Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 250mg/5ml Granules for Oral Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution 1 ml oral suspension contains 50 mg clarithromycin, 5 ml oral suspension contain 250 mg clarithromycin.

Excipient with known effect: the product contains 2.4 g sucrose per 5 ml ready-for-use suspension.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Granules for oral suspension.

White to beige granules.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clarithromycin 50 mg/ml granules for oral suspension is indicated in adults, adolescents and children, 6 months to 12 years, for the treatment of the following acute and chronic infections, when caused by clarithromycin susceptible organisms.

- Infections of the upper respiratory tract such as tonsillitis/pharyngitis, as an alternative when beta lactam antibiotics are not appropriate.
- Acute otitis media in children.
- Infections of the lower respiratory tract such as community acquired pneumonia.
- Sinusitis and acute exacerbation of chronic bronchitis in adults and adolescents over 12 years of age
- Skin infections and soft tissue infections of mild to moderate severity.

In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing medicinal product for the eradication of *Helicobacter pylori* in adult patients with *H. pylori* associated ulcers. See section 4.2.

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

4.2 Posology and method of administration

The dosage of Clarithromycin depends on the clinical condition of the patient and has to be defined in any case by the physician.

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

Elimination of Helicobacter pylori in adults:
In patients with gastro-duodenal ulcers due to *H. pylori* infection clarithromycin as part of the first line triple therapy is given in a dosage of 500 mg twice daily. The national recommendations for *Helicobacter pylori* eradication have to be considered.

Dosage in renal functional impairment:
The maximum recommended dosages should be reduced proportionately to renal impairment.

At creatinine clearance rate of less than 30 ml/min, the dosage should be halved to 250 mg daily or in the most severe infections to 250 mg twice daily. The duration of treatment should not exceed 14 days in these patients.

Children 6 months to 12 years of age:
The recommended dose is 7.5 mg/kg twice a day.

For 250 mg/5 ml oral suspension:

Weight	Age	Dosage
12 – 19 kg	2 – 4 years	2.5 ml twice daily
20 – 29 kg	4 – 8 years	3.75 ml twice daily
30 – 40 kg	8 – 12 years	5 ml twice daily

Children weighing less than 8 kg should be treated based on their bodyweight.

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 is limited experience of treatment of children below 6 months of age.
For the indication community acquired pneumonia effect in children under 3 years of age is not documented.

In patients with renal impairment with creatinine clearance less than 30 ml/min, the dosage of clarithromycin should be halved, i.e. 7.5 mg/kg once a day, and the duration of treatment should not exceed 14 days.

Duration of therapy:
The duration of therapy with Clarithromycin depends on the clinical condition of the patient. The duration of therapy has in any case to be determined by the physician.

- The usual duration of treatment of children up to 12 years of age is 5 to 10 days.
- The usual duration of treatment of adults and adolescents is 6 to 14 days.
- Therapy should be continued at least for 2 days after symptoms have subsided.
- In *streptococcus pyogenes* (as a beta-haemolytic streptococcal) infections the duration of therapy should be at least 10 days.
- Combination therapy for the eradication of *H. pylori* infection, e.g. clarithromycin 500 mg twice daily in combination with amoxicillin 1000 mg twice daily and omeprazole 20 mg twice daily should be continued for 7 days.

Method of administration:
Before administration the granules must be reconstituted with water, see section 6.6. For administration after reconstitution an oral PE/PP-measuring syringe or a PP-measuring spoon are used.

Granules of the oral suspension can cause a bitter aftertaste when remaining in the mouth. This can be avoided by eating or drinking something immediately after the intake of the suspension

Clarithromycin may be given irrespective of food intake. Food does not affect the extent of bioavailability. Food does only slightly delay the onset of absorption of clarithromycin.

4.3 Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to the active substance, other macrolide antibiotics or to any of the excipients listed in section 6.1.

Concomitant administration of clarithromycin and any of the following active drugs is contraindicated: astemizole, cisapride, pimozide, terfenadine, as 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.

