SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin 500 mg Powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500mg clarithromycin.

Excipient(s) with known effect: This medicinal product contains less than 1 mmol sodium (23 mg) per 500 mg, i.e. essentially "sodium-free".

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White or almost white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Clarithromycin 500 mg powder for solution for infusion is indicated in adults and children 12 years and older.

Clarithromycin 500 mg powder for solution for infusion is indicated whenever parenteral therapy is required for treatment of infections caused by susceptible organisms in the following conditions;

- Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia (see section 4.4 and 5.1 regarding Sensitivity Testing).

- Upper respiratory tract infections for example, sinusitis and pharyngitis.

- Skin and soft tissue infections (e.g. folliculitis, cellulitis, erysipelas) (see section 4.4 and 5.1 regarding Sensitivity Testing).

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

4.2 Posology and method of administration

Posology

Intravenous therapy may be given for 2 to 5 days and should be changed to oral clarithromycin therapy when appropriate.

Adults: The recommended dosage is 1 gram daily, divided into two 500 mg doses, appropriately diluted as described below (see section 6.6).

*Children older than 12 years***:** As for adults.

Children under 12 years: Use of "invented name" 500 mg powder for solution for infusion is not recommended for children younger than 12 years.

Elderly: As for adults.

Renal impairment: In patients with renal impairment who have creatinine clearance less than 30ml/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

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

Method of administration

Clarithromycin should be administered into one of the larger proximal veins as an intravenous infusion over 60 minutes, using a solution concentration of about 2 mg/ml.

Clarithromycin should not be given as a bolus or an intramuscular injection.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6. The reconstituted product is a clear solution.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Concomitant administration with ticagrelor or ranolazine is contraindicated.
- Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5).
- Concomitant administration of clarithromycin and any of the following medicinal products 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).
- Clarithromycin must not be given to patients with electrolyte disturbance (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of QT-interval)
- Clarithromycin must not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- 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 must 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).
- Concomitant administration of clarithromycin and ergotamine or dihydroergotamine is contraindicated, as this may result in ergot toxicity.
- As with other strong CYP3A4 inhibitors, Clarithromycin must not be used in patients taking colchicine.
- Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).

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 mainly 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.

Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C. difficile. Clostridium difficile-Associated Disease (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. Medicinal products 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 clarithromycin and colchicine 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

Cardiovascular Events

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 for 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 (< 50 bpm) bradycardia
- Clarithromycin must not be given to patients with hypokalaemia (see section 4.3).
- Patients concomitantly taking other medicinal products with a QT-prolonging effect (see section 4.5).
- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfendine is contraindicated (see section 4.3).
- Clarithromycin is contraindicated in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term, risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin.

Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Pneumonia: In view of the emerging resistance of Streptococcus pneumoniae to macrolides, it is important that sensitivity testing is performed when prescribing clarithromycin for community-acquired pneumonia. In hospital, acquired pneumonia clarithromycin should only be used in combination with further 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 species are often resistant to macrolides. Therefore, it is important that sensitivity testing is performed. In cases, where beta lactams cannot be used (e.g. allergy towards beta lactams) other antibiotics, such as clindamycin, are the medicinal products of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections such as infections caused by Corynebacterium minutissimum (erythrasma), acne vulgaris, and in erysipelas and in situations where penicillin treatment is not possible.

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

Clarithromycin should be used with caution when administered concurrently with medicines that induce CYP3A4 due to the possibility of subtherapeutic 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 it 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. Rare reports of rhabdomyolysis have been reported in patients taking these medicinal products concomitantly. 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. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) should be considered (see section 4.5).

Oral hypoglycemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulphonylureas) 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.

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding (see section 4.5).

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. 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). If concomitant administration of colchicine and clarithromycin is necessary, patients should be monitored for clinical symptoms of colchicine toxicity.

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

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

Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy (see section 4.8).

Concomitant administration of clarithromycin with lomitapide is contraindicated due the potential for markedly increased transaminases (see section 4.3).

4.5 Interaction with other medicinal products and other forms of interaction

Cisapride, pimozide, astemizole and terfenadine

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

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac

arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two to three fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine

Post-marketing reports indicate that 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 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.

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.

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 CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR < 30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

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.

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 medicinal products are co-administered with clarithromycin.

Theophylline, carbamazepine

Results of clinical studies indicate there was a modest but statistically significant ($p < 0.05$) increase of circulating theophylline or carbamazepine levels when either of these medicinal products was 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.

Aminoglycosides

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

Triazolobenzodiazepines (e.g. alprazolam, midazolam, triazolam)

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam and 7-fold after oral administration. Concomitant administration of oral midazolam and clarithromycin should be avoided.

