Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Claryl 500mg Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film-coated tablet contains 500 mg of clarithromycin

For list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Yellow, oval, biconvex marked with `500` on one side and 'CL' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clarithromycin is indicated for the treatment of infections due to susceptible organisms. Such infections include:-

1. Lower respiratory tract infections (e.g. bronchitis, pneumonia).
2. Upper respiratory tract infections (e.g. pharyngitis, sinusitis).
3. Skin and soft tissue infections (e.g. folliculitis, cellulitis, erysipalis).
4. Disseminated or localised mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localised infections due to *Mycobacterium chelonae*, *Mycobacterium fortuitum* or *Mycobacterium kansasii*.
5. Clarithromycin is indicated for the prevention of disseminated *Mycobacterium avium complex* infection in HIV - infected patients with CD4 lymphocyte counts less than or equal to 100/mm^3.
6. Clarithromycin in the presence of acid suppression is indicated for the eradication of *H. pylori*, resulting in decreased recurrence of duodenal ulcer. (See further information).

As with other antibiotics, it is recommended that guidelines on the prevalence of local resistance, and associated medical practice regarding the prescription of antibiotics, be consulted before prescribing clarithromycin.

Further Information: *H. pylori* is strongly associated with peptic ulcer disease. 90 to 100% of patients with duodenal ulcers are infected with this agent. Eradication of *H. pylori* has been shown to markedly reduce the rate of duodenal ulcer recurrence, thereby reducing the need for maintenance anti-secretory therapy. In a well controlled double-blind study, *H. pylori* infected patients with duodenal ulcer received clarithromycin 500 mg TID for 14 days with omeprazole 40 mg daily for 28 days. Clarithromycin has been used in other treatment regimens for the eradication of *H. pylori.* These regimens include: Clarithromycin plus tinidazole and omeprazole; and clarithromycin plus tetracycline, bismuth subsalicylate, and ranitidine.

4.2 Posology and method of administration

The usual recommended dosage of clarithromycin in adults is one 250 mg tablet twice daily. In more severe infections, the dosage can be increased to 500 mg twice daily. The usual duration of therapy is 6 to 14 days.

In patients with renal impairment with creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be reduced by one-half, i.e.: 250 mg once daily, 250 mg twice daily in more severe infections. Treatments should not be continued beyond 14 days in these patients.

Dosage in patients with mycobacterial infections: The recommended starting dose is 500 mg twice daily. If no clinical or bacteriologic response is observed in 3 to 4 weeks, the dose may be increased to 1000 mg twice daily. Treatment of disseminated *Mycobacterium Avium Complex* (MAC) infections in AIDS patients should be continued, as long as clinical microbiological benefit is demonstrated. Clarithromycin should be used in conjunction with other antimycobacterial agents.

Treatment of other non-tuberculous mycobacterial infections should continue at the discretion of the physician.

Dosage for MAC prophylaxis: The recommended dosage of clarithromycin in adults is 500 mg twice daily.

Eradication of H. pylori:
Dual Therapy (14 days): The recommended dose of clarithromycin is 500 mg three times daily for 14 days. (see Further Information above).
Triple Therapy (7 days): Clarithromycin (500 mg) twice daily and a proton pump inhibitor (at the approved daily dose) * should be given with amoxycillin 1000 mg twice daily for 7 days.
Triple Therapy (7 days): Clarithromycin (500 mg) twice daily and a proton pump inhibitor (at the approved daily dose) * should be given with metronidazole 400 mg twice daily for 7 days.
Triple Therapy (7-10 days): Clarithromycin (500 mg) twice daily should be given with amoxycillin 1000 mg twice daily and omeprazole 20mg daily for 7-10 days.

*see individual data sheets/SPCs for the dose recommendations for *H. pylori* eradication.

4.3 Contraindications

Use in patients with known hypersensitivity to macrolide antibiotic drugs.

Clarithromycin and ergot derivatives should not be co-administered.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: cisapride, pimozide and terfenadine. Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these drugs and clarithromycin concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular fibrillation and torsade de pointes. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

4.4 Special warnings and precautions for use

Clarithromycin is excreted principally by the liver and kidney so that caution must be exercised in its use in patients with impaired hepatic or renal function or in those concomitantly receiving potentially hepatotoxic drugs.

Attention should be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

Prolonged or repeated use of clarithromycin may result in overgrowth of non-susceptible bacteria. If super-infections occurs, clarithromycin should be discontinued and appropriate therapy instituted.

4.5 Interaction with other medicinal products and other forms of interaction

Results of clinical studies indicate that there was a modest but statistically significant ($p < 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs are administered concomitantly with clarithromycin.

