Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Klariger LA 500 mg Modified-release Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 500 mg of clarithromycin as clarithromycin citrate.

Excipient(s) with known effect: Each tablet contains 283.1 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Modified-release tablets.

Yellow coloured, oblong shaped, biconvex film-coated tablets of length 19.15 ± 0.2mm, width 8.95 ± 0.2mm and thickness 7.55 ± 0.2mm with both sides plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Klariger LA is indicated for the treatment of the following infections caused by clarithromycin susceptible bacteria. (see sections 4.4 and 5.1)

- Acute bacterial exacerbation of chronic bronchitis.
- Mild to moderate community-acquired pneumonia.
- Acute bacterial sinusitis
- Bacterial pharyngitis.

- Skin and soft tissue infections of mild to moderate severity, for example; folliculitis, cellulites and erysipelas.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Klariger LA is indicated in adults and children 12 years and older.

4.2 Posology and method of administration

Posology:
Adults:
The usual recommended dosage of Klariger LA in adults is one 500 mg modified-release tablet daily to be taken with food.
In severe infections, the dosage can be increased to two 500 mg modified-release tablets taken as one dose daily.
Dose must be taken at the same time every day. Tablets must be swallowed whole.
The usual duration of treatment is 6 to 14 days.

Paediatric population

Children 12 years and older:
As for adults.

Children younger than 12 years:
Use of Klariger LA tablet is not recommended for children younger than 12 years.Use clarithromycin Paediatric Suspension.

Clinical trials have been conducted using clarithromycin pediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin pediatric suspension (granules for oral suspension). There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

Elderly patients:
As for adults. (In case of renal impairment, see below and section 4.3).

Patients with renal impairment:

In patients with renal impairment with creatinine clearance less than 30mL/min, the dosage of clarithromycin should be reduced by one-half, *i.e*. 250mg once daily, or 250mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients. Because the tablet cannot be split, the dose cannot be reduced from 500mg daily, Klariger LA modified-release tablet should not be used in this patient population (see section 4.3).

Patients with hepatic impairment:
The use of Klariger LA is not recommended in patients with severe liver impairment

4.3 Contraindications

Clarithromycin is contra-indicated in patients with known hypersensitivity to macrolide antibiotic drugs or any of the excipients listed in section 6.1.

As the dose cannot be reduced from 500 mg daily, Klariger LA modified-release tablets is contra-indicated in patients with creatinine clearance less than 30 ml/min. All other formulations maybe used in this patient population.

Concomitant administration of clarithromycin and any of the following drugs is contra-indicated: astemizole, cisapride, pimozide, terfenadine as this may result in QT prolongation and cardiac arrythmias, including ventricular tachycardia ventricular fibrillation, and torsades de pointe (see section 4.5). Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointe (see sections 4.4 and 4.5).

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins), lovastatin or simvastatin, due to the risk of rhabdomylosis. Treatment with these agents should be discontinued during clarithromycin treatment (see section 4.4).

Clarithromycin should not be given to patients with hypokalaemia (risk of prolongation of QT-time).

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

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 (see section 4.6).

Caution is advised in patients with severe renal insufficiency (see section 4.2).
Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

Cases of fatal hepatic failure (see section 4.8) have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, Pruritus, or tender abdomen.

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 antibacterial 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 antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

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

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5). If concomitant administration of colchicines and clarithromycin is necessary, patients should be monitored for clinical symptoms of colchicine toxicity.

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and midazolam (see section 4.5).

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesemia, bradycardia (<50bpm), or when co-administered with other medicinal products associated with QT prolongation (see section 4.5). Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Pneumonia: In view of the merging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia. In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity: These infections are most often caused by *Staphylococcus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing performed. In cases where *beta*-lactam antibiotics cannot be used (e.g.allergy), other antibiotics, such as clindamycin, may be the drug of choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum* (erythrasma), acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

HMG-CoA reductase inhibitors: Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (see section 4.5). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy. Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin or pravastatin) should be considered.

Oral hypoglycemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended. Oral anticoagulants: There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is coadministered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

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

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

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

Klariger LA contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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:

Cisapride, pimozide, astemizole and terfenadine
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).

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). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two to three 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 coadministration of clarithromycin with ergotamine or dihydroergotamine has been

associated with acute ergot toxicity characterised 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).

Effect of other medicinal products on clarithromycin

Drugs that are inducers of CYP3A4 e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St. John Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inhibitor administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

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-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 CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <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.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, bidirectional pharmacokinetic interactions).

Effect of clarithromycin on other medicinal products

CYP3A-based Interactions
Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised 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 metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised 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, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics

There have been post-marketing reports of torsade de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of clarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycin therapy.

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 $t_{1/2}$ 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.

