SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Zetro Capsules 250mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

Azithromycin USP….250mg (as dihydrate)

Excipient with known effect

Each capsule contains 120mg lactose monohydrate For the full list of excipients please refer to Section 6.1

3. PHARMACEUTICAL FORM

Hard gelatin capsule with light blue opaque cap and white opaque body, containing white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZETRO (Azithromycin) is indicated for the treatment of patients with mild to moderate infections caused by susceptible strains of the designated micro-organisms in the specific conditions listed below:

- Lower respiratory tract infections (acute bacterial bronchitis and community acquired pneumonia in patients suitable for outpatient oral treatment and in patients who require initial intravenous therapy).
- Upper respiratory tract infections (acute sinusitis, acute streptococcal pharyngitis/tonsillitis and acute otitis media in children).
- Uncomplicated skin and skin structure infections.
- Sexually transmitted diseases (uncomplicated urethritis and cervicitis).
- Antimicrobial agents used in high doses for short periods of times to treat non-gonococcal urethritis may mask or delay the symptoms of incubating syphilis. All patients with sexually transmitted urethritis or cervicitis should have serologic test for syphilis and appropriate cultures for gonorrhea performed at the time of diagnosis. Appropriate antimicrobial therapy and follow-up test for these diseases should be initiated if the infection is confirmed.
- Pelvic inflammatory disease in patients who require initial intravenous therapy.
- Chlamydia trachomatis conjunctivitis and trachoma in adults and in children 12 months or older.
- Prevention of infection due to *Mycobacterium avium-intracellulare Complex* (MAC) disease in adults and children aged more than 12 years.

4.2 Posology and method of administration

The capsule formulation should be given at least an hour before or 2 hours after meals.

Adults:

For all indications except for those given below, the usual adult dose of ZETRO (Azithromycin) is 500mg as a single dose daily for 3 days. Alternatively, an initial dose of 500mg may be followed by 250mg daily for a further 4 days.

Sexually transmitted uncomplicated urethritis and cervicitis: 1g as a single dose.

Conjunctivitis and trachoma due to Clamydia trachomatis: 1g either as a single dose or once weekly for up to 3 weeks.

Treatment of community acquired pneumonia following IV therapy: 500mg as a single daily dose to complete a 7 to 10 day course of therapy.

Treatment of pelvic inflammatory disease following IV therapy: 250mg as a single daily dose to complete a 7 day course of therapy.

Prevention of disseminated *Mycobacterium avium* complex (MAC): disease in adults with HIV infection: 1200mg taken as a single dose once weekly, either alone, or in combination with rifabutin, at its recommended dosage.

Children

ZETRO (Azithromycin) should be used for children ≤25kg. The dose in children is 10mg/kg as a single daily dose for 3 days. Alternatively, 10mg/kg as a single dose on the first day followed by 5mg/kg/day on days 2-5.

Conjunctivitis and trachoma due to Chlamydia trachomatis in children 12 months or older: 20mg/kg either as a single dose or once weekly for up to three weeks.

Prevention of disseminated Mycobacterium avium complex (MAC) disease in children aged more than 12 years:
1200mg taken as a single dose once weekly, either alone, or in combination with rifabutin, at its recommended dosage.

Streptococcal pharyngitis and tonsillitis:
20mg/kg once daily for 3 consecutive days providing a total dose of 60mg/kg over a 3 day treatment period. Do not exceed a daily dose of 500mg (or 12.5mL of the reconstituted powder for oral suspension).

Acute Otitis Media:
Total dose of 30mg/kg given as 30mg/kg as a single dose or 10mg/kg once daily for 3 days or 10mg/kg as a single dose on the first day followed by 5mg/kg/day on days 2-5.

4.3 Contraindications

- Azithromycin is contraindicated in patients with a known hypersensitivity to azithromycin or any macrolide antibiotics.
- The theoretical possibility of ergotism contraindicates the concurrent use of azithromycin with ergot derivatives.

