SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZITHROSET 500 (Azithromycin Tablets USP 500mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Azithromycin dihydrate USP Eq. to Azithromycin 500 mg

Excipient with known effect:
'Contains Lactose: 40mg/Tablet'

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablet

Yellow coloured biconvex, capsule shaped film coated tablet, having break line on one side.
'The tablet can be divided into equal doses.'

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZITHROSET 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

Adults

In uncomplicated Chlamydia trachomatis urethritis and cervicitis the dosage is 1000 mg as a single oral dose.
For all other indications the dose is 1500 mg, to be administered as 500 mg per day for three consecutive days. As an alternative the same total dose (1500 mg) can also be administered over a period of five days with 500 mg on the first day and 250 mg on the second to the fifth day.

Older people

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

Paediatric population
Azithromycin tablets should only be administered to children weighing more than 45 kg when normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycin, 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
ZITHROSET Tablets should be given as a single daily dose. The tablets may be taken with food.

4.3 Contraindications

ZITHROSET is contraindicated in patients with a known hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

4.4 Special warnings and precautions for use

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema 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.

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 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.

In patients receiving ergotamine derivatives, ergotism has been precipitated by co-administration 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.
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 older people) 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.
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. 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-peristaltic are contraindicated.

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy.
Safety and efficacy for the prevention or treatment of Mycobacterium Avium Complex (MAC) in children have not been established.

<u>The following should be considered before prescribing azithromycin:</u>
ZITHROSET tablets are not suitable for treatment of severe infections where a high concentration of the antibiotic in the blood is rapidly needed.
ZITHROSET is not the first choice for the empiric treatment of infections in areas where the prevalence of resistant isolates is 10% or more.
“If you have been told by your doctor that you have been an intolerance to some sugars, contact your doctor before taking this medicinal product,”
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. This should be taken into account when treating infections caused by Streptococcus pneumoniae.

<u>Pharyngitis/ tonsilitis</u>
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.

Skin and soft tissue infections

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.

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. palladium should be excluded.

Neurological or psychiatric diseases

Azithromycin should be used with caution in patients with neurological or psychiatric disorders.

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

In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Excipients

Lactose

Azithromycin Film-coated Tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously. Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

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

Fluconazole

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 co-administration of fluconazole, however, a clinically insignificant decrease in C_{max} (18%) of azithromycin was observed.

Nelfinavir
Co-administration 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
Co-administration 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.

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 (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.

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.

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 co-administration 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

Co-administration 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

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.

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.**

Didanosins (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, co-administration 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, co-administration 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.

Breast-feeding
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
There is no evidence to suggest that azithromycin 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 experience and post-marketing surveillance by system organ class and frequency. Adverse reactions identified from post-marketing experience are included in italics. 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); 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 Vaginal infection Pneumonia Fungal infection Bacterial infection Pharyngitis Gastroenteritis Respiratory disorder Rhinitis Oral candidiasis
	Not known	Pseudomembranous colitis
Blood and lymphatic system disorders	Uncommon	Leukopenia Neutropenia Eosinophilia

	Not known	Thrombocytopenia Haemolytic anaemia
Immune system disorders	Uncommon	Angioedema Hypersensitivity
	Not known	Anaphylactic reaction
Metabolism and nutrition disorders	Uncommon	Anorexia
Psychiatric disorders	Uncommon	Nervousness Insomnia
	Rare	Agitation Depersonalisation
	Not known	Aggression Anxiety Delirium Hallucination
Nervous system disorders	Common	Headache
	Uncommon	Dizziness Somnolence Dysgeusia Paraesthesia
	Not known	Syncope, convulsion Hypoaesthesia Psychomotor hyperactivity Anosmia Ageusia Parosmia Myasthenia gravis
Eye disorders	Uncommon	Visual impairment
Ear and labyrinth disorders	Uncommon	Ear disorder Vertigo
	Not known	Hearing impairment including deafness and/or tinnitus
Cardiac disorders	Uncommon	Palpitations
	Not known	Torsades de pointes Arrhythmia including ventricular tachycardia Electrocardiogram QT prolonged
Vascular disorders	Uncommon	Hot flush
	Not known	Hypotension

Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea
	Common	Vomiting Abdominal pain Nausea
	Uncommon	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominal distension Dry mouth Eructation Mouth ulceration Salivary hypersecretion
	Not known	Pancreatitis Tongue discolouration
Hepatobiliary disorders	Uncommon	Hepatitis
	Rare	Hepatic function abnormal Jaundice cholestatic
	Not known	Hepatic failure (which has rarely resulted in death)* Hepatitis fulminant Hepatic necrosis
Skin and subcutaneous tissue disorders	Uncommon	Rash Pruritus Urticaria Dermatitis Dry skin Hyperhidrosis
	Rare	Photosensitivity reaction
	Not known	Steven-Johnson syndrome Toxic epidermal necrolysis Erythema multiforme
Musculoskeletal and connective tissue disorders	Uncommon	Osteoarthritis Myalgia Back pain Neck pain
	Not known	Arthralgia

