Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Klaram 250mg Film Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250mg clarithromycin

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
Product imported from the UK:
Yellow, oval, biconvex marked with `250` 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.

Use in patients with severe impairment of hepatic function.

Clarithromycin and ergot derivatives should not be co-administered.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: astemizole, 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

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

Clarithromycin is excreted principally by the liver and kidney, therefore 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-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life threatening.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with anti bacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile.*

CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of anti bacterial agents.

Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.

4.5 Interaction with other medicinal products and other forms of interaction

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and Torsades de Pointes. Similar effects have been observed in patients, taking clarithromycin and pimozide concomitantly *(see section 4.3, Contraindications).*

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias, such as QT prolongation, ventricular tachycardia, ventricular fibrillation and Torsades de Pointes *(see section 4.3 Contraindications).* In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a 2 to 3-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated *(see section 4.3 Contraindications).*

Effects of Other Medicinal Products on Clarithromycin
The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine
Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-(R)-clarithromycin (14-OH-clarithromycin), a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Fluconazole
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir
A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. 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 CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be coadministered with ritonavir.

Effect of Clarithromycin on Other Medicinal Products
Antiarrhythmics
There have been postmarketed reports of Torsade de Pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide.
Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.

CY3A4-based interactions
Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolized by this enzyme. Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

HMG-CoA Reductase Inhibitors
As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly.

Omeprazole
Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (Cmax, AUC0-24, and t1/2 increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

Oral anticoagulants
Spontaneous reports in the post-marketing period suggest that concomitant administration of clarithromycin and oral anticoagulants may potentiate the effects of the oral anticoagulants. Prothrombin times should be carefully monitored while patients are receiving clarithromycin and oral anticoagulants simultaneously.

Sildenafil, tadalafil and vardenafil
Each of these phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure.

Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

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

Tolterodine
The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other drug interactions
Colchicine
Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity *(see section 4.4 Warnings and Precautions)*.

Digoxin
Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine
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. This interaction does not appear to occur in paediatric HIV infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine.

Bi-directional drug interactions
Atazanavir
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function.

For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Itraconazole
Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir
Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatine capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are coadministered for a limited time at the doses/formulations studied.

Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with the combination therapy of saquinavir and ritonavir, therefore when this combination therapy is co-administered with clarithromycin consideration should be given to the potential effects of ritonavir on clarithromycin *(see Section 4.5-Ritonavir).*

Verapamil
Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

4.6 Fertility, 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

Table 1 displays adverse events reported in patients taking clarithromycin in clinical studies. Adverse events are displayed by body system and frequency (common ≥ 1/100, < 1/10).

Table 1
Adverse Events Reported in Clinical Studies

System Organ Class	Frequency	Adverse Events
Nervous system disorders	Common	headache taste perversion
Gastrointestinal disorders	Common	diarrhoea nausea abdominal pain dyspepsia vomiting
Investigations	Common	hepatic enzyme increased

Post Marketing Experience
Clarithromycin in marketed in several different formulations. Table 2 is a compilation of adverse reactions for all formulations including clarithromycin immediate release tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.

Table 2
Adverse Reactions from Post-Marketing Surveillance

System Organ Class	Adverse Reaction
Infections and infestations	oral candidiasis
Blood and lymphatic system disorders	leukopenia thrombocytopaenia
Immune system disorders	anaphylactic reaction hypersensitivity
Metabolism and nutrition disorders[1]	hypoglycaemia
Psychiatric disorders	psychotic disorder hallucination disorientation confusional state depersonalisation depression anxiety insomnia abnormal dreams
Nervous system disorders	convulsion dizziness ageusia anosmia dysguesia parosmia
Ear and labyrinth disorders	deafness vertigo tinnitus
Cardiac disorders[2]	Torsades de Pointes electrocardiogram QT prolonged ventricular tachycardia
Gastrointestinal disorders	pancreatitis acute glossitis stomatitis tongue discolouration tooth discolouration
Hepatobiliary disorders[3]	hepatic failure hepatitis hepatitis cholestatic jaundice cholestatic jaundice hepatocellular hepatic function abnormal
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome toxic epidermal necrolysis urticaria rash
Musculoskeletal and connective tissue disorders	myalgia

Renal & urinary disorders	nephritis interstitial
Investigations	blood creatinine increased hepatic enzyme increased

[1]There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

[2]As with other macrolides, QT prolongation, ventricular tachycardia, and Torsades de Pointes have rarely been reported with clarithromycin.

[3]In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients *(see sections 4.4 Warnings and Precautions and 4.5 Interactions with other medicinal products and other forms of interactions)*

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 immuncompromised 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 can be expected to produce gastrointestinal symptoms. Adverse reactions accompanying overdosage should be treated by gastric lavage 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 hypoxaemia.

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.

Klaram is usually active against the following organisms in vitro. Please see below for table of MIC breakpoints.

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.

Breakpoints

The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, μg/ml)		
Microorganism	Susceptible (≤)	Resistant (>)
Streptococcus spp.	0.25 μg/ml	0.5 μg/ml
Staphylococcus spp.	1 μg/ml	2 μg/ml
Haemophilus spp.	1 μg/ml	32 μg/ml
Moraxella catarrhalis	0.25 μg/ml	0.5 μg/ml
Clarithromycin is used for the eradication of *H. pylori* ; minimum inhibitory concentration (MIC) ≤0.25 μg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).		

5.2 Pharmacokinetic properties

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Klaram tablets. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Klaram may be given without regard to meals as food does not affect the extent of bioavailability of Klaram 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.
Klaram 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. Klaram 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.

5.3 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.
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 from 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
croscarmellose sodium
pregelatinised maize starch
providone
talc
magnesium stearate
colloidal anhydrous silica
titanium dioxide (E171)
polydexterose
hypromellose
triacetin,
macrogol
quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life expiry date of this product is the date shown on the blister strips and outer carton of the product as marketed in the country of origin.

6.4 Special precautions for storage

Do not store above 30^{o}C

6.5 Nature and contents of container

Blister packs of 14 tablets contained in an over labelled outer cardboard carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

PCO Manufacturing Ltd
Unit 10, Ashbourne Business Park
Rath
Ashbourne
Co Meath

8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA565/33/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th May 2011

10 DATE OF REVISION OF THE TEXT