SUMMARY OFPRODUCTCHARACTERISTICS

1. NAME OF THE FINISHED PHARMACEUTICALPRODUCT

Azithromycin Tablets USP 500 mg (ORTIZA500)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION:

Each film coated tablet contains:

Azithromycin DihydrateUSP Equivalent to Anhydrous Azithromycin500mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICALFORM

Yellow coloured oval shaped film coatedtablets.

4. Clinicalparticulars

4.1 Therapeuticindications

Azithromycin is indicated for the treatment of the following infections, when caused bymicroorganisms sensitive to azithromycin:

- Acute bacterial sinusitis (adequatelydiagnosed)
- Acute bacterial otitis media (adequatelydiagnosed)
- Pharyngitis/tonsillitis
- Acute exacerbation of chronic bronchitis (adequatelydiagnosed)
- Mild to moderately severe community-acquiredpneumonia
- Skin and soft tissueinfections
- Uncomplicated *Chlamydia trachomatis* urethritis andcervicitis

Consideration should be given to official guidance on the appropriate use of antibacterialagents.

4.2 Posology and method of administration

Posology

<u>Children and adolescents over 45 kg body weight and adults</u>

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

For all other indications the dose is 1,500 mg, to be administered as 500 mg per day forthree consecutivedays.

Elderlypeople

Thesamedoserangeasinadultpatientsmaybeusedintheelderly.Sinceolderelderlypeoplecanbe patientswithongoingproarrhythmicconditionsaparticularcautionisrecommendedduetotheriskof developing cardiac arrhythmia and torsades de pointes (see section4.4).

Paediatricpopulation

Azithromycin film-coated tablets should only be administered to children weighing more than 45 kgwhen normal adult dose should be used. For children under 45 kg other pharmaceutical forms of azithromycin,
e.g. suspensions, may beused.

Patients with renalimpairment:

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

Patients with hepaticimpairment:

Adoseadjustmentisnotnecessaryforpatientswithmildtomoderatelyimpairedliverfunction.

Method ofadministration

Azithromycin500mgfilm-coatedtabletshouldbeadministeredasadailysingledose.Azithromycin 500mg film-coated tablet may be taken withfood.

4.3 Contraindications

Hypersensitivitytotheactivesubstance,erythromycin,anymacrolideorketolideantibiotic,ortoanyof the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions, includingangioneuroticoedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalisedexanthematouspustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal)and drugreactionwitheosinophiliaandsystemicsymptoms(DRESS)havebeenreported.Someofthese reactions with azithromycin have resulted in recurrent symptoms and required a longer periodof observation andtreatment.

Ifanallergicreactionoccurs,themedicinalproductshouldbediscontinuedandappropriatetherapy shouldbeinstituted.Physiciansshouldbeawarethatreappearanceoftheallergicsymptomsmayoccur when symptomatic therapy isdiscontinued.

Hepatoxicity

Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have had pre-existing hepatic 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.

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

Infantile hypertrophic pyloric stenosis (IHPS)

Following the use of azithromycin in neonates (treatment up to 42 days of life), infantilehypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should beinformed to contact their physician if vomiting or irritability with feeding occurs.

Ergot derivatives

In patients receiving ergotamine derivatives, ergotism has been precipitated bycoadministration of some macrolide antibiotics. There are no data concerning thepossibility 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.

Superinfection

As with any antibiotic preparation, observation for signs of superinfection with nonsusceptibleorganisms, including fungi is recommended.

Cross resistance

Because of existing cross-resistance with erythromycin-resistant gram-positive strains andmost strains of methicillin resistant staphylococci, use of azithromycin is notrecommended.

Local epidemiology and susceptibility patterns should be taken into consideration.

_Clostridium difficile_associated diarrhea

*Clostridium difficile*associated diarrhea (CDAD) has been reported with use of nearly allantibacterial agents, including azithromycin, and may range in severity from mild diarrheato fatal colitis. Treatment with antibacterial agents alters the normal flora of the colonleading 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, asthese infections can be refractory to antimicrobial therapy and may require colectomy.CDAD must be considered in all patients who present with diarrhea following antibioticuse. Careful medical history is necessary since CDAD has been reported to occur overtwo months after the administration of antimicrobial agents. In case of CDAD, antiperistalticsare contraindicated.