Renal and urinary disorders	Uncommon	Dysuria Renal pain
	Not known	Renal failure acute Nephritis interstitial
Reproductive system and breast disorders	Uncommon	Metrorrhagia Testicular disorder
General disorders and administration site conditions	Uncommon	Oedema Asthenia Malaise Fatigue Face oedema Chest pain Pyrexia Pain Peripheral oedema
Investigations	Common	Lymphocyte count decreased Eosinophil count increased Blood bicarbonate decreased Basophils increased Monocytes increased Neutrophils increased
	Uncommon	Aspartate aminotransferase increased Alanine aminotransferase increased Blood bilirubine increased Blood urea increased Blood creatinine increased Blood potassium abnormal Blood alkaline phosphatase increased Chloride increased Glucose increased Platelets increased Hematocrit decreased Bicarbonate increased Abnormal sodium
Injury and poisoning	Uncommon	Post procedural complication

* Which has rarely resulted in death

Adverse reactions possibly or probably related to Mycobacterium Avium Complex prophylaxis and treatment based on clinical trial experience and post-marketing surveillance. These adverse reactions differ from those reported with immediate release or the prolonged release formulations, either in kind or in frequency:

System Organ Class	**Frequency**	**Adverse reaction**

Metabolism and nutrition disorders	Common	Anorexia
Nervous system disorders	Common	Dizziness Headache Paraesthesia Dysgeusia
	Uncommon	Hypoaesthesia
Eye disorders	Common	Visual impairment
Ear and labyrinth disorders	Common	Deafness
	Uncommon	Hearing impaired Tinnitus
Cardiac disorders	Uncommon	Palpitations
Gastrointestinal disorders	Very common	Diarrhoea Abdominal pain Nausea Flatulence Abdominal discomfort Loose stools
Hepatobiliary disorders	Uncommon	Hepatitis
Skin and subcutaneous tissue disorders	Common	Rash Pruritus
	Uncommon	S t e v e n - J o h n s o n syndrome Photosensitivity reaction
Musculoskeletal and connective tissue disorders	Common	Arthralgia
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Asthenia Malaise

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to **TMDA**

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

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.

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.

Breakpoints

EUCAST (European Committee on Antimicrobial Susceptibility Testing)

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	≤ 0.5	> 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 of susceptibility

Commonly susceptible species
Aerobic Gram-negative microorganisms

Haemophilus influenzae*
Moraxella catarrhalis*
Other microorganisms
Chlamydophila pneumoniae
Chlamydia trachomatis
Legionella pneumophila
Mycobacterium avium
Mycoplasma pneumonia*
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Staphylococcus aureus*
Streptococcus agalactiae
Streptococcus pneumoniae*
Streptococcus pyogenes*
Other microorganisms
Ureaplasma urealyticum
Inherently resistant organisms
Aerobic Gram-positive microorganisms
Staphylococcus aureus – methicillin resistant and erythromycin resistant strains
Streptococcus pneumoniae – penicillin resistant strains
Aerobic Gram-negative microorganisms
Escherichia coli
Pseudomonas aeruginosa
Klebsiella spp.
Anaerobic Gram-negative microorganisms
Bacteroides fragilis group

* Clinical effectiveness is demonstrated by sensitive isolated organisms for approved clinical indications.

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.

Excretion

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

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

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

Pharmacokinetics in special populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, mean 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 10-80 ml/min) compared with normal renal function (GFR > 80 ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 33% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to normal hepatic function. In these patients, urinary recovery of azithromycin appears to increase perhaps to compensate for reduced hepatic clearance.

Elderly

The pharmacokinetics of azithromycin in elderly men was similar to that of young adults; however, in elderly women, although higher peak concentrations (increased by 30-50%) were observed, no significant accumulation occurred.

Infants, toddlers, children and adolescents

Pharmacokinetics have been studied in children aged 4 months – 15 years taking capsules, granules or suspension. At 10 mg/kg on day 1 followed by 5 mg/kg on days 2-5, the C_{max} achieved is slightly lower than adults with 224 ug/l in children aged 0.6-5 years and after 3

days dosing and 383 ug/l in those aged 6-15 years. The $t_{1/2}$ of 36 h in the older children was within the expected range for adults.

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 dosages 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Starch, Dicalcium Phosphate, Lactose, PVPK-30, Talcum, Magnesium Stearate, Colloidal Silicon Dioxide, Croscarmellose Sodium, Sodium Starch Glycolate, Ready-mix Coat Material and Yellow oxide of iron

Qualitative composition of Ready-Mix coat - Hydroxypropyl methylcellulose (H.P.M.C.) E-5, PVP K-30, Talcum, Titanium Dioxide & Polyethylene glycol 4000.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light.

6.5 Nature and contents of container

1 x 3 Tablets Alu-PVC Blister packed in a unit carton.

6.6 Special precautions for disposal and other handling

“Any unused product or waste material should be disposed of in accordance with local requirements”.

7. MARKETING AUTHORIZATION HOLDER & MANUFACTURER:

INNOVA CAPTAB LIMITED
1281/1, Hilltop Industrial Estate,
Near EPIP Phase-1, Jharmajri, Baddi
Distt. Solan (H.P.) India
Pin-173205

Local Technical Representative:
KAS MEDICS LTD.
P.O.BOX No. 7856,
Umoja Complex, Vingunguti Industrial Area.
Dar es Salaam, Tanzania

8. MARKETING AUTHORISATION NUMBER(S)

TAN 22 HM 0484

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05th December, 2022

10. DATE OF REVISION OF THE TEXT