4.4 Special warnings and special precautions for use

- Azithromycin should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of risk factors such as:
  - Patients with cystic fibrosis.
  - Patients with nosocomially acquired infections.
  - Patients with known or suspected bacteraemia.
  - Patients requiring hospitalization.
  - Elderly or debilitated patients.
  - Patients with significant underlying health problems that may compromise their ability to respond to their illness (including immunodeficiency or functional asplenia).
- It is important to consider the diagnosis of pseudomembranous colitis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy) Mild cases may respond to drug discontinuation alone. In moderate to severe cases appropriate therapy with a suitable oral antibacterial agent may be required.
- No dose adjustment is needed in patients with mild or moderate renal impairment.
- Caution should be exercised when azithromycin is administered to patients with severe renal impairment (GFR < 10ml/min).
- Since Azithromycin is metabolized in the liver and excreted in the bile, the drug should not be given to patients suffering from severe liver disease.
- As with any antibiotic preparation, observation for signs of superinfection with non- susceptible organisms including fungi, is recommended.
- Ventricular arrhythmias associated with prolonged QT intervals, including ventricular tachycardia and torsades de pointes have been reported with macrolide products. Azithromycin should be used with caution in patients predisposed to QT interval prolongation or in patients taking other medications known to prolong the QT interval.

4.5 Interaction with other medicaments and other forms of interaction

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

Cyclosporin: Caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporine levels should be monitored and the dose adjusted accordingly.

Theophylline: Theophylline levels may be increased in patients taking Azithromycin.

Coumarin-type oral anticoagulants: Consideration should be given to the frequency of monitoring prothrombin time, when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

Digoxin: In patients receiving concomitant azithromycin, a related azalide antibiotic, and digoxin, the possibility of raised digoxin levels should be borne in mind.

4.6 Uses in Pregnancy and Lactation Pregnancy

There are no adequate and well-controlled studies in pregnant women. Therefore, azithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether azithromycin is excreted into human milk. Azithromycin should only be used in lactating women where adequate alternatives are not available.

4.7 Effects on ability to drive and operate machines

There is no evidence to suggest that azithromycin may have an effect on a patients ability to drive or operate machinery.

4.8 Undesirable effects

Azithromycin is well tolerated with a low incidence of side effects. Gastrointestinal disturbances are the most frequent adverse effects but are usually mild. Transient elevations of liver enzyme values have been reported and rarely cholestatic jaundice. Rashes, headache, and dizziness may occur. Severe hypersensitivity reactions occur rarely but may be prolonged. Transient alterations in neutrophil counts have been seen in patients receiving azithromycin.

4.9 Overdosage

Adverse events experienced in higher than recommended doses were similar to those seen at normal doses. The typical symptoms of an overdose with macrolide antibiotics include reversible loss of hearing, severe nausea, vomiting and diarrhea. In the event of overdose, the administration of medicinal charcoal and general symptomatic treatment and supportive measures are indicated as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacokinetic properties

Following oral administration about 40% of the dose of azithromycin is bioavailable. Absorption from the capsule formulation is reduced by food. Peak plasma concentrations are achieved 2 to 3 hours after a dose, but azithromycin is extensively distributed to the tissues, and tissue concentration subsequently remain much higher than those in blood. High concentrations are taken up into white blood cells. Small amount of azithromycin are demethylated in liver and it is excreted in bile as unchanged drug and metabolites. About 20% of the amount in the systemic circulation is excreted in the urine. The terminal elimination half-life is probably in excess of 40 hours.

Special Populations

Renal Insufficiency

Following a single dose of azithromycin 1g orally, the pharmacokinetics in subjects with mild to moderate renal impairment (GFR 10 - 80 mL/min) were not affected. Significant differences in AUC, C_{max} and Cl_{cr} were observed between subjects with severe renal impairment (GFR < 10mL/min) and subjects with normal renal function.

