PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAME (AND DOSAGE FORM):

ZITHROGEN 250 (Film-coated tablet)

ZITHROGEN 500 (Film-coated tablet)

COMPOSITION:

ZITHROGEN 250 tablets contain azithromycin monohydrate hemiethanolate equivalent to 250 mg azithromycin. Sugar free.

ZITHROGEN 500 tablets contain azithromycin monohydrate hemiethanolate equivalent to 500 mg azithromycin. Sugar free.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 – Medium and broad spectrum antibiotics

PHARMACOLOGICAL ACTION:

Azithromycin is a macrolide (azalide) antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive microorganisms, thereby inhibiting bacterial RNA-dependent protein synthesis. The *in vitro* antibacterial spectrum of pathogens sensitive to azithromycin includes:

(*in vitro* sensitivity does not necessarily imply *in vivo* efficacy)

Staphylococcus aureus

Streptococcus spp., including *Streptococcus pyogenes* (Group A) and *Streptococcus pneumoniae*

Haemophilus influenzae, Haemophilus ducreyi

Moraxella catarrhalis

Legionella pneumophila

Bordatella pertussis

Borrelia burgdorferi

Mycoplasma pneumoniae

Chlamydia trachomatis

Treponema pallidum

Pharmacokinetics:

Azithromycin is absorbed rapidly from the gastro-intestinal tract, with an oral bioavailability of approximately 37 %. No significant decrease in bioavailability occurs when azithromycin is administered with a meal. Peak concentration occurs approximately 2 to 3 hours after oral administration. Protein binding of azithromycin is low (51 %) and appears to be concentration dependent, decreasing with increasing concentrations. Azithromycin is widely distributed throughout the body and concentrates intracellularly. Azithromycin (35 % of the dose) is metabolised by the liver to inactive metabolites and excreted in the bile. More than 50 % of the dose is eliminated unchanged via the bile, while 6,5 % of the dose is eliminated in the urine, unchanged. The elimination half-life of azithromycin closely reflects the tissue depletion half-life of 2 to 4 days.

The mean Cmax ± S.D. is 3,63 ± 1,60 µg/ml after single daily one-hour intravenous infusions of 500 mg azithromycin at a concentration of 2 mg/ml in patients hospitalized with community acquired pneumonia. The 24 hour trough level is 0,20 ± 0,15 µg/ml and the AUC is 9,60 ± 4,80 µg.h/ml.

The amount of azithromycin excreted in urine in 24 hours was found to be about 11 % after the first dose and 14 % after the fifth dose after administration of a 500 mg (1 mg/ml) one-hour intravenous dosage regimen for five days.

INDICATIONS:

ZITHROGEN is indicated for the treatment of the following conditions in adults and children one year and older.

- Lower respiratory tract infections such as bronchitis and pneumonia caused by sensitive *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* or *Streptococcus pneumoniae*.
- Upper respiratory tract infections such as sinusitis or pharyngitis caused by sensitive *Haemophilus influenzae*, *Staphylococcus aureus* or *Streptococcus pneumoniae*.
- Uncomplicated skin and soft tissue infections caused by sensitive *Staphylococcus aureus*.
- Uncomplicated genital tract infections caused by sensitive *Chlamydia trachomatis*.

For children 1 year and older, **ZITROGEN** is indicated for the treatment of pharyngitis/tonsillitis and otitis media caused by susceptible organisms.

CONTRA-INDICATIONS:

Hypersensitivity to macrolide antibiotics or to any component of the formulation.

Co-administration with ergot alkaloids.

Liver function impairment – Since biliary excretion is the major route of elimination.

Safety and efficacy in pregnancy and lactation have not been established.

Safety and efficacy in children under 1 year of age have not been established.

WARNINGS:

ZITHROGEN should be used with caution in renal function impairment as there are no data regarding the use of **ZITHROGEN** in patients with impaired renal function.

Less frequently, serious allergic reactions, such as anaphylaxis, angioedema, fever, eosinophilia and skin eruptions have been reported in patients taking **ZITHROGEN**. Despite discontinuation of **ZITHROGEN** and successful symptomatic treatment of the allergic reactions, allergic symptoms have recurred in some patients when the symptomatic therapy was discontinued. These patients

require prolonged periods of observation and symptomatic treatment.

Pseudomembranous colitis has been reported ranging from mild to life threatening. Therefore it is important to consider this diagnosis in patients with diarrhoea subsequent to administration of **ZITHROGEN**.