Sildenafil, tadalafil, and vardenafil

Each of these phosphodiesterase inhibitors is metabolised, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin.
Coadministration 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 co-administered with clarithromycin.

Theophylline, carbamazepine

Results of clinical studies indicate there was a modest but statistically significant (p 0.05) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin. Dose reduction may need to be considered.

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 metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines, which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), an 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.

Verapamil

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

Other 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).

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 HIVinfected 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 allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate
There have been spontaneous or published reports of interactions with CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolised by CYP3A, (e.g. phenytoin and valproate).
Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased concentrations have been reported.

Bidirectional pharmacokinetic 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 bidirectional drug interaction.
Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatine capsules, 1200 mg three times daily) 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 co-administered 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 saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of
ritonavir on clarithromycin.

4.6 Fertility, pregnancy and lactation

The safety of clarithromycin for use during pregnancy and breast feeding of infants has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk. Clarithromycin is excreted into human breast milk.

4.7 Effects on ability to drive and use machines

There are no data available on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile
The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics. (see section b of section 4.8)

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.

b. Tabulated summary of adverse reactions
The following table displays adverse reactions reported in clinical trials and from postmarketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified release tablets. The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class	very common (≥1/10),	common (≥1/100 to <1/10)	uncommon (≥1/1,000 to <1/100)	not known (cannot be estimated from the available data).
Infections and infestations			Cellulitis1, candidiasis, gastroenteritis2,infection3, vaginal infection	Pseudomembranous colitis, erysipelas, erythrasma
Blood and lymphatic system disorders			Leukopenia, neutropenia4, thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrompcytopenia

Immune system disorders[5]			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction
Metabolism and nutrition disorders			Anorexia, decreased appetite	Hypoglycaemia6
Psychiatric disorders		Insomnia	Anxiety, nervousness3, screaming3	Psychotic disorder, confusional state, depersonalization, depression, disorientation, hallucination, abnormal dreams
Nervous System disorders		Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[7], tremor	Convulsion, ageusia, parosmia, anosmia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged[8], extrasystoles[1], palpitations	Torsade de pointes[8], ventricular tachycardia[8]
Vascular disorders		Vasodilation[1]		Haemorrhage[9]
Respiratory, thoracic and mediastinal disorders			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhea[10], vomiting, dyspepsia, nausea, abdominal pain	Esophagitis[1], gastroesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4],constipation,dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discolouration.
Hepato-biliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increase, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure[11], jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash hyperhidrosis	Dermatitis bullous[1], Pruritus, Urticaria, rash maculo-papular[3]	Stevens-Johnson syndrome[5], toxic epidermal necrolysis[5], drug rash with eosinophilia and systemic symptoms (DRESS), acne
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2,12], myopathy
Renal and urinary disorders			Blood creatinine increase[1], blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1], blood alkaline	International normalised ration increased[9], prothrombin time

			phosphatase increased[4], blood lactate dehydrogenase increased[4]	prolonged[9], urine colour abnormal

1 ADRs reported only for the Powder for Solution for Injection formulation
2ADRs reported only for the Extended-Release Tablets formulation
3 ADRs reported only for the Granules for Oral Suspension formulation
4 ADRs reported only for the Immediate-Release Tablets formulation
5,8,10,11,12See section a)
6,7,9See section c)

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, vessel puncture site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.

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 (see section 4.4).

A special attention to diarrhea should be paid as *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. (see section 4.4)

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome and toxic epidermal necrolysis, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated (see section 4.4).

As with other macrolides, QT prolongation, ventricular tachycardia, and *torsade de pointes* have rarely been reported with clarithromycin (see section 4.4 and 4.5).

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

Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents (see section 4.4).

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and 4.4).

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome. (see sections 4.4 and 4.5).

There have been rare reports of hypoglycemia, some of which have occurred in patients on concomitant oral hypoglycemic agents or insulin (see section 4.4 and 4.5).

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 (see section 4.5).

There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently (see section 4.4 and 4.5).

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin

formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients (see section e)

d. Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children
6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. ***Other special populations***

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 Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1000 mg and 2000mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum Glutamic Pyruvate Transaminase (SGPT) elevations. Additional low-frequency events included
dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000mg and 2000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000mg 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 1000mg or 2000mg 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 levels. Slightly higher incidences of abnormal values were noted for patients who received 4000mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via

IMB Pharmacovigilance,
Earlsfort Terrace ,
IRL- Dublin 2,
Tel: +353 1 6764971;
Fax: +353 1 6762517.
Website: www.imb.ie;
e-mail: imbpharmacovigilance@imb.ie

4.9 Overdose

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal 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.

In the case of overdosage, clarithromycin IV (powder for solution for injection) should be discontinued and all other appropriate supportive measures should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-infectious, ATC code: J01F A09

Mode of action
Clarithromycin is an antibiotic belonging to the macrolide antibiotics group. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria.