Pseudomembranous colitis

Pseudomembranous colitis has been reported with the use of macrolide antibiotics. Thisdiagnosis should therefore be considered in patients who get diarrhoea after startingtreatment with azithromycin.

Renal impairment

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

Cardiovascular events

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiacarrhythmia and torsades de pointes, have been seen in treatment with macrolidesincluding azithromycin (see section 4.8). Therefore as the following situations may leadto an increased risk for ventricular arrhythmias (including torsade de pointes) which canlead to cardiac arrest, azithromycin should be used with caution in patients with ongoingproarrhythmic 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 QTinterval such as

antiarrhythmics of class IA (quinidine and procainamide) and classIII (dofetilide, amiodarone and sotalol), cisapride and terfenadine; antipsychoticagents such as pimozide; antidepressants such as citalopram; and fluoroquinolonessuch as moxifloxacin and levofloxacin

- With electrolyte disturbance, particularly in cases of hypokalaemia andhypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiacinsufficiency
- Elderly patients: elderly patients may be more susceptible to drug-associated effectson the QT interval.

Carefully consider the balance of benefits and risks before prescribing azithromycin forany patients taking hydroxychloroquine or chloroquine, because of the potential for anincreased risk of cardiovascular events and cardiovascular mortality.

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including azithromycin.

Consideration of these findings should be balanced with treatment benefits when prescribing azithromycin.

Myasthenia gravis

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

Paediatric population

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

Long-term use

There is no experience on safety and effectiveness of long-term use of azithromycin in indications mentioned before. At fast recurrent infections, treatment with other antibiotics should be considered.

The following should be considered before prescribing azithromycin:

Serious infections

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

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

In areas with a high incidence of erythromycin A resistance, it is especially important totake into consideration the evolution of the pattern of susceptibility to azithromycin andother antibiotics.

As for other macrolides, high resistance rates of *Streptococcus pneumoniae*(> 30 %) havebeen reported for azithromycin in some European countries. This shouldbe taken into account when treating infections caused by *Streptococcus pneumoniae*.

Pharyngitis/ tonsillitis

Azithromycin is not the substance of first choice for the treatment of pharyngitis andtonsillitis caused by Streptococcus pyogenes. For this and for the prophylaxis of acuterheumatic 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 otitismedia.

Skin and soft tissue infections

The main causative agent of soft tissue infections, *Staphylococcus aureus*, is frequentlyresistant to azithromycin. Therefore, susceptibility testing is considered a precondition fortreatment 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 beexcluded.

Neurological or psychiatric diseases

Azithromycin should be used with caution in patients with neurological or psychiatricdisorders.

Azithromycin film-coated tablets contain Lactose.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency orglucose-galactosemalabsorption should not take this medicine.

Azithromycin film-coated tablets contains 0.025 mmol (0.57 mg) sodium per dose whichis less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.

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 ofantacid with azithromycin, no effect on overall bioavailability was seen although peakserum concentrations were reduced by approximately 24%. In patients receiving bothazithromycin and antacids, the medicinal products should not be taken simultaneously.

Azithromycin must be taken at least 1 hour before or 2 hours after the antacids.

Efavirenz

Co-administration of a 600 mg single dose of azithromycin and 400 mg efavirenz dailyfor 7 days did not result in any clinically significant pharmacokinetic interactions.

Fluconazole

Coadministration of a single dose of 1200 mg azithromycin did not alter thepharmacokinetics of a single dose of 800 mg fluconazole. Total exposure and half-life ofazithromycin were unchanged by the coadministration of fluconazole, however, aclinically insignificant decrease in Cmax (18%) of azithromycin was observed.

Nelfinavir

Coadministration of azithromycin (1200 mg) and nelfinavir at steady state (750 mg threetimes daily) resulted in increased azithromycin concentrations. No clinically significantadverse effects were observed and no dose adjustment is required.

Rifabutin

Coadministration of azithromycin and rifabutin did not affect the serum concentrations ofeither medicinal product.

