

## PIL OF ZITHROX 500 MG FILM COATED TABLETS

### 13. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Zithrox 500 mg film coated Tablet

#### 13.1 *Strength*

500 mg

#### 13.2 *Pharmaceutical form*

Film coated Tablet

### 14. QUALITATIVE AND QUANTITATIVE COMPOSITION

#### 14.1 *Qualitative declaration*

Lactose BP, Aerosil BP, Crospovidone BP, Povidone BP, Isopropyl alcohol BP, Magnesium stearate BP, Purified Talc BP, Maize starch BP, Microcrystalline cellulose BP, Croscarmellose sodium BP, Hypromellose BP, Macrogol 300 BP, Titanium dioxide BP, Yellow iron oxide, Isopropyl alcohol BP, Dichloromethane BP, Carnauba wax, Hard paraffin, Chloroform BP

#### 14.2 *Quantitative declaration*

Azithromycin BP	530.00
Lactose BP	121.00
Colloidal Anhydrous Silica BP	5.00
Crospovidone BP	8.00
Povidone BP	25.00
*Isopropyl Alcohol BP	q.s
Magnesium Stearate BP	16.00
Purified Talc BP	20.00
Maize Starch BP (Dried)	40.00
Microcrystalline Cellulose BP (Dried)	52.00
Crospovidone BP	30.00
Croscarmellose Sodium BP	13.00
<b>Film Coating Materials</b>	
Hypromellose BP	24.00
Macrogol 300 BP	2.40
Titanium Dioxide BP	4.80
Yellow Iron Oxide	0.41
*Isopropyl Alcohol	q.s
*Dichloromethane BP	q.s
<b>Polishing Materials</b>	
Carnauba Wax	0.27
Hard Paraffin BP	0.27
*Chloroform BP	q.s

\*Not present in formulation

**14.3 Salts and hydrates**

NA

**14.4 Esters and pro-drugs**

NA

**14.5 Oral powders for solution or suspension**

NA

**14.6 Parenterals excluding powders for reconstitution**

NA

**14.7 Powders for reconstitution prior to parenteral administration**

NA

**14.8 Concentrates**

NA

**14.9 Transdermal patches**

NA

**14.10 Multidose solid or semi-solid products**

NA

**14.11 Biological medicinal products**

NA

**14.11.1 Expression of strength**

mg

**14.11.2 The biological origin of the active substance**

NA

**14.11.3 Special provisions for normal immunoglobulins**

NA

**14.11.4 Herbal pharmaceutical products**

NA

**15. PHARMACEUTICAL FORM**

Film coated Tablets

**16. CLINICAL PARTICULARS**

**16.1 Therapeutic indications**

Azithromycin is indicated for the following bacterial infections induced by micro-organisms susceptible to azithromycin

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

### **16.2 Posology and method of administration**

Azithromycin 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.

• For patients who are allergic to penicillin and/or cephalosporins, prescribers should consult local treatment guidelines.

• *Children and adolescents with a body weight below 45 kg:*

• Azithromycin 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

### **16.3 Method of administration**

Oral.

### **16.4 Contraindications**

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

### **16.5 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

• 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. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

- In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

- Ergot 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.

- Prolongation of the QT interval

- 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 azithromycin 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 Ia and 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.

## **16.6 Paediatric population**

NA

## **16.7 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 azithromycin 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 azithromycin and after its discontinuation are necessary.

*Zidovudine:*

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

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

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

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

*Atorvastatin:* Coadministration 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).

*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 coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

*Ciclosporin:* In a pharmacokinetic study with healthy volunteers that were administered a 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  $C_{max}$  and  $AUC_{0-5}$  were found to be significantly elevated (by 24% and 21% respectively), however no significant changes were seen in  $AUC_{0-\infty}$ . Consequently, caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, ciclosporin levels should be monitored and the dose adjusted accordingly.

*Efavirenz:* Co-administration 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*: 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<sub>max</sub> (18%) of azithromycin was observed.

*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.

*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 was required.

*Rifabutin*: Co-administration of azithromycin and rifabutin did not affect the serum concentrations of either drug.

#### **16.8 Additional information on special populations**

NA

#### **16.9 Paediatric population**

NA

#### **16.10 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.

#### **16.11 Effects on ability to drive and use machines**

None known.