If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of medicinal product 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.

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine.

Patients should be monitored for clinical symptoms of colchicine toxicity (see section 4.4).

Oral hypoglycemic agents/Insulin

With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia 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.

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, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Direct acting oral anticoagulants (DOACs)

The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

Antiarrhythmics

There have been post-marketing 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.

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional medicinal product 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 medicinal product interaction.

Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional medicinal product 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 values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C values were approximately 40%

higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicinal products are co-administered for a limited time at the doses/formulations studied. Observations from medicinal product interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule.

Observations from medicinal product 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 (see section 4.5: Ritonavir).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of clarithromycin for use in pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofoetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results.

Therefore, use during pregnancy is not advised without carefully weighing the benefits against risks.

Breastfeeding

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

Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin.

Fertility

There is no data available on the effect of clarithromycin on fertility in humans. In rats, the limited data available do not indicate any effects on fertility.

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 immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.

The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class	Very common	Common	Uncommon	Not Known* (cannot be estimated from the available data)
Infections and infestations			Cellulitis[1], candidiasis, gastroenteritis[2],infection[3], vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders			Anaphylactoid reaction, hypersensitivity	Anaphylactic reaction, angioedema
Psychiatric disorders		Insomnia	Anxiety, nervousness[3], screaming[3]	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams
Nervous system disorders		Dysgeusia, Headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[7], tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest, atrial fibrillation, electrocardiogram QT prolonged, extrasystoles, palpitations	Torsades de pointes, ventricular Tachycardia, *ventricular fibrillation*
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Vascular disorders		Vasodilation[1]		Hemorrhage[9]

Gastrointestinal disorders		Diarrhea[10], vomiting, dyspepsia, nausea, abdominal pain	Esophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence,	Pancreatitis acute, tongue discolouration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal,	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous , pruritus, urticaria, rash maculo-papular[3]	Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis [2,12], myopathy
Renal and urinary disorders			Blood creatinine increased , blood urea increased	Renal failure, nephritis interstitial
Investigations			Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased[9], prothrombin time prolonged[9], urine color abnormal

General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	

[1] ADRs reported only for the Powder for Solution for Injection formulation

[2]ADRs reported only for the Extended-Release Tablets formulation

[3] ADRs reported only for the Granules for Oral Suspension formulation

[4] ADRs reported only for the Immediate-Release Tablets formulation

[5,8,10,11,]See section a)

[6,7,9, 12]See section c)

c. Description of selected adverse reactions

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

In 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).

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

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

d. Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin intravenous 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 2000 mg 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 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 the national reporting system listed in The Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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 behavior, hypokalemia, and hypoxemia.

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, macrolides, ATC code: J01FA09

Mechanism of action

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal sub-unit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria.

The 14-hydroxy metabolite of clarithromycin, a product of parent drug metabolism also has anti-microbial activity. The metabolite is less active than the parent compound for most organisms, including mycobacterium spp. An exception is *Haemophilus influenza* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

PK/PD Relationship

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.

Mechanisms of resistance

Resistance to clarithromycin can be based on the following mechanisms:

- Target site modification: (conferred by the ermB gene) As a result of the methylation of 23S rRNS, the affinity for the ribosomal binding sites is reduced, leading to high-level macrolide resistance to macrolides (M) and cross reference to lincosamides (L) and Group B streptograms (SB) (so called MLSB phenotype);

- Active drug efflux: Resistance can be caused as a result of an increase in the number of active efflux pumps in the cytoplasmic membrane (so-called M phenotype); active drug efflux among pneumococci is mediated by a membrane efflux pump encoded by the mefA gene. This mechanism results in low to mid-level resistance.

- The enzymatic inactivation of macrolides is only of subordinate clinical importance.

Breakpoints

The following breakpoints have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, mg/l)		
Microorganism	Susceptible (≤)	Resistant (>)
Staphylococcus spp.	1 mg/l	2 mg/l
Streptococcus A, B, C and G	0.25 mg/l	0. 5 mg/l
Streptococcus pneumonia	0.25 mg/l	0. 5 mg/l
Viridans group streptococcus	IE	IE
Haemophilus spp.	1 mg/l	32 mg/l
Moraxella catarrhalis	0.25 mg/l	0. 5 mg/l
Helicobacter pylori	0.25 mg/l	0. 5 mg/l

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.

