamic properties

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

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.

(Cross)-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 MICsfor *S. pyogenes, H. influenzae* and *Enterobacterciae* after nine sub-lethal passages of active substanceand three dilution increase for *S. aureus* and development of *in vitro* resistance due to mutation is rare.

Azithromycin susceptibility breakpoints for typical bacterial pathogens:

- *Staphylococcus* spp.: susceptible ≤ 1 mg/l and resistant >2 mg/l

- *Haemophilus influenzae*: susceptible ≤ 0.12 mg/l and resistant > 4 mg/l
- *Moraxella catarrhalis*: susceptible ≤ 0.5 mg/l and resistant > 0.5 mg/l
- *Streptococcus* spp. including groups A, B, C, G and *Streptococcus pneumoniae*: susceptible
  ≤ 0.25 mg/l and resistant > 0.5 mg/l

  The prevalence of acquired resistance may vary geographically and with time for selected species andlocal 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 theagent in at least some types of infections is questionable.

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

  List: 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 Species
Chlamydia
pneumoniae
Chlamydia
trachomatis

Listeria spp.
Mycobacterium avium
Complex *Mycoplasma*
pneumoniae Ureaplasma
urealyticum

Species for which acquired resistance may bea
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

+ Resistance is greater than 50%.

Pharmacokinetic properties

Absorption

Following oral administration the bio-availability of azithromycin is approximately 37%. Peak plasma
levels are reached after 2-3 hours.

Distribution

Orally administered azithromycin is widely distributed throughout the body. Pharmacokinetic studieshave shown considerably higher azithromycin concentrations in the tissues (up to 50 times themaximum concentration observed in the plasma) than in the plasma. This indicates that the substanceis extensively bound in the tissues (steady-state volume of distribution approximately 31 l/kg). Themean maximum concentration observed (Cmax) after a single dose of 500 mg is approximately0.4 μg/ml, 2-3 hours after administration. With the recommended dosage no accumulation in theserum/plasma occurs. Accumulation does occur in the tissues where the levels are much higher than inthe serum/plasma. Three days after administration of 500 mg as a single dose or in divided dosesconcentrations of 1.3-4.8 μg/g, 0.6-2.3 μg/g, 2.0-2.8 μg/g and 0-0.3 μg/ml are found in lung, prostate,tonsil and serum respectively.
Mean peak concentrations measured in peripheral leukocytes are higher than the MIC90 of the mostcommon pathogens.
In experimental *in vitro* and *in vivo* studies, azithromycin accumulates in phagocytes; release ispromoted by active phagocytosis. In animal models this process appeared to contribute to theaccumulation of azithromycin in the tissue.
The binding of azithromycin to plasma proteins is variable, and varies from 52 % at 0.05 μg/ml to 18% at 0.5 μg/ml, depending on the serum concentration.

Biotransformation and Elimination

The terminal plasma elimination half-life follows the tissue depletion half-life of 2 to 4 days. In oldervolunteers (>65 years), higher (29 %) AUC values were always observed after a 5- day course than inyounger volunteers (<45 years). However, these differences are not considered to be clinicallyrelevant; no dose adjustment is therefore recommended. Approximately 12% of an intravenouslyadministered dose is excreted in unchanged form with the urine over a period of 3 days; the majorproportion in the first 24 hours. Concentrations of up to 237 μg/ml azithromycin, 2 days after a 5-daycourse of treatment,

have been found in human bile, together with 10 metabolites (formed by N- andO-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of thecladinose conjugate). A comparison of HPLC and microbiological determination suggests that themetabolites 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 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renalimpairment (GFR < 10 ml/min), 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 inserum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients,urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepaticclearance. There are no data on azithromycin use in cases of more severe hepatic impairment.

Older People

The pharmacokinetics of azithromycin in older men was similar to that of young adults; however, inelderly women, although higher peak concentrations (increased by 30-50%) were observed, nosignificant accumulation occurred.

Pediatric population

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules orsuspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the Cmax achieved is slightlylower than adults with 224 μg/l in children aged 0.6-5 years and after 3 days dosing and 383 μg/l inthose 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 noassociated toxicological consequences. The relevance of this finding to humans receivingazithromycin 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* testmodels.

Reproductive toxicity

No teratogenic effects were observed in embryotoxicity studies in rats after oral administration ofazithromycin. In rats, azithromycin dosages of 100 and 200 mg/kg body weight/day led to mildretardations in fetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mildretardations following treatment with 50 mg/kg/day azithromycin and above were observed.

6. PHARMACEUTICAL PARTICULARS

List of Excipients Tablet

Core

Maize Starch
Di basic Calcium
Phosphate Microcrystalline
cellulose Kyron T-314
Sodium Benzoate
Sodium Methyl
Paraben Sodium
Propyl Paraben
Talcum
Magnesium Stearate
Sodium Starch
Glycolate

Coating Material

Isopropyl Alcohol
Methylene Dichloride
Lake of Tartrazine

Incompatibilities

Not Known

Shelf life

24 Months

Special precautions for storage

Do not store above 25°C. Protect from moisture and light.

Nature and contents of container

Blister Pack

3 Tablets are blister packed with Aluminum-PVC foil; such 1 blisters packed in one carton pack.

Pack size: 1 X 3 Tablets in one carton (3 Tablets) along with packing leaflet.

Special precautions for disposal

No special requirements

7. MANUFACTURARE

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8. Date of Publication or Revision

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