PIL OF CLARICOS 500MG TABLETS

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT
Claricos 500mg Film Coated Tablets

1.1 *Strength*
500 mg

1.2 *Pharmaceutical form*
Film coated Tablet

Yellow capsule shaped biconvex film coated, tablet embossed '500' on one side and plain on the other side.

2. CLINICAL PARTICULARS
2.1 *Therapeutic indications*
It is indicated for the treatment of the following bacterial infections.

- Bacterial pharyngitis
- Mild to moderate community acquired pneumonia
- Acute bacterial sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis
- Skin infections and soft tissue infections of mild to moderate severity,
- In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent for the eradication of Helicobacter pylori in patients with Helicobacter pylori associated ulcers

2.2 *Posology and method of administration*
The dosage of Clarithromycin film-coated tablets depends on the type and severity of the infection and has to be defined in any case by the physician.

Adults

- Standard dosage: The usual dose is 250 mg twice daily (in the morning and in the evening)
- High dosage treatment (severe infections): The usual dose may be increased to 500 mg twice daily in severe infections.

Children

7.5mg per kg body-weight twice daily.

For disseminated infection due to Mycobacterium avium complex, 500mg twice daily by mouth, in conjunction with other mycobacterial.

Leprosy -500mg daily by mouth has been given as part of an alternative multidrug therapy regimen.

H. pylori association with peptic ulcer disease

Clarithromycin, usually in an oral dose of 500mg twice daily, is given with another antibacterial and either a proton pump inhibitor or a histamine H_2 – receptor antagonist for 7-14 days.

3 ***Method of administration***

Oral.

4 Contraindications

Clarithromycin should be avoided in those known to be hypersensitive to it or those who have previously developed liver disorders while receiving it. It should be used with care in patients with existing liver disease or hepatic impairment.

5 ***Special warnings and precautions for use***

Use of any antimicrobial therapy, such as clarithromycin, to treat H. pylori infection may select for drug-resistant organisms.

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy (see section 4.6).

Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function.

Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment

6 ***Interaction with other medicinal products and other forms of interaction***

Increased rifabutin toxicity has been reported in patients receiving Clarithromycin and rifabutin and there has been a report of delirium following concurrent use with fluoxetine

7 ***Additional information on special populations***

NA

8 ***Paediatric population***

Interaction studies have only been performed in adults.

9 *Fertility, pregnancy and lactation*

Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.

Breast-feeding

The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excreted into human breast milk in small amounts.

11 *Effects on ability to drive and use machines*

N/A

12 *Undesirable effects*

Gastro-intestinal disturbances are the most frequent adverse effects but are usually mild and less frequent. Taste disturbances, stomatitis, glossitis, tooth discoloration and headache have occurred. There have also been reports of transcient CNS Effects such as anxiety, dizziness, hallucinations and confusion. Other adverse effects include hypoglycaemia, leukopenia and thrombocytopenia

13 *Overdose*

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

14. PHARMACOLOGICAL PROPERTIES

14.1 *Pharmacodynamic properties*

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal sub-unit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria.

The 14-hydroxy metabolite of clarithromycin, a product of parent drug metabolism also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including mycobacterium spp. An exception is Haemophilus influenza where the 14-hydroxy metabolite is two-fold more active than the parent compound.

14.2 Pharmacokinetic properties

H. pylori is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with the agent. H. pylori is also implicated as a major contribution factor in the development of gastric and ulcer recurrence in such patients.

Clarithromycin has been used in small numbers of patients in other treatment regimens. Possible kinetic interactions have not been fully investigated. These regimens include:

Clarithromycin plus tinidazole and omeprazole; clarithromycin plus tetracycline, bismuth subsalicylate and ranitidine; clarithromycin plus ranitidine alone.

Clinical studies using various different H. pylori eradication regimens have shown that eradication of H. pylori prevents ulcer recurrence.

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract after oral administration. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin tablets. Food does slightly delay the onset of absorption of clarithromycin and formation of the 14-hydroxymetabolite.

The pharmacokinetics of clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.

When clarithromycin 500 mg is given three times daily, the clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.

Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.

Clarithromycin also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

14.3 *Preclinical safety data*

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5g/kg).

In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included

the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

15. PHARMACEUTICAL PARTICULARS

15.1 *Shelf life*
2 Years

15.2 *Special precautions for storage*
Store in a dry place below 30˚C. Protect from light.
Keep all medicines out of the reach of children.

15.2 *Nature and contents of container*

PVDC/Aluminium foil, Packs of 14 Tablets in a carton

15.3 *Special precautions for disposal and other handling*
No special requirements.

16. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESSES

Cosmos Limited

Rangwe Road; Off Lunga Lunga, 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