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Streptococcus pyogenes [1]
Aerobic Gram-negative micro-organisms
Haemophilus influenzae[$]
Helicobacter pylori[2]
Moraxella catarrhalis°
Other micro-organisms
Chlamydophila pneumoniae°
Legionella pneumophila°
Mycobacterium avium°
Mycobacterium chelonae°

Mycobacterium intrazellulare°
Mycoplasma pneumoniae°
Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Staphylococcus aureus (Methicillin-susceptible)
Staphylococcus aureus (Methicillin-resistant)+
Streptococcus pneumoniae
Inherently resistant organisms
Aerobic Gram-negative micro-organisms
Escherichia coli
Klebsiella spp.
Pseudomonas aeruginosa

° No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.

$ Inherent susceptibility of most of the isolates shows intermediate resistance.

+ At least one region shows resistance rates higher than 50%.

1 The resistance rates are in some studies ≥10%.

2 The resistance rate is ≥10% by pre-treated patients.

5.2 Pharmacokinetic properties

Absorption

The following table shows the pharmacokinetics parameters measured after intravenouse single dose administration of clarithromycin.

Dose Clarithromycin (mg)	**C_{max} (µg/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**	**AUC (h.µg/ml)**
75	1,23	0,5	2,1	2,29
125	1,87	0,5	2,3	3,61
250	4,75	0,5	2,6	11,44

The observed mean steady-state peak clarithromycin (C_{max}) concentration increased from 2.1 mcg/ml with the 125 mg dose to 3.2 and 5.5 mcg/ml with the 250 and 500 mg doses, respectively. The mean apparent terminal half-lives increased gradually from 2.8 hours after infusion of the 125 mg dose over a 30-minute period to 6.3 hours after infusion of the 500 mg dose over a 60-minute period.

Dose **Clarithromycin (mg)**	**Duration of infusion** **(min)**	**$C_{máx}$** **(µg/ml)**	**$t_{1/2}$** **(h)**
125	30	2,1	2,8
250	30	3,2	3,4
500	60	5,5	6,3

Distribution

The protein binding of clarithromycin in human plasma averaged about 72% at concentrations of 0.45 – 4.5 mcg/ml. A decrease in binding only occurred at concentrations far in excess of the therapeutic drug levels. 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

Clarithromycin is metabolised in the liver by the cytochrome P-450 enzyme system quickly and to large extent. The microbiologically active metabolite 14+hydroxyclarithromycin is formed by first pass metabolism as indicated by lower bioavailability of the metabolite. Following intravenous administration.

Elimination

The measure of radiolabeled clarithromycin 70-80% of radioactivity was found in the faeces. About 20-30% of the clarithromycin dose is excreted in the urine in the unchanged form.

Linearity/non-linearity

The pharmacokinetics of clarithromycin and the 14-hydroxy metabolite are non linear; steady state is achieved by day 3 of intravenous dosing.

Elderly Population

A study was also conducted to evaluate and compare the safety and pharmacokinetic profiles of multiple 500 mg oral doses of clarithromycin in healthy elderly male and female subjects to those in healthy young adult male subjects. In the elderly group, circulating plasma levels were higher and elimination slower than in the younger group for both parent medicinal product and 14-OH metabolite. However, there was no difference between the two groups when renal clearance was correlated with creatinine clearance. It is concluded from those results that any effect on the handling of clarithromycin is related to renal function and not to age itself.

5.3 Preclinical safety data

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

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

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

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactobionic acid

sodium hydroxide

water for injection.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

36 months

Reconstituted solution:

Chemical and physical in-use stability has been demonstrated for 24 hours at 5 - 25ºC when reconstituted in water for injections, and for 48 hours at (5ºC).

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions .

For storage conditions after reconstitution/dilution of the medicinal product see section 6.3.

6.5 Nature and contents of container

Type I clear glass 20 ml vial with grey coloured bromobutyl stopper and green aluminium flip-off cap. Pack size: 1 vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitute each vial with 10 ml sterile water for injections. The reconstitution of the drug product can be taken up to 3 minutes.

The reconstituted solution can be diluted in 250 ml of the following diluents:

• sodium chloride 9 mg/ml (0.9%) solution for infusion

• dextrose 5 mg/ml (5%) solution

• dextrose 0.05 mg/ml (5%) in sodium chloride (0.003 mg/ml (0.3%) or 0.0045 mg/ml (0.45%)) solution for infusion

• dextrose 0.05 mg/ml (5%) in Ringers solution

• dextrose 0.05 mg/ml (5%) in Ringers Lactate solution

After reconstitution/dilution the solution is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

The ready to use solution for Infusion should be administered into one of the larger proximal veins as an intravenous infusion over 60 minutes, using a solution concentration of about 2mg/ml. The medicinal product should not be given as a bolus or an intramuscular injection.

For single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Dublin 2, D02 FK02, Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 46788/0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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