Neutropenia was observed in subjects receiving concomitant treatment of azithromycinand rifabutin. Although neutropenia has been associated with the use of rifabutin, a causalrelationship to combination with azithromycin has not been established.

Terfenadine

Pharmacokinetic studies have reported no evidence of an interaction betweenazithromycin and terfenadine. There have been rare cases reported where the possibilityof such an interaction could not be entirely excluded; however there was no specificevidence that such an interaction had

occurred.

Cimetidine

In a pharmacokinetic study investigating the effects of a single dose of cimetidine, given2 hours before azithromycin, on the pharmacokinetics of azithromycin, no alteration ofazithromycin pharmacokinetics was seen.

Effect of azithromycin on other medicinal products:

Ergot derivatives

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

Digoxin and colchicine (P-gp substrates)

Concomitant administration of macrolide antibiotics, including azithromycin, with Pglycoproteinsubstrates such as digoxin and colchicine, has been reported to result inincreased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and Pgpsubstrates such as digoxin are administered concomitantly, the possibility of elevatedserum concentrations of the substrate should be considered.

Coumarin-Type Oral Anticoagulants

In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effectof a single 15-mg dose of warfarin administered to healthy volunteers. There have beenreports received in the post-marketing period of potentiated anticoagulation subsequent tocoadministration of azithromycin and coumarin-type oral anticoagulants. Although acausal relationship has not been established, consideration should be given to thefrequency of monitoring prothrombin time when azithromycin is used in patientsreceiving coumarin-type oral anticoagulants

Cyclosporin

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/dayoral dose of azithromycin for 3 days and were then administered a single 10 mg/kg oraldose of cyclosporin, the resulting cyclosporinCmax and AUC0-5 were found to besignificantly elevated. Consequently, caution should be exercised before consideringconcurrent administration of these drugs. If coadministration of these drugs is necessary,cyclosporin levels should be monitored and the dose adjusted accordingly.

Theophylline

There is no evidence of a clinically significant pharmacokinetic interaction whenazithromycin and theophylline are co-administered to healthy volunteers. As interactionsof other macrolides with theophylline have been reported, alertness to signs that indicate arise in theophylline levels is advised.

Trimethoprim/Sulfamethoxazole

Coadministration of trimethoprim/Sulfamethoxazole DS (160 mg/800 mg) for 7 days withazithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, totalexposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycinserum 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 littleeffect on the plasma pharmacokinetics or urinary excretion of zidovudine or itsglucuronide metabolite. However, administration of azithromycin increased theconcentrations of phosphorylated zidovudine, the clinically active metabolite, inperipheral 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. Itis not believed to undergo the pharmacokinetic drug interactions as seen witherythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivationvia cytochrome-metabolite complex does not occur with azithromycin.

Astemizole, alfentanil

There are no known data on interactions with astemizole or alfentanil. Caution is advisedin the co-administration of these medicines with azithromycin because of the knownenhancing effect of these medicines when used concurrently with the macrolid antibioticerythromycin.

Atorvastatin

Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did notalter the plasma concentrations of atorvastatin (based on a HMG CoA-reductaseinhibition assay). However, post-marketing cases of rhabdomyolysis in patients receivingazithromycin with statins have been reported.

Carbamazepine

In a pharmacokinetic interaction study in healthy volunteers, no significant effect wasobserved on the plasma levels of carbamazepine or its active metabolite in patientsreceiving concomitant azithromycin.

Chloroquine / Hydroxychloroquine

Observational data have shown that co-administration of azithromycin withhydroxychloroquine in patients with rheumatoid arthritis is associated with an increasedrisk of cardiovascular events and cardiovascular mortality. Carefully consider thebalance of benefits and risks before prescribing azithromycin for any patients takinghydroxychloroquine. Similar careful consideration of the balance of benefits and riskshould also be undertaken before prescribing azithromycin for any patients takingchloroquine, because of the potential for a similar risk with chloroquine

Cisapride

Cisapride is metabolized in the liver by the enzyme CYP 3A4. Because macrolides inhibitthis enzyme, concomitant administration of cisapride may cause the increase of QTinterval prolongation, ventricular arrhythmias and torsades de pointes.

