Zithrodose 500mg Hard gelatin capsules

Qualitative and quantitative composition

Azithromycin dihydrate 524 mg eq.to Azithromycin 500 mg.

Clinical particulars

1-Therapeutic indications

Zithrodose is indicated for the following bacterial infections induced by micro-organisms susceptible to Azithromycin *(see sections Special warnings and precautions for use and Pharmacodynamic properties):*

- Acute bacterial sinusitis (adequately diagnosed)
- Acute bacterial otitis media (adequately diagnosed)
- Pharyngitis, tonsillitis (see section 4.4 regarding streptococcal infections)
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderately severe community acquired pneumonia
- Infections of the skin and soft tissues of mild to moderate severity e.g. folliculitis, cellulitis, erysipelas
- Uncomplicated Chlamydia trachomatis urethritis and cervicitis
- Consideration should be given to official guidance on the appropriate use of antibacterial agents.

2- Posology and method of administration

Zithrodose should be given as a single daily dose. Duration of the treatment for the different infection diseases is given below.

Adults, children and adolescents with a body weight of 45 kg or over:

The total dose is 1500 mg, administered as 500 mg once daily for 3 days. Alternatively, the same total dose (1500 mg) can be administered in a period of 5 days, 500 mg on the first day and 250 mg on day 2 to 5.

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

Children and adolescents with a body weight below 45 kg:

Zithrodose tablets are not suitable for patients under 45 kg body weight. Other dosage forms are available for this group of patients.

Elderly patients

For elderly patients the same dose as for adults can be applied. Since elderly patients can be patients with ongoing proarrhythmic conditions a particular caution is recommended due to the risk of developing cardiac arrhythmia and torsades de pointes *(see section Special warnings and precautions for use).*

Patients with renal impairment:

Dose adjustment is not required in patients with mild to moderate renal impairment (GFR 10-80 ml/min). Caution should be exercised when Zithrodose is administered to patients with severe renal impairment (GFR < 10 ml/min) *(see section Special warnings and precautions for use and section Pharmacokinetic properties).*

Patients with hepatic impairment:

Since Zithrodose is metabolised in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease. No studies have been conducted regarding treatment of such patients with Zithrodose *(see section Special warnings and precautions for use).*

Method of administration

Zithrodose Film-coated Tablets are for oral administration only. The tablets can be taken with or without food. The tablets should be taken with ½ glass of water.

3-Contraindications

- Hypersensitivity to Azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipient listed in *section List of excipients*.
- Zithrodose is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of Zithrodose.

4-Special warnings and precautions for use

Hypersensitivity

As with erythromycin and other macrolides, rare serious allergic reactions including angioneurotic oedema and anaphylaxis (rarely fatal), dermatologic reactions including acute generalised exanthematous pustulosis (AGEP), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) (rarely fatal) and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. Some of these reactions with Azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.

Hepatotoxicity

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

Since the 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 undesirable effect).* 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. Zithrodose administration should be stopped if liver dysfunction has emerged.

Ergot derivatives

In patients receiving ergot 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 *(see section Interaction with other medicinal products and other forms of interaction).*

Prolongation of the QT interval

Zithrodose have been associated with cardiovascular effects; specifically, prolongation of the QT interval.

Prolongation of the QT interval can lead to Torsades de Pointes (TdP), an abnormal heart rhythm, which can be fatal.

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. A similar effect with Zithrodose cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarisation; therefore caution is required when treating patients:

- With congenital or documented QT prolongation.
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes Iaand III, cisapride and terfenadine.

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

Superinfection:

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

Clostridium difficile associated diarrhoea

Clostridium difficile associated diarrhoea (CDAD) has been reported with the use of nearly all antibacterial agents, including Zithrodose, and may range in severity from mild diarrhoea to fatal colitis.

Strains of *C. difficile* producing hypertoxins A and B 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. Therefore, CDAD must be considered in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Discontinuation of therapy with Zithrodose and the administration of specific treatment for *C. difficile* should be considered.