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 (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 metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see section 4.5).

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.

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 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. 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 diarrhea 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.

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 colchicine and clarithromycin is contraindicated (see section 4.3).

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.

Prolongation of the QT interval
Prolonged cardiac repolarization 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 for ventricular arrhythmias (including torsade de pointes), clarithromycin should be used with caution in the following patients:

- Patients with coronary artery disease, severe cardiac insufficiency, , conduction disturbances or clinically relevant bradycardia ,
- Patients with electrolyte disturbances such as hypomagnesemia. Clarithromycin must not be given to patients with hypokalaemia (see section 4.3).
- Patients concomitantly taking other medicinal products associated with 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.

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* , 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 (statins): 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 and 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 registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see 4.5).

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

Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalized 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.

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.

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 it is clearly indicated (see section 4.5).

Exacerbation or aggravation of Myasthenia gravis may occur.

This medicinal product contains 2.4 g sucrose per 5 ml ready-for-use suspension. This should be taken into account in patients with diabetes mellitus.

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency 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
Postmarketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

HMG –CoA reductase inhibitors (statins)
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see sections 4.3) as these statins are extensively metabolized 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.

Effects of other medicinal products on clarithromycin

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 inducer 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.

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).

Effect of clarithromycin on other medicinal products

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

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. 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 hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Cyclosporin, tacrolimus and sirolimus
Concomitant use of oral clarithromycin and cyclosporin or tacrolimus have resulted in more than a 2-fold increase of the C_{min}-levels of both cyclosporin and tacrolimus. Similar effects are also expected for sirolimus. When initiating treatment with clarithromycin in patients already receiving any of these immunosuppressive agents, cyclosporin, tacrolimus or sirolimus plasma levels must be closely monitored and their doses decreased as necessary. When clarithromycin is discontinued in these patients, close monitoring of plasma levels of cyclosporin, tacrolimus or sirolimus, is again necessary to guide dose adjustment.

Warfarin
The use of clarithromycin in patients receiving warfarin may result in potentiation of the effects of warfarin. Prothrombin time should be frequently monitored in these patients (see section 4.4 and 4.8).

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 hypoglycemia 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 metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

Theophylline, carbamazepine
Results of clinical studies indicate 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 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) a clinically important interaction with clarithromycin is unlikely.

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

Other drug interactions

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 (see section 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 metabolized 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 metabolized 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects, or of adverse effects on the health of the neonate. Data from a limited number of pregnant women exposed in the first trimester indicate a possible increased risk of abortions. To date no other relevant epidemiological data are available.
Data from animal studies have shown reproductive toxicity (see section 5.3). The risk for humans is unknown. Clarithromycin should only be used during pregnancy after a careful benefit/risk assessment.

Breast-feeding
Clarithromycin and its active metabolite are excreted in breast milk. Therefore, diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be born in mind. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

4.7 Effects on ability to drive and use machines

There are no data 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 post-marketing experience with clarithromycin granules for oral suspension.

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).

Infections and infestations
Uncommon: Candidiasis, infection, vaginal infection
Not known: Pseudomembranous colitis, erysipelas

Blood and lymphatic system disorders
Uncommon: Leucopenia, thrombocythemia
Not known: Agranulocytosis, thrombocytopenia

Immune system disorders*
Uncommon: Hypersensitivity
Not known: Anaphylactic reaction, angioedema

Metabolism and nutrition disorders
Uncommon: Anorexia, decreased appetite

Psychiatric disorders
Common: Insomnia
Uncommon: Anxiety, nervousness
Not known: Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams

Nervous system disorders
Common: Dysgeusia, headache, taste perversion
Uncommon: Dizziness, somnolence*, tremor
Not known: Convulsion, ageusia, parosmia, anosmia, paraesthesia

Ear and labyrinth disorders
Uncommon: Vertigo, hearing impaired, tinnitus
Not known: Deafness

Cardiac disorders
Uncommon: Electrocardiogram QT prolonged*, palpitations
Not known: Torsades de Pointes*, ventricular tachycardia*, ventricular fibrillation