Cetirizine

In healthy volunteers, coadministration of a 5-day regimen of azithromycin withcetirizine 20 mg at steady-state resulted in no pharmacokinetic interaction and nosignificant changes in the QT interval.

Didanosine (Dideoxyinosine)

Coadministration of 1200 mg/day azithromycin with 400 mg/day didanosine in 6 HIVpositivesubjects did not appear to affect the steady-state pharmacokinetics of didanosineas compared with placebo.

Efavirenz

Coadministration of a 600 mg single dose of azithromycin and 400 mg efavirenz dailyfor 7 days did not result in any clinically significant pharmacokinetic interactions.

Indinavir

Coadministration of a single dose of 1200 mg azithromycin had no statisticallysignificant effect on the pharmacokinetics of indinavir administered as 800 mg threetimes daily for *5* days.

Methylprednisolone

In a pharmacokinetic interaction study in healthy volunteers, azithromycin had nosignificant effect on the pharmacokinetics of methylprednisolone.

Midazolam

In healthy volunteers, coadministration of azithromycin 500 mg/day for 3 days did notcause clinically significant changes in the pharmacokinetics and pharmacodynamics of asingle 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 Cmax of sildenafil or its major circulatingmetabolite.

Triazolam

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

Other antibiotics

On a possible co-resistance between macrolide antibiotics and azithromycin (e.g.erythromycin) as well as lincomycin and clindamycin is to look at. Concomitant use ofseveral medicinal products

from the same group of substances is not recommended.

Medicinal products known to prolong the QT interval

Azithromycin should not be co-administered with other medicinal products, known to prolong the QT interval.

4.6 Fertility, pregnancy andlactation

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 (see section 5.3). The safety of azithromycin has not been confirmed with regard to the use of the active substance during pregnancy. Therefore azithromycin should only be used during pregnancy if the benefit outweighs the risk.

Breastfeeding

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

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

Fertility

In fertility studies conducted in rat, reduced pregnancy rates were noted following administration of azithromycin. The relevance of this finding to humans is unknown.

4.7 Effects on ability to drive and usemachines

There is no evidence to suggest that azithromycin may have an effect on a patient's ability to driveor operate machinery. Visual impairment and vision blurred may have an effect on a patient's ability todrive or operate machinery.

4.8 Undesirable effects

The table below lists the adverse reactions identified through clinical trial experience and postmarketing surveillance by system organ class and frequency.
The frequency grouping is defined using the following convention:

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to<1/1,000); Very rare (<1/10,000) and Not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of

decreasing seriousness.

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

System OrganClass	**Frequency**	**Adversereaction**
Infections andinfestations	Uncommon	Candidiasis Vaginalinfection Pneumonia Fungalinfection Bacterialinfection Pharyngitis Gastroenteritis Respiratorydisorder Rhinitis Oralcandidiasis
	Notknown	Pseudomembranous colitis(see section4.4)
Blood and lymphaticsystem disorders	Uncommon	Leukopenia Neutropenia Eosinophilia
	Notknown	Thrombocytopenia Haemolyticanaemia
Immune systemdisorders	Uncommon	Angioedema Hypersensitivity
	Notknown	*Anaphylactic reaction* (seesection 4.4)
Metabolism and nutritiondisorders	Uncommon	Anorexia
Psychiatricdisorders	Uncommon	Nervousness Insomnia
	Rare	Agitation Depersonalisation

	Notknown	Aggression Anxiety Delirium Hallucination
Nervous systemdisorders	Common	Headache
	Uncommon	Dizziness
		Somnolence DysgeusiaP araesthesia
	Notknown	Syncope,convulsion Hypoaesthesia Psychomotorhyperactivity Anosmia Ageusia Parosmia Myasthenia gravis (see section4.4).
Eyedisorders	Uncommon	Visualimpairment
	Notknown	Blurredvision
Ear and labyrinthdisorders	Uncommon	Eardisorder Vertigo
	Notknown	Hearing impairmentincluding deafness and/ortinnitus
Cardiacdisorders	Uncommon	Palpitations
	Notknown	Torsades de pointes (see section4.4) Arrhythmia (see section4.4) including ventriculartachycardia electrocardiogram QTprolonged (see section4.4)
Vasculardisorders	Uncommon	Hotflush
	Notknown	Hypotension

