Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Clarithromycin Martindale Pharma 500 mg Powder for Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 500 mg clarithromycin as clarithromycin lactobionate.
When reconstituted and diluted, the final diluted solution contains approximately 2 mg/ml of clarithromycin.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for Concentrate for Solution for Infusion
A white to off-white caked powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Clarithromycin is indicated when parenteral therapy is required for treatment of infections caused by susceptible organisms in the following conditions (see sections 4.4 and 5.1);

- - 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, pharyngitis and tonsilitis.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 in the appropriate use of antibacterial agents.

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

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 whenever possible as determined by the physician.. The total duration of treatment should not exceed more than 14 days. The usual duration of treatment is 6 to 14 days.

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

Paediatric population
Children older than 12 years: As for adults.

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

Elderly
As for adults.

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

Preparation for use
See section 6.6

Method of Administration:
For intravenous use only.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5).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 and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular fibrillation, and torsades de pointes (see section 4.5). Elevated cisapride, pimozide and terfenadine levels have been reported in patients receiving either of these medicinal products and clarithromycin concomitantly. 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 pointes (see sections 4.4 and 4.5).
Concomitant administration with ticagrelor or ranolazine is contraindicated.
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).
As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine (see sections 4.4 and 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.

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).
Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment (see section 4.2).
Clarithromycin is principally metabolized by the liver. Therefore caution should be exercised in administering this antibiotic to patients with impaired hepatic function..
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.
Prolonged or repeated use of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted. Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridium difficile*- associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of *C. difficile.* CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.
Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous midazolam (see section 4.5).

Cardiovascular Events
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades 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 *torsades 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 hypomagnesaemia.
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).*

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 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, severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)), 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 section 4.5).
Oral hypoglycaemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylureas) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended (see section 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.
Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.
Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin.

4.5 Interaction with other medicinal products and other forms of interactions

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 2- to 3-fold increase in the serum level of the acid metabolite of terfenadine and in

prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids:
Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated (see section 4.3).

Oral midazolam:
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin 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.

Effects of other medicinal products on clarithromycin

Clarithromycin is metabolised via enzyme CYP3A4. Therefore, strong inhibitors of this enzyme may inhibit clarithromycin metabolism, this results in increased plasma concentrations of clarithromycin.
CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, phenobarbital, products containing St. John Wort) may induce clarithromycin metabolism. This may result in sub-therapeutic levels of clarithromycin which decrease the product´s 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 has resulted in increased rifabutin levels and decreased clarithromycin levels in serum, and in 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.

Ritonavir
It has been demonstrated that ritonavir (200 mg of ritonavir three times daily) is an inhibitor of clarithromycin (500 mg twice daily) metabolism, whereas an increase of Cmax, Cmin and AUC in concomitant administration with ritonavir are 31, 182 and 77%, respectively. Formation of the active metabolite 14-OH-clarithromycinhydroxyclarithromycin has been almost completely inhibited. In patients with normal renal function the dose of clarithromycin need not be decreased, however, clarithromycin daily dose must not exceed 1 g. A dose reduction should be considered in patients with renal impairment. In patients with creatinine clearance of 30-60 ml/min (0.5 – 1 ml/s) the dose of clarithromycin should be reduced by 50% and in patients with creatinine clearance of <30 ml/min (<0.5 ml/s) the dose should be reduced by 75%.
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).
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 (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Effects of clarithromycin on other medicinal products

CYP3A-based interactions

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

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

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, see 4.4), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine but this list is not exhaustive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Antiarrhythmics

There have been post-marketed reports of torsades de pointes occuring with the concurrent use of clarithromycin and quinidine or disopyramid. 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.

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.

Antacids

Increased plasma concentrations of clarithromycin may also occur when it is coadministered with antacids or ranitidine. No adjustment to the dosage is necessary.

Omeprazole

Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with clarithromycin.

Sildenafil, tadalafil and vardenafil

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

Theophylline, carbamazepine

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

Tolterodine

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of

CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metaboliser population.
Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)In concomitant administration of midazolam with clarithromycin tablets (500mg twice daily), AUC of midazolam was increased 2.7-fold following intravenous administration of midazolam.. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also be applied while using other benzodiazepines metabolised via CYP3A, in particular triazolam as well as alprazolam. An interaction with clarithromycin is unlikely in benzodiazepines which are not metabolised via CYP3A4 (temazepam, nitrazepam, lorazepam).