Hepatic Insufficiency

In patients with mild (Class A) to moderate (Class B) hepatic impairment, there is no evidence of a marked change in serum pharmacokinetics of azithromycin compared to those with normal hepatic function.

5.2 Pharmacodynamic properties Mechanism of Action

Azithromycin exerts it antibacterial action by binding to the 50S ribosomal subunit of susceptible
organisms and thus interfering with microbial protein synthesis and inhibition of peptide translocation. Nucleic acid synthesis is not effected.

Microbiology:

Azithromycin has been shown to be active against most isolates of the following micro- organisms, both *in vitro* and in clinical infections.

Aerobic and facultative gram-positive organisms.
Streptococcus pneumoniae, penicillin-resistant, penicillin-intermediate, *Streptococcus pyogenes, Staphylococcus aureus, Streptococcus agalactiae, Streptococci (Groups C, F, G) Viridans group streptococci, Corynebacterium diptheriae.* Azithromycin demonstrates cross-resistance with erythromycin-resistant Gram-positive strains, including *Streptococcus faecalis (entrococcus)* and most strains of methicillin-resistant staphylococci.

Aerobic and facultative gram-negative organisms.
Haemophilus ducreyi, Haemophilus influenzae, Moraxella catarrhalis, Neisseria gonorrhoeae, Bordetella pertussis, Legionella pneumophila, Haemophilus parainfluenzae, Acinetobacter species, Yersinia species, Shigella species, Pasteurella species, *Vibrio cholerae* and *parahaemolyticus, Plesiomonas shigelloides.*

Anaerobic micro-organisms
Peptostreptococcus species, *Prevotella bivia, Bacteroides fragilis* and Bacteroides species, *Clostridium perfringens,* Peptococcus species, *Fusobacterium necrophorum* and *Propionibacterium acnes.*

Others
Chlamydia pneumoniae, Chlamydia trachomatis, Mycoplasma pneumoniae, Ureaplasma urealyticum, Escherichia coli, Salmonella, Shigella spp., *Mycobacterium avium, Toxoplasma gondii, Plasmodium fakiparum.*

5.3 Safety, Efficacy & Toxicology

Azithromycin was found to have caused reversible phospholipidosis, but as a rule there were no associated toxicological consequences. The relevance of this finding to humans receiving azithromycin in accordance with the recommendations is unknown.

5.4 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential.
There is no evidence of a potential for genetic and chromosome mutations in *in-vivo* and *in-vitro* test models. In rats, azithromycin dosages of 100 and 200 mg/kg bodyweight/ day led to mild retardation in foetal ossification and in maternal weight gain. In peri- and postnatal studies in rats mild retardations in physical and reflex development were noted following treatment with 50 mg/kg/day azithromycin and above.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Avicel PH-102 (Microcrystalline Cellulose)

- Lactose Monohydrate
- Pharmacoat 606(HPMC)
- Sodium Lauryl Sulfate
- Croscarmellose Sodium
- Magnesium Stearate
- EGC Zetro Capsules 250mg Size # '0'

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

2 Years
The expiration dates refers to the product correctly stored in the required conditions.

6.4 Special precautions for storage

- Store below 30°C.
- Protect from sunlight & moisture.
- The expiration date refers to the product correctly stored at the required conditions.

6.5 Nature and contents of container

Zetro Capsules 250mg are packed in Alu-Alu blister pack of 1x10's in a unit carton along with the package information leaflet.

6.6 Instructions for use/handling

Keep out of reach of children.
To be dispensed on prescription only.

7. **MARKETING AUTHORISATION HOLDER**

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area Karachi 74900, Pakistan Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

8. **DATE OF REVISION OF THE TEXT**

Nil

9. **PRODUCT REGISTRATION NUMBER**

045375

10. **DATE OF PRODUCT REGISTRATION ISSUED**

May 22, 2007