Respiratory, thoracic andmediastinaldisorders	Uncommon	Dyspnoea Epistaxis
Gastrointestinaldisorders	Verycommon	Diarrhoea
	Common	Vomiting Abdominalpain Nausea
	Uncommon	Constipation Flatulence Dyspepsia Gastritis Dysphagia Abdominaldistension Drymouth Eructation Mouthulceration Salivaryhypersecretion
	Notknown	*Pancreatitis* *Tonguediscolouration*
Hepatobiliarydisorders	Uncommon	Hepatitis
	Rare	Hepatic functionabnormal Jaundicecholestatic
	Notknown	Hepatic failure (which hasrarely resulted in death) (see section4.4)* Hepatitisfulminant Hepaticnecrosis
Skin and subcutaneoustissue disorders	Uncommon	Rash Pruritus Urticaria Dermatitis Dryskin Hyperhidrosis

	Rare	Photosensitivityreaction Acute generalisedexanthematous pustulosis(AGEP)
Skin and subcutaneoustissue disorders	Notknown	Steven-Johnsonsyndrome Toxic epidermalnecrolysis Erythemamultiforme
Musculoskeletal andconnective tissuedisorders	Uncommon	Osteoarthritis Myalgia Backpain Neckpain
	Notknown	Arthralgia
Renal and urinarydisorders	Uncommon	Dysuria Renalpain
	Notknown	Renal failureacute Nephritisinterstitial
Reproductive system andbreast disorders	Uncommon	Metrorrhagia Testiculardisorder
General disorders andadministration siteconditions	Uncommon	Oedema Asthenia Malaise Fatigue Faceoedema Chestpain Pyrexia Pain Peripheraloedema
Investigations	Common	Lymphocyte countdecreased Eosinophil countincreased Blood bicarbonatedecreased BasophilsincreasedMonocyt esincreased

		Neutrophilsincreased
	Uncommon	Aspartateaminotransferase increased Alanine aminotransferaseincreasedBlood bilirubineincreased Blood ureaincreased Blood creatinineincreased Blood potassiumabnormal Blood alkalinephosphatase increased ChlorideincreasedGlu coseincreasedPlatelet sincreasedHematocrit decreasedBicarbonate increasedAbnormalso
Injury andpoisoning	Uncommon	Post proceduralcomplication

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinalproduct is important. It allows continued monitoring of the benefit/risk balanceof the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in theGooglePlay or Apple App Store.

4.9 Overdose

Adverse events experienced in higher than recommended doses were similar to thoseseen at normal doses. The typical symptoms of an overdose with macrolide antibioticsinclude reversible loss of hearing, severe nausea, vomiting and diarrhoea.

In the event of overdose, the administration of medicinal charcoal and generalsymptomatic treatment and supportive measures are indicated as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties

Pharmacotherapeutic group:antibacterials for systemic use, macrolides,azithromycin,

ATC code: J01FA10

Mode of action

Azithromycin is an azalide, a sub-class of the macrolid antibiotics. By bindingto the 50S-ribosomal sub-unit, azithromycin avoids the translocation ofpeptide chains from one side of the ribosome to the other. As a consequence ofthis, RNA-dependent protein synthesis in sensitive organisms is prevented.PK/PD Relationship

The efficacy of azithromycin is best described by the relationship AUC/MIC,where AUC describes the area under the curve and MIC represents the meaninhibitory concentration of the microbe concerned.

Following the assessment of studies conducted in children, the use ofazithromycin is not recommended for the treatment of malaria, neither asmonotherapy nor combined with chloroquine or artemisinin based drugs, asnon-inferiority to anti-malarial drugs recommended in the treatment ofuncomplicated malaria was not established.