As with other macrolide antibiotics the use of clarithromycin in patients concurrently taking drugs metabolised by the cytochrome P450 system (e.g. warfarin, ergot alkaloids, triazolam, midazolam, disopyramide, lovastatin, phenytoin, cyclosporin, tacrolimus and rifabutin) may be associated with elevations in serum levels of these other drugs. (*See also section 4.3, Contraindications*).

The effects of digoxin may be potentiated with concomitant administration of clarithromycin. Monitoring of serum digoxin levels should be considered.

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine. To date, this interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine.

Ritonavir increases the area under the curve (AUC), C_{max} and C_{min} of clarithromycin when administered concurrently. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} < 30ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

Rhabdomyolysis conincident with the co-administration of clarithromycin and HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, has rarely been reported.

There are no known clinically significant interactions between clarithromycin and proton pump inhibitors.

4.6 Pregnancy and lactation

Safe use in pregnancy has not been established. Use in women breast feeding infants is not recommended. Some animal studies have suggested a teratogenic effect at doses significantly in excess of those recommended for clinical use. clarithromycin has been found in the milk of lactating animals and humans.

4.7 Effects on ability to drive and use machines

None known.

4.8 Undesirable effects

The most frequently reported side effects of Clarithromycin in clinical studies were gastrointestinal-related complaints, i.e. nausea, dyspepsia, abdominal pain, vomiting and diarrhoea. Other side effects included headache, altered taste, and transient elevations of liver enzymes.

Stomatitis, glossitis, oral monilia and tongue discolouration have been reported.

Allergic reactions ranging from urticaria and mild skin eruptions to anaphylaxis and Stevens-Johnson Syndrome/toxic epidermal necrolysis have occurred with orally administered clarithromycin. There have been reports of transient central nervous system side effects including dizziness, vertigo, anxiety, insomnia, bad dreams, tinnitus, confusion, disorientation, hallucinations, psychosis, and depersonalisation, however, a cause and effect relationship has not been established.

As with other macrolides, hepatic dysfunction (which is usually reversible), including altered liver function tests, hepatitis and cholestasis with or without jaundice, has been reported. Dysfunction may be severe and very rarely fatal hepatic failure has been reported.

Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received. There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning.

Reversible cases of hearing loss have been reported with clarithromycin. There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin. Isolated cases of thrombocytopenia have been reported.

Pseudomembranous colitis has been reported rarely with clarithromycin and may range in severity from mid to life threatening.

Isolated cases of increased serum creatinine have been reported but an association has not been established.

As with other macrolides, QT prolongation, ventricular tachycardia and Torsade de Pointes have been rarely reported with clarithromycin.

Adverse events in immunocompromised patients: In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness. In adult patients, the most frequently reported adverse events by patients treated with total daily doses of 1000 mg and 2000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, SGOT and SGPT elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000 mg and 2000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 mg of clarithromycin.

In these immunocompromised patients evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1000 mg or 2000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts.

A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen (BUN) levels. Slightly higher incidences of abnormal values were noted for patients who received 4000 mg daily for all parameters except WBC.

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin orally can be expected to produce gastrointestinal symptoms. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and general supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

One patient who has a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypomania.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

Clarithromycin is usually active against the following organisms *in vitro*:-

Gram positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); *Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes*.

Gram-negative Bacteria: *Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae; Legionella pneumophila; Bordetella pertussis; Helicobacter pylori; Campylobacter jejuni.*

Mycoplasma: *Mycoplasma pneumoniae; Ureaplasma urealyticum*.

Other Organisms: *Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae.*

Anaerobes: Macrolide-susceptible *Bacteroides fragilis*; *Clostridium perfringens*; Peptococcus species; Peptostreptococcus species; *Propionibacterium acnes*.

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include *Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae, H. pylori* and Campylobacter spp.

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.

5.2 Pharmacokinetic properties

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of clarithromycin tablets. 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 with clarithromycin is administered alone.

5.3 Preclinical safety data

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

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Spraque-Dawley (p.o. and i.v.), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity for clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels which were clearly toxic to the mothers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Starch, pregelatinised
Croscarmellose sodium
Povidone (k-value 81.0 – 96.3)
Talc
Magnesium stearate
Silica, colloidal anhydrous
Titanium dioxide (E171)
Polydextrose (E1200)
Hypromellose ((E464)
Triacetin (E1518)
Macrogol
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/PVC/PVdC Strip or HDPE Tablet Container with LDPE Cap
Pack sizes: 7, 14, 21, 28, 30, 50, 100, 250, 500 or 1000 tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Limited
Ballymacarbry
Clonmel
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA0281/131/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13 January 2006

10 DATE OF REVISION OF THE TEXT

March 2007