

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Klariger 250 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 250 mg of clarithromycin
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Yellow, oval, biconvex film coated tablets with “C250” on one side and “G” on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clarithromycin Tablets are indicated for treatment of infections caused by susceptible organisms. Indications include:

Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia.

Upper respiratory tract infections for example, sinusitis and pharyngitis.

Clarithromycin is appropriate for initial therapy in community acquired respiratory infections and has been shown to be active *in vitro* against common and atypical respiratory pathogens as listed in the microbiology section.

Clarithromycin is also indicated in skin and soft tissue infections of mild to moderate severity (such as cellulitis, pyoderma, impetigo).

Clarithromycin in the presence of acid suppression effected by omeprazole or lansoprazole is also indicated for the eradication of *Helicobacter pylori* in patients with duodenal ulcers. See section 4.2.

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

Clarithromycin is indicated in adults and children 12 years and older.

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

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-haemolytic streptococci); alpha-haemolytic streptococci (viridans groups); *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* species.

The activity of clarithromycin against *H. pylori* is greater at neutral pH than at acid pH.

4.2 Posology and method of administration

Posology

For doses of 250 mg twice daily, the 250 mg tablet must be used, as the 500 mg tablet cannot be halved.

Patients with respiratory tract/skin and soft tissue infections.

Adults: Clarithromycin Tablets are available in two strengths, 250 mg and 500 mg. The usual dose is 250 mg twice daily although this may be increased to 500 mg twice daily in severe infections. The usual duration of treatment is 6 to 14 days.

Children older than 12 years: As for adults.

Eradication of *H. pylori* in patients with duodenal ulcers (Adults)

The usual duration of treatment is 6 to 14 days.

Triple Therapy: Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with amoxicillin 1000mg twice daily.

Triple Therapy: Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given with metronidazole 400mg twice daily (susceptibility testing is recommended if the potential effectiveness of metronidazole therapy is uncertain).

Triple Therapy: Clarithromycin 500 mg twice daily and omeprazole 40 mg daily should be given with amoxicillin 1000mg twice daily or metronidazole 400mg twice daily (susceptibility testing is recommended if the potential effectiveness of metronidazole therapy is uncertain).

Triple Therapy: Clarithromycin 500 mg twice daily should be given with amoxicillin 1000 mg twice daily and omeprazole 20 mg daily.

Dual Therapy: The usual dose of Clarithromycin is 500 mg three times daily for 14 days. Clarithromycin should be administered with omeprazole 40 mg once daily.

The tablets should be swallowed whole with some liquid.

Elderly: As for adults.

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

Patients with hepatic dysfunction: Dosage adjustments are not usually required, but caution should be exercised when administering clarithromycin to patients with impaired hepatic function.

Paediatric population

Children younger than 12 years: Use of Clarithromycin tablets is not recommended for children younger than 12 years. 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 (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.

Method of administration

The tablets should be swallowed whole with some liquid.

Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability.

4.3 Contraindications

Hypersensitivity to clarithromycin, to any other macrolide antibiotic drug, or to any of the excipients listed in section 6.1.

Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated:

- astemizole, an antihistamine
- cisapride, a motility stimulant
- pimozide, an antipsychotic
- terfenadine, an antihistamine.

Elevated astemizole, 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 tachycardia, ventricular fibrillation and Torsade de Pointes (see section 4.5).

Concomitant administration with ticagrelor or ranolazine is contraindicated.

Similar effects have been observed with concomitant administration of other macrolides.

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired 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) that are extensively metabolised by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis. 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.

As with other strong CYP3A4 inhibitors, clarithromycin should not be used in patients taking colchicine.

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.

Clarithromycin can be used in patients with known hypersensitivity to penicillin or when penicillin would be inappropriate for other reasons.

Attention should be paid to the possible cross-resistance and cross-allergy between clarithromycin and other macrolides, clindamycin and lincomycin.

Clarithromycin should not be combined with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

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.

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

Prolongation of the QT Interval

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsade de pointes, have been seen in treatment with macrolides including clarithromycin (see section 4.8). Therefore as the following situations may lead to an increased risk of ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution in the following patients:

- Patients with a coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia
- Patients with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia (see section 4.3)
- Patients concomitantly taking other medicinal products associated with a QT prolongation (see section 4.5)
- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindicated (see section 4.3)
- 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 emerging 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.

Clarithromycin should be used with caution whenever indicated for use in patients receiving treatment with an inducer of CYP3A4 due to the possibility of sub therapeutic levels of clarithromycin (see section 4.5).

Clarithromycin is an inhibitor of CYP3A4, and concomitant use with other medicinal products that are metabolised to a large extent by this enzyme should be restricted to situations where is clearly indicated (see section 4.5)

HMG-CoA reductase inhibitors: Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin with statins. Patients should be monitored for signs and symptoms of myopathy. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest possible doses of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g.

fluvastatin) should be considered.