Mechanism of resistance

Resistance to azithromycin may be inherent or acquired. There are 3 mainmechanisms of resistance affecting azithromycin:

- Efflux: resistance may be due to an increase in the number of efflux pumpson the cell membrane. In particular, 14- and 15-link macrolides are affected.(M-phenotype)
- Alterations of the cell structure: methylisation of the 23s rRNS may reducethe affinity of the ribosomal binding sites, which can result in microbialresistance to macrolides, lincosamides and group B streptogramins (SB)(MLSB-phenotype).
- Enzymatic deactivation of macrolides is only of limited clinical significance.In the presence of the M-phenotype, complete cross resistance exists betweenazithromycin and clarithomycin, erythromycin and roxithromycin. With theMLSB-phenotype, additional cross resistance exists with clindamycin andstreptogramin B. A partial cross resistance exists with spiramycin.

Breakpoints

According to EUCAST (European Committee on Antimicrobial Susceptibility Testing) the following breakpoints have been defined for azithromycin:

Species	Susceptible	Resistant
*Staphylococcus*spp.	≤ 1mg/l	> 2mg/l
Streptococcus (GroupA,B,C,G)	≤ 0,25mg/l	> 0,5mg/l
Streptococcuspneumoniae	≤ 0,25mg/l	> 0,5mg/l
Haemophilusinfluenzae	≤ 0,12mg/l	> 4mg/l
Moraxellacatarrhalis	≤ 0,5mg/l	> 0,5mg/l
Neisseriagonorrhoeae	≤ 0,25mg/l	> 0,5mg/l

Susceptibility

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

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

Table of Susceptibility

Commonly susceptiblespecies
Aerobic Gram-negativemicroorganisms
Mycobacterium avium∗
Streptococcus pyogenes1
Aerobic Gram-negative microorganisms
Legionella pneumophila◦
Moraxella catarrhalis
Neisseria gonorrhoeae
Other microorganisms
*Mycoplasma pneumonia**
Chlamydophilapneumoniae
Chlamydia trachomatis◦

Species for which acquired resistance may be aproblem
Aerobic Gram-positivemicroorganisms
Staphylococcus aureus(methicillin-susceptible)
Staphylococcus aureus(methicillin-resistant)+
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus agalactiae
Streptococcus pneumoniae
Inherently resistant organisms
Aerobic Gram-negativemicroorganisms *Escherichiacoli*
Pseudomonasaeruginosa

*At the time of publication there are no current data. In primary literature,standard works and treatment guidelines susceptibility is assumed.

+ Resistance rate more than 50% in at least one region within the EU.

1 Resistance rate in some studies ≥10%.

5.2Pharmacokineticproperties

Absorption

Bioavailabilityafteroraladministrationisapproximately37%.Peakconcentrationsintheplasmaare attained2-3hoursaftertakingthemedicinalproduct.(C_{max}afterasingledoseof500mgorallywas approximately 0.4mg/l).

Distribution

Kinetic studies have shown markedly higher azithromycin levels in tissue than in plasma (up to 50times themaximumobservedconcentrationinplasma)indicatingthattheactivesubstanceisheavilytissue bound (steady state distribution volume of approximately 31 l/kg). Concentrations in target tissuessuch as lung, tonsil, and prostate exceed the MIC_{90} for likely pathogens after a single dose of 500mg.

In experimental in vitro and in vivo studies azithromycin accumulates in the phagocytes, freeingis

stimulated by active phagocytosis. In animal studies this process appeared to contribute tothe accumulation of azithromycin in thetissue.

Inserumtheproteinbindingofazithromycinisvariableanddependingontheserumconcentration varies from 50% in 0.05 mg/l to 12% in 0.5mg/l.

Elimination

Terminal plasma elimination half-life closely reflects the elimination half-life from tissues of 2-4days.

Approximately12%ofanintravenouslyadministereddoseofazithromycinisexcretedunchangedin urinewithinthefollowingthreedays;themajorityinthefirst24hours.Biliaryexcretionof azithromycin, predominantly in unchanged form, is a major route of elimination. In the same source,10 metaboliteswerealsodetected,whichwereformedthroughN-andO-demethylation,hydroxylationofdesosamine-andaglyconeringsanddegradationofcladinoseconjugate.Comparisonoftheresultsof liquid chromatography and microbiological analyses has shown that the metabolites of azithromycinare not microbiologicallyactive.