Vascular disorders
Not known: Haemorrhage#

Gastrointestinal disorders
Common: Diarrhoea*, vomiting, dyspepsia, nausea, abdominal pain
Uncommon: Gastritis, stomatitis, glossitis, constipation, dry mouth, eructation, flatulence
Not known: Pancreatitis acute, tongue discoloration, tooth discoloration

Hepatobiliary disorders
Common: Liver function test abnormal
Uncommon: alanine aminotransferase increased, aspartate aminotransferase increased
Not known: Hepatic failure*, jaundice hepatocellular

Skin and subcutaneous tissue disorders
Common: Rash, hyperhidrosis
Uncommon: Pruritus, urticaria, rash maculo-papular
Not known: Stevens-Johnson syndrome* and toxic epidermal necrolysis*, drug rash with eosinophilia and systemic symptoms (DRESS), acne

Musculoskeletal, connective tissue and bone disorders
Uncommon: Muscle spasms
Not known: Myopathy

Renal and urinary disorders
Not known: Renal failure, interstitial nephritis.

General disorders and administration site conditions
Uncommon: Pyrexia, asthenia

Investigations
Not known: International normalised ratio increased#, prothrombin time prolonged#, urine colour abnormal

* See section a)
# 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.

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 2000 mg 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 1000 mg and 2000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1000 mg or 2000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4000 mg 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 of intoxication:
Reports indicate the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

Therapy of intoxication:
There is no specific antidote on overdose. As with other macrolides serum levels of clarithromycin are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

Adverse reactions accompanying overdose should be treated by the prompt elimination of unabsorbed drug and supportive measures. Severe acute allergic reactions may be seen very rarely, e.g. anaphylactic shock. At first signs of hypersensitivity reactions therapy with clarithromycin must be discontinued and the required measures should be initiated immediately.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties

Pharmacological-therapeutical group:
Macrolides. ATC Code J01FA09.

Mechanism of action:
Clarithromycin, a semi-synthetic derivative of erythromycin, exerts its anti-bacterial 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 *Haemophilus influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

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.

Mechanism of resistance:
Resistance mechanisms against macrolide antibiotics include alteration of the target site of the antibiotic or are based on the modification and/or active efflux of the antibiotic.
Resistance development can be mediated via chromosomes or plasmids, be induced to exist constitutively. Macrolide-resistant bacteria generate 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 streptogramine 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 and oxacillin-resistant staphylococci (MRSA) and penicillin-resistant *Streptococcus pneumoniae* are resistant to all currently available Beta-lactam antibiotics and macrolides such as clarithromycin.

Breakpoints
The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST) *2010-12-20 (v 1.2):*

	Species-related breakpoints for clarithromycin [B,C]	
Pathogens	**Susceptible ≤ (mg/L)**	**Resistant > (mg/L)**
Enterobacteriaceae	-	-
Pseudomonas spp.	-	-
Acinetobacter spp.	-	-
Staphylococcus spp.	1	2
Enterococcus spp.	-	-
Streptococcus groups A, B, C, G	0,25	0.5
Streptococcus pneumoniae [D]	0.25	0.5
Other streptococci	IE	IE
Haemophilus influenzae	1	32
Moraxella catarrhalis	0.25	0.5
Neisseria gonorrhoeae	-	-
Neisseria meningitidis	-	-
Gram-positive anaerobes (except Clostridium difficile)	-	-
Gram-negative anaerobes	-	-
Non-species related break-points [A]	IE	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.
"IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug.

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).

Susceptibility

The prevalence of acquired resistance 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 the agent in at least some types of infections is questionable.