Streptococcal infections

Penicillin is usually the first choice for treatment of pharyngitis/tonsillitis due to *Streptococcus pyogenes* and also for prophylaxis of acute rheumatic fever. Azithromycin is in general effective against streptococcus in the oropharynx, but no data are available that demonstrate the efficacy of Azithromycin in preventing acute rheumatic fever.

Renal impairment

In patients with severe renal impairment (GFR < 10 ml/min) a 33% increase in systemic exposure to Azithromycin was observed *(see section Pharmacokinetic properties).*

Myasthenia gravis

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving Zithrodose therapy *(see section undesirable effect).*

Excipients

Lactose

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

5- Interaction with other medicinal products and other forms of interaction

Antacids:

In a pharmacokinetic study investigating the effects of simultaneous administration of antacids with Azithromycin, no effect on overall bioavailability was seen, although peak serum concentrations were reduced by approximately 24%. In patients receiving both Zithrodose and antacids, the drugs should not be taken simultaneously.

Cetirizine:

In healthy volunteers, coadministration of a 5-day regimen of Azithromycin with 20 mg cetirizine at steady-state resulted in no pharmacokinetic interaction and no significant changes in the QT interval.

Didanosine (Dideoxyinosine):

Coadministration of 1200 mg/day Azithromycin with 400 mg/day didanosine in 6 HIV-positive subjects did not appear to affect the steady-state pharmacokinetics of didanosine as compared with placebo.

Digoxin and colchicine:

Concomitant administration of macrolide antibiotics, including Azithromycin, with P-glycoprotein substrates such as digoxin and colchicine, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if Azithromycin and P-glycoprotein substrates such as digoxin are administered concomitantly, the possibility of elevated serum digoxin concentrations should be considered. Clinical monitoring, and possibly serum digoxin levels, during treatment with Zithrodose and after its discontinuation are necessary.

Zidovudine:

Single 1000 mg doses and multiple 1200 mg or 600 mg doses of Zithrodose had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of Zithrodose increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with Azithromycin.

Ergot derivatives:

Due to the theoretical possibility of ergotism, the concurrent use of Azithromycin with ergot derivatives is not recommended *(see section Special warnings and precautions for use).*

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

Atorvastatin:

Coadministration of atorvastatin (10 mg daily) and Zithrodose (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase-inhibition assay).

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 a single dose of 15 mg warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of Azithromycin and coumarintype oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when Azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Ciclosporin:

In a pharmacokinetic study with healthy volunteers that were administered a 500 mg/day oral dose of Azithromycin for 3 days and were then administered a single 10 mg/kg oral dose of ciclosporin, the resulting ciclosporin Cmax and AUC0-5 were found to be significantly elevated (by 24% and 21% respectively), however no significant

Changes were seen in AUC0-∞. Consequently, caution should be exercised before considering concurrent administration of these drugs. If coadministration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

Efavirenz:

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

Fluconazole:

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

Indinavir:

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

Methylprednisolone:

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

Midazolam:

In healthy volunteers, coadministration of Azithromycin 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 was required.

Rifabutin:

Coadministration of Azithromycin and rifabutin did not affect the serum concentrations of either drug.

Neutropenia was observed in subjects receiving concomitant treatment of Azithromycin and rifabutin. Although neutropenia has been associated with the use of rifabutin, a causal relationship to combination with Azithromycin has not been established *(see section undesirable effect).*

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.

Terfenadine:

Pharmacokinetic studies have reported no evidence of an interaction between Azithromycin and terfenadine. There have been rare cases reported where the possibility of such an interaction could not be entirely excluded; however there was no specific evidence that such an interaction had occurred.

Theophylline:

There is no evidence of a clinically significant pharmacokinetic interaction when Azithromycin and theophylline are co-administered to healthy volunteers.