Pharmacokinetics in Special Populations

Renal insufficiency

Following a single oral dose of azithromycin 1 g, 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 renal impairment, the mean Cmax and AUC0-120 increased 61% and 33% respectively compared to normal.

Hepatic insufficiency

In patients with mild to moderate hepatic impairment, there is no evidence of a markedchange in serum pharmacokinetics of azithromycin compared to normal hepatic function. Inthese patients, urinary recovery of azithromycin appears to increase perhaps to compensatefor 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 Cmaxachieved is slightly

lower than adults with 224 ug/l in children aged 0.6-5 years and after3 days dosing and 383 ug/l in those aged 6-15 years. The t1/2 of 36 h in the older childrenwas within the expected range for adults.

5.3 Preclinical safety data

In animal tests in which the dosages used amounted to 40 times the clinicaltherapeutic dosages, azithromycin was found to have caused reversiblephospholipidosis, but as a rule, no true toxicological consequences were observedwhich were associated with this. The relevance of this finding to humans receivingazithromycin in accordance with the recommendations is unknown.

Carcinogenic potential:

Long-term studies in animals have not been performed to evaluate carcinogenicpotential as the drug is indicated for short-term treatment only, and there were nosigns indicative of carcinogenic activity.

Mutagenic potential:

There was no evidence of a potential for genetic and chromosome mutations in invivoand in-vitro test models.

Reproductive toxicity:

In animal studies of the embryotoxic effects of the substance, no teratogenic effectwas observed in mice and rats. In rats, azithromycin dosages of 100 and 200 mg/kgbodyweight/day led to mild retardations in foetal ossification and in maternal weightgain. In peri- and postnatal studies in rats, mild retardation in physical developmentand delay in reflex development following treatment with 50 mg/kg/day azithromycinand above were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each film coated tablet contains

- Azithromycin (1% overages) USP
- Microcrystalline Cellulose (pH 101) BP
- Sodium lauryl sulphate BP
- Sodium Starch Glycolate BP
- Polyvinyl pyrollidone USP
- Croscarmellose Sodium NF
- Talc USP
- Magnesium Stearate BP

- Hydroxy Propyl methyl cellulose E5 BP
- Propylene glycol BP
- Iron Oxide yellow NF
- Titanium dioxide BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a dry place below 30°C. Protect from light.

6.5 Nature and contents ofcontainer

Presentation: Azithromycin tablets USP 500 mg (ORTIZA 500) is available as 1x3’s, 10x3's & 10x10'sPVC blister pack.

Primary Container (s):

Azithromycin tablets USP 500 mg (ORTIZA 500) is available as Blister pack.

1x3’s, 10x3's - Each blister contains 3 tablets

10x10's - Each blister contains 10 tablets

Secondary packing:

Such blisters are packed in cartons of GSM 300, made of ITC cyber XL board with aqua varnish.Carton is printed in Multicolor.

Leaflet: leaflet made with 70 GSM Map Lithopaper.

Outer Container:

Such cartons are packed in Export Worthy 5/7 Ply Shippers. These shippers are labelled with product name and relevant batch details and sealed with BOPP tape. Shippers are then strapped with Polypropylene tapes.

Transportation: Should be transported with precautions.

The Cautions like- This Side Up

- Not For Loose Handling
- Protect from Water
- Avoid Vigorous Transportation Not all pack sizes may be marketed.

6.6 Special precautions for disposal and otherhandling

No special requirements.

7. MARKETING AUTHORIZATIONHOLDER

Name and Permanent address of the Marketing authorization holder: Medopharm,

"MEDO HOUSE"

25, Puliyur II Main road, Trustpuram, Chennai-600 024, Tamil Nadu, India.

PH: +91 44-30149992/30149955

Fax: 260211 286283

Manufacturing Site address:

Medopharm

No. 13-B Industrial area, Malur 563160, Karnataka, India.

8. NUMBER (S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

08318/09888/NMR/2022

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

30.01.2023

10. DATE OF REVISION OF THE TEXT

11.07.2023

11. REFERENCE

- https://www.medicines.org.uk/emc/product/6541/smpc