Pathogens for which resistance may be a problem: prevalence of resistance is equal to or greater than 10% in at least one country in the European Union

Commonly susceptible species
Aerobic Gram-positive microorganisms
Corynebacterium diphteriae
Streptococcus Group F
Aerobic Gram-negative microorganisms
Bordetella pertussis
Legionella spp.
Moraxella catarrhalis
Pasteurella multocida
Anaerobes
Clostridum spp. other than *C. difficile*
Other microorganisms
Chlamydia trachomatis
Chlamydia pneumoniae
Clamydophilapsitacci
Mycobacterium spp.
Mycoplasma pneumoniae
Species for which acquired resistance may be a problem
Aerobic Gram-positive microorganisms
Enterococcus spp.+
Staphylococcus aureus (methicillin-susceptible and methicillin-resistant+)
Staphylococcus epidermidis+
Streptococcus Group A*, B, C, G
Streptococcus viridans
*Streptococcus pneumoniae**+
Aerobic Gram-negative microorganisms
Haemophilus influenzae§
Helicobacter pylori
Anaerobes
Bacteroides spp.
Peptococcus / Peptostreptococcus spp.
Inherently resistant organisms
Aerobic Gram-negative microorganisms
Acinetobacter
Enterobacteriacea

Pseudomonas aeruginosa
Anaerobes
Fusobacterium spp.
Other microorganisms
Mycobacterium tuberculosis

≥ 10% resistance in at least one country of the European Union
* Species against efficacy has been demonstrated in clinical investigations (if susceptible)
+ 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
§ Breakpoints for macrolides and related antibiotics were set to categorise wild type *H. influenzae* as intermediate

Other information

Susceptibility and resistance of *Streptococcus pneumoniae* and *Streptococcus* spp. to clarithromycin can be predicted by testing erythromycin.
Most available clinical experience from controlled randomised clinical trials indicate that clarithromycin 500 mg twice daily in combination with another antibiotic e.g. amoxicillin or metronidazole and e.g. omeprazole (given at approved levels) for 7 days achieve > 80% *H. pylori* eradication rate in patients with gastro-doudenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant *H. pylori* isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for *H. pylori* eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antimicrobial medicinal product should be taken into the considerations for a new retreatment regimen.

5.2 Pharmacokinetic properties

Absorption:
Clarithromycin is rapidly and well absorbed from the gastrointestinal tract – primarily in the jejunum - but undergoes extensive first-pass metabolism after oral administration. The absolute bioavailability of a 250-mg clarithromycin tablet is approximately 50%. The bioavailability of the suspension is identical to or slightly higher than the bioavailability of the tablets. The pharmacokinetic profile of the suspension in children corresponds to the pharmacokinetic profile of the suspension in adults. Food slightly delays the absorption but does not affect the extent of bioavailability. Therefore, clarithromycin may be given without regard to food. Due to its chemical structure (6-O-Methylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. Peak plasma levels of 1 – 2 µg/ml clarithromycin were observed in adults after oral administration of 250 mg twice daily. After administration of 500 mg clarithromycin twice daily the peak plasma level was 2.8 µg/ml. In children the following steady-state parameters were observed after the ninth dose in a dose regimen of 7.5 mg/kg twice daily on average for clarithromycin: C_{max} 4.60 µg/ml, AUC 15.7 µg.hour/ml and T_{max} 2.8 hours. The corresponding average values for the 14-OH metabolite were respectively: 1.64 µg/ml, 6.69 µg.hour/ml and 2.7 hours.

After administration of 250 mg clarithromycin twice daily the microbiologically active 14-hydroxy metabolite attains peak plasma concentrations of 0.6 µg/ml. Steady state is attained within 2 days of dosing.

Distribution:
Clarithromycin penetrates well into different compartments, with an estimated volume of distribution of 200-400 L. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating level of the active substance. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus.

Clarithromycin is approximately 70% bound to plasma proteins at therapeutic levels.

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

The pharmacokinetics of clarithromycin is non-linear due to saturation of hepatic metabolism at high doses. Elimination half-life increased from 2-4 hours following administration of 250 mg clarithromycin twice daily to 5 hours following administration of 500 mg clarithromycin twice daily. With a 250 mg every 12 hours dosing, the half-life of the active 14-hydroxy metabolite ranges between 5 to 6 hours following administration of 250 mg clarithromycin twice daily.