### 16.12 Undesirable effects

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
<b>Infections and infestations</b>					
		Candidiasis, oral candidiasis, vaginal infection			Pseudomembranous colitis
<b>Blood and lymphatic system disorders</b>					
		Leukopenia, neutropenia			Thrombocytopenia, haemolytic anaemia
<b>Immune system disorders</b>					
		Angioedema, hypersensitivity			Anaphylactic reaction
<b>Metabolism and nutrition disorders</b>					
	Anorexia				
<b>Psychiatric disorders</b>					
		Nervousness	Agitation		Aggression anxiety
<b>Nervous system disorders</b>					
	Dizziness, headache, paraesthesia, dysgeusia	Hypoesthesia somnolence, insomnia			Syncope, convulsion, psychomotor hyperactivity, anosmia, ageusia, parosmia, Myasthenia gravis
<b>Eye disorders</b>					
	Visual impairment				
<b>Ear and labyrinth disorders</b>					
	Deafness	Hearing impaired, tinnitus	Vertigo		

<b>Cardiac disorders</b>					
		Palpitations			Torsades de pointes arrhythmia including ventricular tachycardia.
<b>Vascular disorders</b>					
					Hypotension
<b>Gastrointestinal disorders</b>					
Diarrhoea, abdominal pain, nausea, flatulence	Vomiting, dyspepsia	Gastritis, constipation			Pancreatitis, tongue discoloration
<b>Hepatobiliary disorders</b>					
		Hepatitis	Hepatic function abnormal		Hepatic failure (which has rarely resulted in death), hepatitis fulminant, hepatic necrosis, jaundice cholestatic
<b>Skin and subcutaneous tissue disorders</b>					
	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.
<b>Musculoskeletal and connective tissue disorders</b>					
	Arthralgia				



<b>Renal and urinary disorders</b>					
					Renal failure acute, nephritis interstitial
<b>General disorders and administration site conditions</b>					
	Fatigue	Chest pain, oedema, malaise, asthenia			

### 16.13 Overdose

None known.

## 17. PHARMACOLOGICAL PROPERTIES

### 17.1 Pharmacodynamic properties

#### *Pharmacodynamic properties*

##### 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.

##### 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.

Azithromycin demonstrates cross resistance with erythromycin resistant gram positive isolates. A decrease in macrolide susceptibility over time has been noted particularly in *Streptococcus pneumoniae* and *Staphylococcus aureus*. Similarly, decreased susceptibility has been observed among *Streptococcus viridans* and *Streptococcus agalactiae* (Group B) streptococcus against other macrolides and lincosamides.

### 17.2 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 0.4 µg/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 (VV<sub>ss</sub>) 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 µg/g, 0,6-2,3 µg/g, 2,0-2,8 µg/g and 0-0,3 µg/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 azithromycin 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 azithromycin, 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.

### **17.3 Preclinical safety data**

Phospholipidosis (intracellular phospholipid accumulation) has been observed in several tissues (e.g. eye, dorsal root ganglia, liver, gallbladder, kidney, spleen, and/or pancreas) of mice, rats, and dogs given multiple doses of azithromycin. Phospholipidosis has been observed to a similar extent in the tissues of neonatal rats and dogs. The effect has been shown to be reversible after cessation of azithromycin treatment. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

Electrophysiological investigations have shown that azithromycin prolongs the QT interval.

#### *Carcinogenic potential:*

Long-term studies in animals have not been performed to evaluate carcinogenic potential as the drug is indicated for short-term treatment only and there were no signs indicative of carcinogenic activity.

#### *Mutagenic potential:*

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

#### *Reproductive toxicity:*

In animal studies for embryotoxic effects of the substance, no teratogenic effect was observed in mice and rats. In rats, azithromycin doses of 100 and 200 mg/kg bodyweight/day led to mild retardation of foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats, mild retardation following treatment with 50 mg/kg/day azithromycin and above was observed.

**17.4 Environmental Risk Assessment (ERA)**

NA

**18. PHARMACEUTICAL PARTICULARS**

**18.1 List of excipients**

Lactose BP

Microcrystalline Cellulose BP

Maize starch BP

Crospovidone BP

Povidone BP

Isopropyl alcohol BP

Magnesium Stearate BP

Aerosil BP

Croscarmellose sodium BP

Purified Talc BP

**FILM COATING**

Hypromellose BP,

Macrogol 300 BP,

Titanium dioxide BP,

Yellow iron oxide,

Isopropyl alcohol BP,

Dichloromethane BP,

Carnauba wax,

Hard paraffin,

Chloroform BP

**18.2 Incompatibilities**

NA

**18.3 Shelf life**

4 Years

**18.4 Special precautions for storage**

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

**18.5 Nature and contents of container**

PVDC-Alu blister

**18.6 Special precautions for disposal and other handling**

NA

**19. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES**

Cosmos Limited

Rangwe Road; Off Lunga Lungu, Industrial Area

P.O Box 41433, GPO 00100-Nairobi

Kenya

Telephone: 020-2519603/4/5, 020-8042200/2/3/4/5

Telefax: +254-020-8096280/1

E-mail: [admin@cosmos-pharm.com](mailto:admin@cosmos-pharm.com)

**20. MARKETING AUTHORISATION NUMBER: - 15402**

**21. DATE OF FIRST REGISTRATION/RENEWAL OF THE REGISTRATION: - 28/06/2005**

**22. DATE OF REVISION OF THE TEXT: N/A**

**23. DOSIMETRY (IF APPLICABLE): N/A**