Triazolam:

In 14 healthy volunteers, coadministration of Azithromycin 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/sulfamethoxazole:

Coadministration of trimethoprim/sulfamethoxazole DS (160 mg/800 mg) for 7 days with Azithromycin 1200 mg on Day 7 had no significant effect on peak concentrations, total exposure or urinary excretion of either trimethoprim or sulfamethoxazole. Azithromycin serum concentrations were similar to those seen in other studies.

6-Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Zithrodose 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 Zithrodose 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 Zithrodose 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.

7-Effects on ability to drive and use machines

No data are available regarding the influence of Azithromycin on a patient's ability to drive or operate machinery.

However, the possibility of undesirable effects like dizziness and convulsions should be taken into account when performing these activities.

8-Undesirable effects

Azithromycin is well tolerated with a low incidence of side effects.

The table below lists the adverse reactions identified through clinical trial 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); 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 Zithrodose based on clinical trial experience and post-marketing surveillance:

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** frequency cannot be estimated from available data
Infections and infestations					
		Candidiasis, oral candidiasis, vaginal infection			Pseudomembranous colitis
Blood and lymphatic system disorders					
		Leukopenia, neutropenia			Thrombocytopenia, haemolytic anaemia
Immune system disorders					
		Angioedema, hypersensitivity			Anaphylactic reaction
Metabolism and nutrition disorders					
	Anorexia				
Psychiatric disorders					
		Nervousness	Agitation		Aggression anxiety
Nervous system disorders					
	Dizziness, headache, paraesthesia, dysgeusia	Hypoaesthesia somnolence, insomnia			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis
Eye disorders					
	Visual impairment				
Ear and labyrinth disorders					
	Deafness	Hearing impaired, tinnitus	Vertigo		
Cardiac disorders					
		Palpitations			Torsades de pointes, arrhythmia including ventricular tachycardia.
Vascular disorders					
					Hypotension
Gastrointestinal disorders					
Diarrhoea, abdominal pain, nausea, flatulence	Vomiting, dyspepsia	Gastritis, constipation			Pancreatitis, tongue discoloration
Hepatobiliary disorders					
		Hepatitis	Hepatic function		Hepatic failure (which

			abnormal		has rarely resulted in death),hepatitis fulminant, hepatic necrosis, jaundice cholestatic
Skin and subcutaneous tissue disorders					
	Rash, pruritus	Stevens-Johnson syndrome, photosensitivity reaction, urticaria	Acute generalised exanthematous pustulosis (AGEP), DRESS (Drug reaction with eosinophilia and systemic symptoms)		Toxic epidermal necrolysis, erythema multiforme
Musculoskeletal and connective tissue disorders					
	Arthralgia				
Renal and urinary disorders					
					Renal failure acute, nephritis interstitial
General disorders and administration site conditions					
	Fatigue	Chest pain, oedema, malaise, asthenia			
Investigations					
	Lymphocyte count decreased, eosinophil count increased, blood bicarbonate decreased	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood urea increased, blood creatinine increased, blood potassium abnormal			

Postmarketing Experience

Liver/Biliary: Adverse reactions related to hepatic dysfunction have been reported in postmarketing experience With Zithrodose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization 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 via:

E-mail:

avs@averroespharma.net

regi@averroes-eg.com

Or on the following address:

Block No 6048, 6th industrial zone Sadat city, Egypt. Tel: 0482630201/2, Fax: 0482630203

55 Hafez badawy street Nasr city, Egypt.

Also you can report via:

Egyptian Pharmaceutical Vigilance Center (EPVC)

21 Abd El Aziz Al Soud Street. El-Manial, Cairo, Egypt.

E-mail: pv.center@eda.mohp.gov.eg

Fax Number: +2 02 23684194

Telephone: +2 02 (23648046, 23640368, 23684381, 23684288), Extension No. 1303

9- Overdose

Pharmacological properties

1- Pharmacodynamic properties

General properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides.