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.

Ciclosporin, tacrolimus and sirolimus
Concomitant administration of the oral form of clarithromycin with ciclosporin or tacrolimus results an in more than two-fold increase of Cmin plasma concentrations of ciclosporin and tacrolimus. Similar effects can also be expected with sirolimus. Plasma levels of ciclosporin, tacrolimus or sirolimus should be thoroughly monitored when commencing treatment with clarithromycin in patients on any of the abovementioned immunosuppresants, and their doses should be decreased, if necessary.
Clarithromycin discontinuation in those patients also requires a thorough monitoring of ciclosporin, tacrolimus or sirolimus plasma levels to guide dose adjustment.

Other drug interactions

Clarithromycin is a potent inhibitor of the transport protein P-glycoprotein (Pgp).This could give rise to increased plasma concentrations of active substances which are transported by this transporter and may also increase distribution of such active substances to organs having Pgp as an distribution barrier e.g. CNS.
Digoxin
Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. The concentration of the Pgp substrate digoxin may be increased when co-administered with clarithromycin. 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. Monitoring of serumdigoxin concentrations should be considered when co-treatment with clarithromycin is initiated or terminated since a dose adjustment may be warranted.
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

As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine (see sections 4.3)

Zidovudine
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV infected adults may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.
Phenytoin and Valproate
There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.
Bi-directional drug interactions
Atazanavir
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin (500 mg twice daily) with atazanavir (400 mg once daily) resulted in a 2-fold

increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Calcium Channel Blockers
Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers 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 (see section 4.5: Ritonavir).

Oral Contraceptive Pill
Patients taking oral contraceptives should be warned that if diarrhoea, vomiting or breakthrough bleeding occur there is a possibility of contraceptive failure.

4.6 Fertility, pregnancy and lactation

Pregnancy
The safety of Clarithromycin during pregnancy has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.
Data on the use of clarithromycin during the first trimester of more than 200 pregnancies show no clear evidence of teratogenic effects or 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 not be given to pregnant women unless it is clearly needed.

Lactation
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 borne 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 paediatric populations are abdominal pain, diarrhoea, 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 pre-existing mycobacterial infections.

b. Tabulated summary of adverse reactions

The undesirable effects have been reported in more than isolated cases, they are listed below according to their organ system and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to <1,1000), very rare (<1/10,000) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

System Organ Class	Very common ≥1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥1/1,000 to < 1/100	Rare (>1/10,000 and <1/1000)	Very rare (<1/10,000, including isolated cases)	Not Known* (cannot be estimated from the available data)
Infections and infestations			Candidiasis, Cellulitis, vaginal infection			Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia,			Agranulocytosis, Thrombocytopenia.
Immune system disorders			Anaphylactoid reaction, hypersensitivity			Angioedema, allergic reactions ranging from exanthema/ urticaria to severe anaphylactic reaction,
Metabolism and nutrition disorders			Anorexia, decreased appetite	Hypoglycaemia*, in particular in concomitant administration of antidiabetic agents and insulin.		
Psychiatric disorders		Insomnia	Anxiety			Mania, hallucinations, psychoses, disorientation, depersonalisation, unpleasant dreams, confusion.
Nervous system disorders		Headache, dysgeusia,	Loss of consciousness, dyskinesia, tremor, dizziness,		Muzziness,	Convulsion, aguesia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Reversible hearing loss.		Deafness
Cardiac disorders			Cardiac arrest, atrial fibrillation, extrasystoles,			Ventricular fibrillation, ventricular tachycardia, Torsades de Pointes.

			palpitations, extended QT interval			
Vascular disorders		Vasodilation.				Haemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma, pulmonary embolism			
Gastrointestinal disorders		Nausea, diarrhoea, vomiting, dyspepsia, abdominal pains,	Oesophagitis, gastritis, constipation, dry mouth, eructation, flatulence, glossitis, stomatitis			Discoloration of teeth and tongue, acute pancreatitis
Hepatobiliary disorders		Liver function test abnormal	Hepatic dysfunction (normally transient and reversible). Hepatitis. Cholestasis. Alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased			Jaundice hepatocellular, fatal hepatic insufficiency (particularly in patients with pre-existent liver disease or patients who are undergoing treatment with other hepatotoxic preparations)
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous.			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			Musculoskeletal stiffness, Arthralgia, myalgia			Myopathy
Renal and urinary disorders			Blood creatinine increased, blood urea increased			Interstitial nephritis, renal failure
General disorders and administration site conditions	Injection site phlebitis	Tenderness at site of administration, injection site pain, injection site inflammation	Asthenia			
Investigations			Extended prothrombin time			

			(increased INR), Albumin globulin ratio abnormal .			

** Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.*

c. Description of selected adverse reactions

Injection site phlebitis, injection 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).

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

d. Paediatric populations

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. *Other special populations*

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

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

In these immunocompromised patients, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1000mg or 2000mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4000mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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

There is no experience of overdose after intravenous administration of clarithromycin. However, reports indicate that the ingestion of large amounts of clarithromycin orally can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia. Adverse reactions accompanying overdose should be treated by the prompt elimination of unabsorbed drug and supportive measures.

Clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

In the case of overdosage, Clarithromycin IV should be discontinued and all other appropriate supportive measures should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial 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.
Clarithromycin 500 mg Powder for Concentrate for Solution for Infusion is usually active against the following organisms in vitro:

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-haemolytic streptococci); alpha-haemolytic streptococcus (viridans group); *Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.*

Gram-negative Bacteria: *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae; Legionella pneumophila, Bordetella pertussis, Helicobacter pylori; Campylobacter jejuni.*

Mycoplasma: *Mycoplasma pneumoniae; Ureaplasma urealyticum.*

Other Organisms: Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae; Chlamydia pneumoniae.

Anaerobes: Macrolide-susceptible *Bacteriodes fragilis;Clostridium perfringens;* Peptococcus species; Peptostreptococcus species; *Propionibacterium acnes.*

Clarithromycin has bactericidal activity against several bacterial strains. These organisms include H. influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Morazella (Brahamella) catarrhalis, Neisseria gonorrhoeae, Helicobacter pylori and Campylobacter spp.

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

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 [1]
Helicobacter pylori	0.25 mg/L[1]	0.5 mg/L
[1] The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduces susceptibility. "IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug		

5.2 Pharmacokinetic properties

The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism as indicated by lower biovailability of the metabolite following IV administration. Following IV administration the blood levels of clarithromycin achieved are well in excess of the MIC_{90}s for the common pathogens and the levels of 14-hydroxyclarithromycin exceed the necessary concentrations for important pathogens, e.g. *H. influenzae*.
The pharmacokinetics of clarithromycin and the 14-hydroxy metabolite are non-linear; steady state is achieved by day 3 of IV dosing. Following a single 500mg IV dose over 60 minutes, about 33% clarithromycin and 11% 14-hydroxyclarithromycin is excreted in the urine at 24 hours.
Clarithromycin 500 mg Powder for Concentrate for Solution for Infusion does not contain tartrazine or other azo dyes, lactose or gluten.

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, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys.

At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactobionic acid

6.2 Incompatibilities

None known. However, Clarithromycin should only be diluted with the diluents recommended. Do not use with diluents containing preservatives or inorganic salts.

6.3 Shelf life

4 years unopened.

Reconstituted/Diluted Solutions: Chemical and physical in use stability has been demonstrated for 6 hours at 25°C.
From a microbiological point of view, the reconstituted and diluted 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

As packaged for sale: Do not store above 30°C. Keep the vial in the outer carton in order to protect from light.

For storage condition of the diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear type II glass vial, closed with a bromobutyl stopper especially designed for lyophilised products and sealed with a tamper-proof aluminium flip-off cap.

Pack sizes: 30 ml vial. Available as single packs.

6.6 Special precautions for disposal

Clarithromycin 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. Clarithromycin should not be given as a bolus or an intramuscular injection. The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Suitable diluents include:

- Dextrose 50 mg/ml (5%) solution for infusion in Lactated Ringer's Solution
- Dextrose 50 mg/ml (5%) solution for infusion
- Lactated Ringer's Solution
- Dextrose 50 mg/ml (5%) in Sodium Chloride 3 mg/ml (0.3%) solution for infusion
- Dextrose 50 mg/ml (5%) in Sodium Chloride 4.5 mg/ml (0.45%) solution for infusion
- Sodium Chloride 9 mg/ml (0.9%) solution for infusion.

For single use only. Discard any unused solution.

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals Ltd
Bampton Road
Harold Hill
Romford
RM3 8UG
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA0361/025/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16th October 2009
Date of last renewal: 15th October 2012

10 DATE OF REVISION OF THE TEXT

December 2019