Oral hypoglycaemic agents/insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulfonylureas) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended (see section 4.5)

Skin and soft tissue infections of mild to moderate severity: These infections are most often caused by *Staphylococcus aureus* and *Streptococcus pyogenes*, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed. In cases where *beta*-lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first 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, toxic epidermal necrolysis, DRESS and Henoch-Schönlein purpura, clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Streptococcus pyogenes: Clarithromycin is generally effective in the eradication of Streptococci from the oropharynx. However, data establishing the efficacy of this antibiotic in the subsequent prevention of rheumatic fever are not available.

In pharyngitis related to beta-haemolytic streptococcal infection the treatment duration should be at least 10 days.

H. pylori:

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 colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

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

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). Concomitant administration of clarithromycin and colchicine is contraindicated (see section 4.3).

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, pimozone, 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 pimozone 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

Postmarketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm, and ischaemia 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).

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see 4.3) as these statins are extensively metabolised by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

*The effect of clarithromycin tablets 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. Alternatively, treatment with these medicinal products may be interrupted during clarithromycin treatment.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, see section 4.4), atypical antipsychotics (e.g. quetiapine), pimozone, 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 postmarketing reports of torsades 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.

There have been post marketing reports of hypoglycaemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycaemic agents/insulin

With certain hypoglycaemic drugs such as nateglinide and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.

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 (C_{\max} , AUC_{0-24} , 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. 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 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. 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 metaboliser 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), 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.

The effect of other medicinal products on clarithromycin tablets

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's 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. A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-hydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz. In such circumstances, it may be

necessary to increase the dose of clarithromycin and monitor the safety and efficacy. Monitoring the plasma levels of the CYP3A4 inducer may be necessary because the levels could be increased owing to the inhibition of CYP3A4 by clarithromycin (see also the relevant medicinal product information for the CYP3A4 inducer administered).

Etravirine

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against *Mycobacterium avium* complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

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 (C_{\min}) 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 C_{\max} increased by 31%, C_{\min} 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, Bi-directional drug interactions)

Other drug interactions

Aminoglycosides

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. See section 4.4.

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. Concomitant administration of clarithromycin and colchicine is contraindicated (see sections 4.3 and 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 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 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 of 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 serum levels have been reported

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.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolised by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

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 twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} 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.

Clarithromycin has been shown not to interact with oral contraceptives.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained

from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breast-feeding

The safety of clarithromycin for use during breast-feeding of infants has not been established. 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 paediatric populations are abdominal pain, diarrhoea, nausea, vomiting, dyspepsia, headache 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 pre-existing mycobacterial infections.

b. Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing 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 ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), very rare ($< 1/10,000$) 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	Common $\geq 1/100$ to $< 1/10$	Uncommon $\geq 1/1,000$ to $< 1/100$	Very rare $< 1/10,000$	Not Known (cannot be estimated from the available data)
Infections and infestations	Oral moniliasis	Candidiasis, vaginal infection		Erysipelas, pseudomembranous colitis,
Blood and lymphatic system		Leukopenia, neutropenia ¹ , eosinophilia ¹		Agranulocytosis, thrombocytopenia
Immune system disorders		Hypersensitivity		Anaphylactic reaction, angioedema
Metabolism and nutrition disorders		Anorexia, decreased appetite		
Psychiatric disorders	Insomnia	Anxiety	Nightmares	Psychotic disorder, confusional state, depersonalisation, depression,

					disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache, taste perversion,	Dizziness, somnolence ² , tremor	Paraesthesia	Convulsion, ageusia parosmia, anosmia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus		Deafness
Cardiac disorders			Electrocardiogram QT prolonged, palpitations		Torsade de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders					Haemorrhage
Gastrointestinal disorders		Diarrhoea ³ , vomiting, dyspepsia, nausea, abdominal pain, stomatitis, glossitis	Abdominal distension ¹ , constipation, dry mouth, eructation, flatulence, gastritis		Pancreatitis acute, tongue discolouration, tooth discolouration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis ¹ , hepatitis ¹ , alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased ¹		Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Pruritus, urticaria		Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, Henoch-Schonlein purpura
Musculoskeletal and connective tissue disorders					Rhabdomyolysis ⁴ , myopathy
Renal and urinary disorders					Renal failure, nephritis interstitial
General disorders and administration site conditions			Malaise ¹ , asthenia, chest pain ¹ , chills ¹ , fatigue ¹		
Investigations		Elevated BUN (blood urea nitrogen)	Serum creatinine raised, blood alkaline phosphatase increased ¹ , blood lactate dehydrogenase increased ¹		International normalised ratio increased, urine colour abnormal prothrombin time prolonged,

¹ ADRs reported only for the Immediate-Release Tablets formulation

³See section a)

^{2,4} See section c)

c. Description of selected adverse reactions

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 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).