INTERACTIONS:

Concomitant use of **ZITHROGEN** with:

- Antacids – Decreases the peak serum concentration of **ZITHROGEN**. Take **ZITHROGEN** one hour before or two hours after taking an antacid.
- Ergot alkaloids – Has been associated with acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia. Co-administration of **ZITHROGEN** and ergot alkaloids is not recommended (See CONTRA-INDICATIONS).
- Anticoagulants such as warfarin – Prothrombin time should be monitored.
- Digoxin – May increase serum digoxin concentrations. Monitoring of digoxin serum concentrations is recommended.
- Medicines metabolised by the cytochrome P450 enzyme system (e.g. alprazolam, cyclosporine, disopyramide, midazolam, omeprazole, quinidine, sildenafil, simvastatin, tacrolimus, triazolam, vinblastine, phenytoin and valproate) – **ZITHROGEN** may increase serum levels of these medicines. Serum concentrations of these medicines may require monitoring.
- Terfenadine – May increase serum concentration of terfenadine. Monitor serum levels of terfenadine.
- Theophylline – The area under the plasma concentration-time curve may be increased. Monitoring of theophylline serum concentrations is recommended.

No interactions have been reported with cimetidine, carbamazepine, methylprednisolone and zidovudine.

PREGNANCY AND LACTATION:

Safety and efficacy in pregnancy and lactation have not been established.

DOSAGE AND DIRECTIONS FOR USE:

Safety and efficacy of **ZITHROGEN** in children under 1 year of age have not been established.

The tablet formulation is not suitable for children under 45 kg in weight.

Swallow tablets whole with some water. **ZITHROGEN** may be taken with or without meals.

Susceptible bacterial infections except sexually transmitted diseases:

Oral:

Adults and children over 45 kg in weight:

500 mg once daily for three days.

Over five days dosage regimen:

Day 1: 500 mg, and then 250 mg daily on days 2 - 5.

Sexually transmitted disease caused by *Chlamydia trachomatis:*

Adults: 1 g given as a single dose.

The normal adult dose is recommended for use in the elderly patient.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects:

Haematological:

- *Frequent:* Neutropaenia

Cardiovascular:

- *Frequent*: Palpitations, arrhythmias including ventricular tachycardia, chest pain

Central Nervous system:

- *Frequent*: Headache, dizziness, tinnitus, hearing loss, convulsions, somnolence, vertigo,

fatigue, asthenia, paraesthesias

Gastro-intestinal:

- *Frequent:* Nausea, anorexia, vomiting, abdominal discomfort, flatulence, diarrhoea, loose stools, constipation, dyspepsia, malaena, taste changes
- *Less frequent*: Pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea, which may also be bloody, fever)

Kidney/Genitourinary:

- *Frequent*: Interstitial nephritis, acute renal failure, vaginitis

Liver:

- *Less frequent:* Transient elevations in liver enzymes, hepatitis, cholestatic jaundice

Skin:

- *Less frequent:* Erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis

Other:

- Allergic reactions (difficulty in breathing, swelling of face, mouth, neck, hands and feet, arthralgia, urticaria, photosensitivity, skin rash, anaphylaxis)

Special Precautions:

Use of **ZITHROGEN** may cause an overgrowth of non-susceptible organisms. Appropriate measures should be taken to prevent or treat such superinfections.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

(See SIDE-EFFECTS AND SPECIAL PRECAUTIONS)

Symptoms of overdose:

There are no data on overdosage of **ZITHROGEN**. Typical symptoms are expected to be those associated with macrolide antibiotics and include severe gastro-intestinal symptoms (nausea, vomiting and diarrhoea) and hearing loss.

Treatment of overdose:

Treatment is symptomatic and supportive. Gastric lavage may be indicated.

IDENTIFICATION:

ZITHROGEN 250: White, film-coated, capsule-shaped tablet with “AZ 250” on one side and “G” on the reverse.

ZITHROGEN 500: White, film-coated, capsule-shaped tablet with “AZ 500” on one side and “G” on the reverse.

PRESENTATION:

ZITHROGEN 250: PVC/PVdC/Aluminium foil blister packs of 5 tablets in a unit carton.

ZITHROGEN 500: PVC/PVdC/Aluminium foil blister packs of 2 or 3 tablets in a unit carton.

STORAGE INSTRUCTIONS:

Store in a cool place (below 25 ºC).

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

ZITHROGEN 250: A38/20.1.1/0692

ZITHROGEN 500: A38/20.1.1/0693

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Viatris South Africa (Pty) Ltd

4 Brewery Street,

Isando

Johannesburg,

1609

DATE OF PUBLICATION OF THE PACKAGE INSERT:

8 September 2005