Approximately 20 -40% of clarithromycin is excreted as the unchanged active substance in the urine. This proportion is increased when the dose is increased. An additional 10% to 15% is excreted in the urine as 14-hydroxy metabolite. The rest is excreted in the faeces. Renal insufficiency increases clarithromycin levels in plasma, if the dose is not decreased. Total plasma clearance has been estimated to approximately 700 ml/min (11.7 mL/s), with a renal clearance of approximately 170 ml/min (2.8 mL/s).

Special populations
Renal impairment: Reduced renal insufficiency function results in increased plasma levels of clarithromycin and the active metabolite levels in plasma.

5.3 Preclinical safety data

In 4-week-studies in animals, toxicity of clarithromycin was found to be related to the dose and to the duration of the treatment. In all species, the first signs of toxicity were observed in the liver, in which lesions were seen within 14 days in dogs and monkeys. The systemic levels of exposure, related to this toxicity, are not known in detail, but toxic doses (300 mg/kg/day) were clearly higher than the therapeutic doses recommended for humans. Other tissues affected included the stomach, thymus and other lymphoid tissues as well as the kidneys. At near therapeutic doses conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400 mg/kg/day some dogs and monkeys developed corneal opacities and/or oedema.
In vitro and *in vivo* studies showed that clarithromycin did not have genotoxic potential.

Studies on reproduction toxicity showed that administration of clarithromycin at doses 2x the clinical dose in rabbit (iv) and 10x the clinical dose in monkey (po) resulted in an increased incidence of spontaneous abortions. These doses were related to maternal toxicity. No embryotoxicity or teratogenicity was generally noted in rat studies. However, cardiovascular malformations were observed in two studies in rats treated with doses of 150 mg/kg/d. In mice at doses 70x the clinical dose cleft palate occurred at varying incidence (3-30%).

Clarithromycin has been found in the milk of lactating animals.

In 3-day old mice and rats, the LD_{50} values were approximately half those in adult animals. Juvenile animals presented similar toxicity profiles to mature animals although enhanced nephrotoxicity in neonatal rats has been reported in some studies. Slight reductions in erythrocytes, platelets and leukocytes have also been found in juvenile animals.

Clarithromycin has not been tested for carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Poloxamer 188
Povidone K 30 (E1201)
Hypromellose (E464)
Macrogol 6000
Titanium dioxide (E171)
Methacrylic acid – ethyl acrylate copolymer (1:1)
Triethyl citrate (E1505)
Glycerol monostearate
Polysorbate 80 (E433)

Sucrose
Maltodextrin
Potassium sorbate (E202)
Colloidal anhydrous silica (E551)
Xanthan gum (E415)
Fruit punch flavouring (natural and artificial flavouring substances including maltodextrin, modified starch and maltol).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After reconstitution 14 days.

6.4 Special precautions for storage

Do not store above 25°C.
After reconstitution: Do not store above 25°C.

6.5 Nature and contents of container

60 ml, 120 ml and 240 ml HDPE bottles with child resistant PP-screw closures, an oral PE/PP-measuring syringe (5 ml) with filling marks at 2.5 ml, 3.75 ml and 5.0 ml and a PE/PP-measuring spoon with filling marks at 1.25 ml, 2.5 ml and 5.0 ml.

1 bottle contains
47.8 g granules for oral suspension for 70 ml ready-for-use suspension (required water amount: 39.9 ml) or
68.3 g granules for oral suspension for 100 ml ready-for-use suspension (required water amount: 57.0 ml).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The bottle should be filled with two-thirds of the overall required quantity of water, then thoroughly shaken and filled with water up to the mark and shaken again. The bottle should be shaken vigorously before each application.

After reconstitution with water the medicinal product results in a white to beige suspension.

If the dose is to be given using the oral dosing syringe, the syringe adaptor should be inserted into the bottle neck.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry,
Co. Cork,
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/197/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd February 2012

10 DATE OF REVISION OF THE TEXT

July 2016