Mode of action

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-homoerythromycin A. The molecular weight is 749.0.

Mechanism of action

The mechanism of action of Azithromycin is based upon the suppression of bacterial protein synthesis by means of binding to the ribosomal 50S sub-unit and inhibition of peptide translocation.

Paediatric population

Following the assessment of studies conducted in children, the use of Zithrodose is not recommended for the treatment of malaria, neither as monotherapy nor combined with chloroquine or artemisinin based drugs, as non-inferiority to anti-malarial drugs recommended in the treatment of uncomplicated malaria was not established.

2-Pharmacokinetic properties

Absorption

Bioavailability of Azithromycin after oral administration is approximately 37%. Peak plasma concentrations are attained after 2-3 hours. The mean maximum concentration observed (C_{max}) after a single dose of 500 mg is approximately 0.4mcg/ml.

Distribution

Orally administered Azithromycin is widely distributed throughout the body.

In pharmacokinetic studies it has been demonstrated that the concentrations of Azithromycin measured in tissues are noticeably higher (as much as 50 times) than those measured in plasma, which indicates that the agent strongly binds to tissues. Binding to serum proteins varies according to plasma concentration and ranges from 12% at 0.5 microgram/ml up to 52% at 0.05 microgram Azithromycin /ml serum. The mean volume of distribution at steady state (VVss) has been calculated to be 31.1 l/kg.

At the recommended dose no accumulation appears in the serum. Accumulation appears in tissues where levels are much higher than in serum. Three days after administration of 500 mg as a single dose or in partial doses concentrations of 1,3-4,8 mcg/g, 0,6-2,3 mcg/g, 2,0-2,8 mcg/g and 0-0,3 mcg/ml have been measured in resp. lung, prostate, tonsil and serum.

In animal tests, high concentrations of Azithromycin have been found in phagocytes. It has also been established that during active phagocytosis higher concentrations of Zithrodose are released from inactive phagocytes. In animal models this results in high concentrations of Azithromycin being delivered to the site of infection.

Elimination

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

Approximately 12% of an intravenously administered dose is excreted in unchanged form with the urine over a period of 3 days; the major proportion in the first 24 hours. Concentrations of up to 237 µg/ml Zithrodose, 2 days after a 5-day course of treatment, have been found in human bile. Ten metabolites have been identified (formed by N- and O-demethylation, by hydroxylation of the desosamine and aglycone rings, and by splitting of the

cladinose conjugate). Investigations suggest that the metabolites do not play a role in the microbiological activity of Azithromycin.

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 > 80ml/min). In subjects with severe renal impairment, the mean C_{max} and AUC_{0-120} increased 61% and 35% 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.

In elderly volunteers (> 65 years) higher (29%) AUC values have been measured after a 5 day treatment than in younger volunteers (< 45 years). These differences are not regarded as clinically relevant; dose adjustment is therefore not recommended.

Infants, toddlers, children and adolescents

Pharmacokinetics has 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 in adults, with 224 µg/l in children aged 0.6-5 years and after 3 days dosing, and 383 µg/l in those aged 6-15 years. The half-life of 36 h in the older children was within the expected range for adults.

Pharmaceutical particulars

1- List of excipients

Lactose monohydrate - Sodium Croscarmellose - Magnesium stearate - Sodium lauryl sulfate – Talc – Gelatin - Titanium Dioxide - Quinoline yellow - Brilliant blue - Carmoisine red.

2-Incompatibilities

Not applicable.

3-Shelf life

3 years.

4- Special precautions for storage

Store at temperature not exceeding than 30°C at dry place. Store in the original packaging to protect from moisture.

5- Nature and contents of container

Carton box containing one (AL / transparent PVC) strip of 5 Hard Gelatin Capsules and insert leaflet.

Produced by Averroes Pharma for pharmaceutical industries

Block No. 6048 6th industrial zone, Sadat city, Egypt.