It selectively binds to the 50S subunit of bacterial ribosomes and thus prevents the translocation of activated amino acids.

The 14(R)-hydroxy metabolite of clarithromycin, a product of parent drug metabolism in humans, also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including Mycobacterium spp. An exception is *Haemophilus influenzae* against which the metabolite is 1 to 2 times more active than the parent compound. Clarithromycin combined with the metabolite showed a straindependent additive or synergistic effect both *in vitro* and *in vivo*.

PK/PD Relationship
Clarithromycin is extensively distributed in body tissues and fluids. Because of high tissue penetration, intracellular concentrations are higher than serum concentrations.

The most important pharmacodynamic parameters for predicting macrolide activity are not conclusively established. The time above MIC (T/MIC) may correlate best with efficacy for clarithromycin, however since clarithromycin concentrations achieved in respiratory tissues and epithelial lining fluids exceed those in plasma, using parameters based on plasma concentrations may fail to predict accurately the response for respiratory tract infections.

Clarithromycin concentrations in tonsil and whole lung tissue are 2- to 6-fold higher than those observed in the serum. Tissue and serum concentrations observed in studies with immediate-release (IR) tablets are presented below.

Mean Clarithromycin Concentration [250 mg BID]		
Tissue Type	**Tissue**	**Serum**
Tonsil	1.6 µg/g	0.8 µg/ml
Lung	8.8 µg/g	1.7 µg/ml

The pharmacokinetics of orally administered modified-release (MR) clarithromycin tablets have been studied in adult humans (refer to section 5.2) and compared with clarithromycin 250 mg and 500 mg IR tablets. The extent of absorption – area under curve (AUC) – was found to be equivalent when equal total daily doses were administered. The equivalent AUCs would be expected to drive tissue levels equivalent to those observed for clarithromycin IR tablets.

In a study in healthy volunteers, it was shown that the concentrations of clarithromycin in epithelial lining fluid (ELF) following administration of the MR formulation remained above 1 µg/ml for 24 hours and above 10 µg/ml for up to 18 hours. In most subjects, the concentrations of clarithromycin in ELF were approximately 30 times greater than those in plasma, and the ratio appeared to be independent of formulation and time of assessment. A peak tissue concentration above 40 µg/ml was observed for the MR formulation, demonstrating extensive uptake of clarithromycin into lung tissue. This level is well above the minimum inhibitory concentration (MIC) values of all common community-acquired respiratory pathogens.

Clarithromycin accumulated extensively in the alveolar macrophages (AM), with AM levels approximately 100- to 600-fold higher than those in plasma and 4- to 18-fold higher than those in ELF for most subjects. While concentrations of 14(R)-hydroxyclarithromycin in AM were not quantifiable in some subjects and were rather variable, the AM levels were generally similar for the MR and IR tablets. The concentrations in AM were greater than those in plasma, but accumulation was less for the metabolite than for parent clarithromycin.

Mechanism of Resistance
Acquired macrolide resistance in *S. pneumoniae*, *S. pyogenes*, and *S. aureus* is mediated primarily by the presence of one of two mechanisms (i.e. *erm* and *mef* or *msr*).

Ribosomal binding of the antimicrobial is prevented through methylation of the ribosome by an enzyme (*erm*). Alternatively an efflux mechanism (*mef* or *msr*) can prevent the antimicrobial from reaching its ribosomal target by pumping the antimicrobial out of the cell. No acquired resistance mechanisms have been identified in Moraxella or Haemophilus spp. Macrolide resistance mechanisms are equally effective against 14- and 15-membered macrolides including erythromycin, clarithromycin, roxithromycin, and azithromycin. The mechanisms for penicillin resistance and macrolide resistance are unrelated.

Attention should be paid to the erm-mediated cross-resistance between macrolides such as clarithromycin and lincosamides such as lincomycin and clindamycin.
Clarithromycin antagonises the bacterial effects of beta-lactam antibiotics. Also the effects of lincomycin and clindamycin are antagonised, at least *in vitro*.

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

The current EUCAST breakpoints are as follows:

EUCAST Breakpoints: Macrolides, lincosamides, streptogramins - EUCAST clinical MIC breakpoints 2010-04-27 (v 1.1)

	Species-related breakpoints (S≤/R>)														*Non-species related break-points[A] S≤/R>*
	Enterobacteriaceae	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*Other streptococci*	*H.influenzae*	*Moraxella catarr-halis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative anaerobes*	*Gram-positive anaerobes*	
Clarithromycin[B,C]	*RD* --	--	--	*1/2*	--	*0.25/0.5*	*0.25/0.5*	*IE*	*1/32[D]*	*0.25/0.5*	–	–	--	--	*IE*

A. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes However, pharmacodynamic data for calculation of macrolide, lincosamines and streptogramins non-species related breakpoints are not robust, hence IE.
B. Erythromycin can be used to determine the susceptibility of the listed bacteria to the other macrolides (azithromycin, clarithromycin and roxithromycin
C. Clarithromycin is used for the eradication of H. pylori (MIC ≤0.25 mg/L for wild type isolates).
D. The correlation between H. influenzae macrolide MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type H. influenzae as intermediate.