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, diarrhoea, 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 HPRa Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms

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.

Management

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic Class: General anti-infectives for systemic use: Antibiotics for systemic use.

ATC Code: J01 FA09

Mechanism of action:

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.

Breakpoints

The following MIC breakpoints, separating susceptible (S) from resistant (R) organisms are suggested

British Society for Antimicrobial Chemotherapy (BSAC) recommendations:

For *Staphylococcus* spp, *Streptococcus* spp and *M. catarrhalis*: S: ≤ 0.5 mg/L, R: ≥ 1.0 mg/L

For *H. influenzae*: S: ≤ 0.5 mg/L, R: ≥ 32.0 mg/L

National Committee for Clinical Laboratory Standards (NCCLS) recommendations:

- For *Staphylococcus* spp S: ≤ 2.0 mg/L, R: ≥ 8.0 mg/L
- For *H influenzae* S: ≤ 8.0 mg/L, R: ≥ 32.0 mg/L
- For *Streptococcus* spp S: ≤ 0.25 mg/L, R: ≥ 1.0 mg/L

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information provides only an approximate guidance on the probability of an organism being susceptible to clarithromycin. Where the resistance range is known to vary considerably across the European Union this is shown in Table 2.

Commonly susceptible species
Aerobic Gram-negative microorganisms <i>Moraxella catarrhalis</i>
Anaerobic microorganisms <i>Peptococcus</i> species <i>Peptostreptococcus</i> species <i>Propionibacterium acnes</i> <i>Clostridium perfringens</i>
Other microorganisms <i>Chlamydia pneumoniae</i> <i>Legionella pneumophila</i>

<i>Mycoplasma pneumoniae</i>

Species for which acquired resistance may be a problem

Aerobic Gram-positive microorganisms <i>Staphylococcus aureus</i> (methicillin-susceptible) <i>Staphylococcus aureus</i> (methicillin-resistant)* <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> <i>Streptococcus pyogenes</i>
--

Aerobic Gram-negative microorganisms <i>Haemophilus influenzae</i>

*Resistance to macrolides among MRSA is commonly more than 50% in the EU and affects nearly all strains in some areas.

§ The species may be regarded as being of intermediate susceptibility to clarithromycin and may also acquire high-level resistance to macrolides.

Resistance

Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on modification and/or the active efflux of the antibiotic. Resistance development can be mediated via chromosomes or plasmids, be induced or exists constitutively. Macrolide/resistant bacteria generates enzymes which lead to methylation of residual adenine at ribosomal RNA and consequently to inhibition of the antibiotic binding to the ribosome. Macrolide/resistant organisms are generally cross/resistant to lincosamides and streptogramin B based on methylation of the ribosomal binding site. Clarithromycin ranks among the strong inducers of this enzyme as well. Furthermore, macrolides have a bacteriostatic action by inhibiting the peptidyl transferase of ribosomes.

A complete cross-resistance exists among clarithromycin, erythromycin and azithromycin. Methicillin/resistant staphylococci and penicillin-resistant *Streptococcus pneumoniae* are resistant to macrolides such as clarithromycin.

5.2 Pharmacokinetic properties

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

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

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

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

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin tablets. The microbiologically active metabolite 14-hydroxyclearithromycin is formed by first pass metabolism. Clarithromycin Tablets 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-hydroxyclearithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.

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

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

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

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 Sprague-Dawley (p.o. and i.v.)), New Zealand White rabbits and cynomolgus 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

Tablet core:

Cellulose, microcrystalline
Maize starch, pregelatinised
Croscarmellose sodium
Povidone
Silica, colloidal anhydrous
Stearic acid
Magnesium stearate

Film-Coating:

Hypromellose (E464)
Hydroxypropyl cellulose (E463)
Titanium dioxide (E171)
Macrogol (E1520)
Vanillin
Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

PVdC coated PVC/Aluminium blisters: 3 years

HDPP containers: 2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVdC coated PVC/Aluminium blisters in cardboard cartons (for some Member States, calendar packs or Blister Unit Dose packs may be required).

HDPP containers with PE lids (with optional ullage filler)

Pack sizes: 4, 6, 7, 8, 10, 12, 14, 20, 21, 24, 28, 30, 42, 50, 60, 100, 250, 500 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories Ltd. T/A Gerard Laboratories
35/36 Baldoyle Industrial Estate,
Grange Road,
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA0577/093/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31 March 2006

Date of last renewal: 25 April 2009

10 DATE OF REVISION OF THE TEXT

August 2016