SUMMARY OF PRODUCT CHARACTERISTICS ZITHROX 500 MG FILM COATED TABLET

1. **Name of the Medicinal Product**

   Zithrox 500 mg Film Coated Tablets

2. **Qualitative and Quantitative Composition**

   Each film tablet contains 500 mg of Azithromycin.

3. **Pharmaceutical Form**

   Film Coated Tablets

4. **Clinical Particulars**

   4.1 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.

• 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.

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 notbelieved 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.

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.

4.6 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.

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 abnormal		Hepatic failure (which has rarely resulted in death), hepatitis

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.

5.2 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 (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

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.

6 Pharmaceutical Particulars

6.1 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

Coating

Hypromellose BP,

Macrogol 300 BP,

Titanium dioxide BP,

Yellow iron oxide,

Isopropyl alcohol BP,

Dichloromethane BP,

Carnauba wax,

Hard paraffin,

Chloroform BP

6.2 Incompatibilities

None Known

6.3 Shelf life

4 Years

6.4 Special precautions for storage

Store in a dry place below 25°C. Protect from Light

6.5 Nature and contents of container

PVDC / Aluminium Foil

6.6 Instructions for use, handling and disposal

No special requirements.

7 REGISTRANT

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8 MANUFACTURER

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