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).

The prevalence of acquired resistance rates may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of an agent in at least some types of infections is questionable.

Category 1: Susceptible organisms		
Gram-positive	**Gram-negative**	**Others**
Clostridium perfringens Peptococcus niger Proprionibacterium acnes Streptococcus group F	Haemophilus influenzae§ Legionella pneumophila Moraxella catarrhalis Pasteurella multocida	Chlamydia pneumoniae (TWAR) Mycobacterium avium Mycobacterium chelonae Mycobacterium fortuitum Mycobacterium intracellulare Mycobacterium kansasii Mycobacterium pneumonia
Category 2: Organisms for which acquired resistance may be problematic#		
Staphylococcus aureus (resistant or susceptible* to methicillin)+ Staphylococcus coagulase negative+ Streptococcus pneumoniae*+ Streptococcus pyogenes* Streptococcus group B, C, G Streptococcus spp.		
Category 3: Intrinsic resistant organisms		
Enterobacteriaceae Pseudomonas aeruginosa		
* Species against efficacy has been demonstrated in clinical investigations (if susceptible)		
§ Breakpoints for macrolides and related antibiotics were set to categorise wild type *H. influenzae* as intermediate		
+ Indicates species for which a high rate of resistance (i.e. greater than 50%) have been observed in one or more area/country/region(s) of the EU		
# ≥10% resistance in at least one country of the European Union		

5.2 Pharmacokinetic properties

Absorption

The kinetics of orally administered modified-release clarithromycin have been studied in adult humans and compared with clarithromycin 250 mg and 500 mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Based upon the finding of equivalent absorption the following in vitro and in vivo data are applicable to the modified-release formulation.

Distribution
In-vitro: Results of in-vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45-4.5 μg/ml. A decrease in binding to 41% at 45.0 μg/ml suggested that the binding sites might become saturated, but this occurred at concentrations far in excess of therapeutic drug levels.

In-vivo: Results of in vivo studies showed that clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were found in the liver and lung tissue, where the tissue to plasma ratios reached 10 to 20.

The pharmacokinetic behaviour of clarithromycin is non-linear. In fed patients given 500 mg clarithromycin modified-release tablets daily, the peak steady-state plasma concentration of clarithromycin and 14 hydroxy clarithromycin were 1.3 and 0.48 μg/ml, respectively. When the dosage was increased to 1000 mg daily, these steady-state values were 2.4 μg/ml and 0.67 μg/ml respectively.

Metabolism
Metabolism is in the liver involving the P450 cytochrome system. Three metabolites are described: N-demethyl clarithromycin, decladinosyl clarithromycin and 14-hydroxy clarithromycin.

Elimination half-lives of the parent drug and metabolite were approximately 5.3 and 7.7 hours respectively. The apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at higher doses.

Excretion
Urinary excretion accounted for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

5.3 Preclinical safety data

In repeated dose studies, clarithromycin toxicity was related to dose and duration of treatment. The primary target organ was the liver in all species, with hepatic lesions seen after 14 days in dogs and monkeys. Systemic exposure levels associated with this toxicity are not known but toxic mg/kg doses were higher than the dose recommended for patient treatment.

No evidence of mutagenic potential of clarithromycin was seen during a range of in vitro and in vivo tests.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague –Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomologous 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 in monkeys embryonic loss was seen but only at dose levels, which were clearly toxic to the mothers.

No other toxicology findings considered to be of relevance to the dose level recommended for patient treatment have been reported.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Hypromellose
Hypromellose phthalate
Talc
Magnesium stearate (E 572)

Tablet coating
Opadry II Yellow (31G52300) made up of:
Hypromellose 15cP (HPMC 2910) (E464)
Lactose Monohydrate
Titanium dioxide (E171)
Macrogol/PEG 4000
Talc (E553b)
Quinoline Yellow Aluminium Lake (E104)
Macrogol/PEG 400

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

PVC/PVDC/Aluminium foil blister packs of 5, 6, 7, 8, 10, 14, 16, 20, 21, 28, 30 and 60 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd t/a Gerard Laboratories
35/36 Baldoyle Industrial Estate
Grange Road
Dublin 13
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 577/93/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21st March 2011

10 DATE OF REVISION OF THE TEXT

March 2014